Development of Organocatalytic Tandem Processes for the Asymmetric Synthesis of Nitrogen-Containing Compounds

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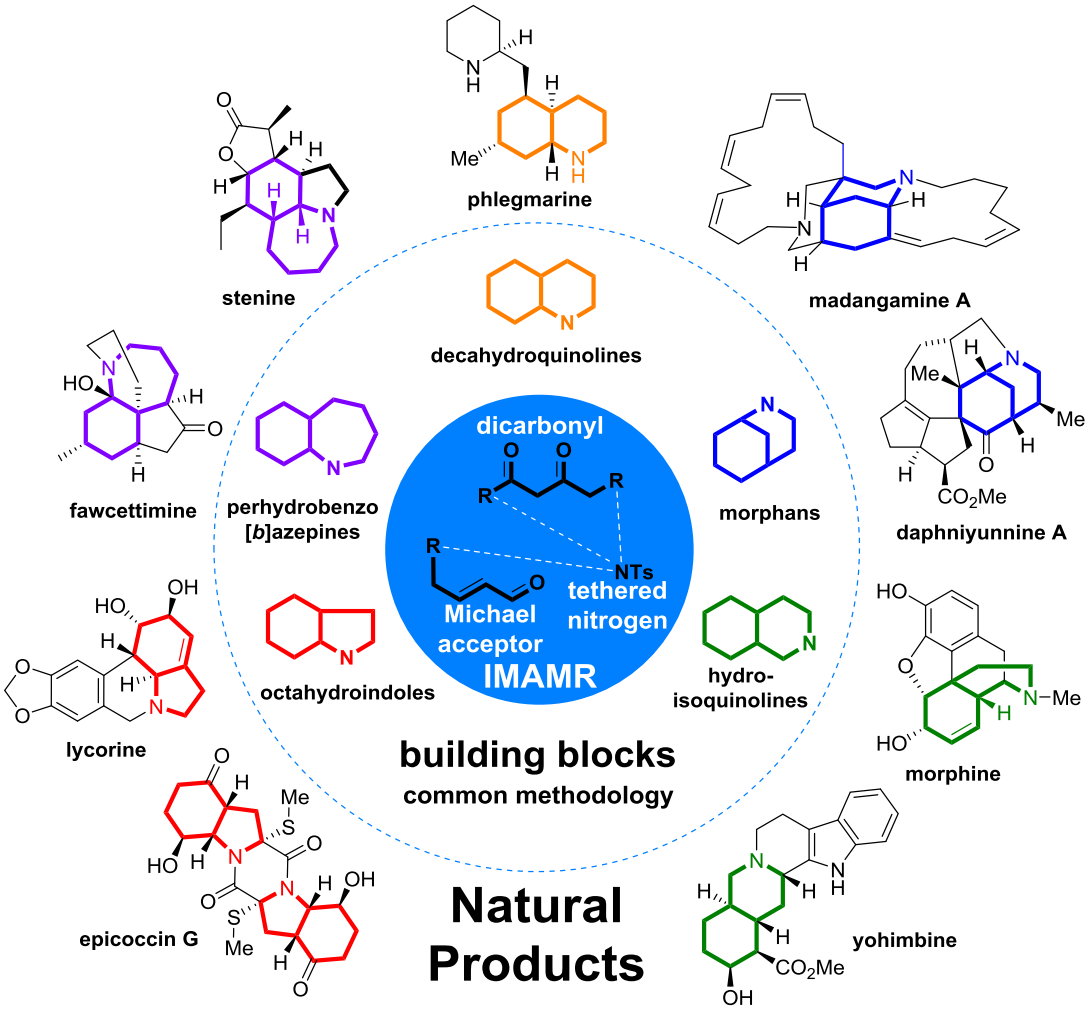

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FACULTAD DE FARMACIA

Programa de Doctorado: Química Orgánica Experimental e Industrial

Development of Organocatalytic Tandem Processes for the Asymmetric Synthesis of Nitrogen-containing Compounds

Presentada por Claudio Parra Montes

para optar al grado de Doctor de la Universidad de Barcelona

Dirigido por:

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Barcelona, Julio 2015

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"Ser joven y no ser revolucionario es una contradicción hasta biológica"

Salvador Allende Gossens.

Mamá y Papá…

Familia, Ana, Amigos, Josep, Ben…

Y a todas las personas con las que he cruzado camino

y han hecho más agradable esta época de mi vida.

A todos… GRACIAS!

PUBLICATIONS AND PERSONAL CONTRIBUTIONS TO CONGRESS

PUBLICATIONS

1. Organocatalyzed Asymmetric Synthesis of Morphans. Bradshaw, B.; Parra, C.; Bonjoch, J.; *Org. Lett.* **2013**, *15*, 2458-2461.

Manuscript in preparation:

2. Organocatalyzed Asymmetric Synthesis of Octahydroindoles: A Modular Synthetic Entry to multiple Diverse Natural Products and Pharmaceuticals. Parra, C.; Bradshaw, B.; Bonjoch, J.

CONGRESSES

1. Síntesis organocatalizada de Morfanos (poster). Parra, C.; Bradshaw, B. and Bonjoch, J.; XXXIV Reunión Bienal de la Real Sociedad Española de Química, Santander, 2013.

2. Métodos para la síntesis rápida de productos complejos (oral communication), Parra, C.; Bradshaw, B.; Bonjoch, J.; ChileGlobal Seminars: Seminario de Ciencias Biológicas, Barcelona, 2014.

ABBREVIATIONS AND ACRONYMS

2^{nd} gen	second generation
2-ABN	2-azabicyclo[3.3.1]nonane
aq.	aqueous
ax	axial
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl carbonate
Bn	benzyl
br	broad
Bz	benzoyl
c	concentration
^{13}C NMR	carbon-13 nuclear magnetic resonance
calcd	calculated
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
d	day(s), doublet (spectra)
δ	chemical shift
DEAD	diethyl azodicarboxylate
DFT	density functional theory
dd	doublet of doublets
dm	doublet of multiplets
DMF	*N*,*N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess

epi	epimer
equiv	equivalent
eq	equatorial
FGIs	functional group interconversions
[H]	reduction
^{1}H-NMR	proton nuclear magnetic resonance
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation spectroscopy
IMAMR	intramolecular aza-Michael reaction
J	coupling constant
LDA	lithium diisopropylamide
Lit.	literature
M	molar
m	multiplet
M^+	molecular ion
m/z	mass to charge ratio
mol	mol(es)
MS	mass spectrometry
Ms	mesyl (methylsulfonyl)
n-BuLi	*n*-butylllithium
n.a	not available
NMO	*N*-Methylmorpholine *N*-oxide
Ns	4-nitrobenzenesulfonyl
[O]	oxidation
OHI	octahydroindole
ppm	parts per million
PS-BEMP	2-tert-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene

R	generalized alkyl group or substituent
R_f	retention factor
rac	racemic
ref.	reference
rt	room temperature
s	singlet
sat.	saturated
sol.	solution
TADDOL	α,α,α´,α´-Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAH	tetrabutylammonium hydroxide (*n*-Bu_4NOH)
t	triplet
td	triplet of doublets
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TPAP	Tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid
wt	weight

CHAPTER 1

INTRODUCTION & OBJECTIVES

1.1 Nitrogen-containing natural products

Nitrogen heterocycles are present in a large number of natural products which possess important biological activities for wide range of therapeutic applications including anticancer, neuroprotective (e.g. Alzheimer's disease), analgesic and immunosuppressive activities (see Fig. 1.1). The various chemical structures presented by these molecules pose a number of considerable synthetic challenges which has made them a constant proving ground for the development of new chemical methodologies. Indeed, the syntheses of numerous highly complex natural products, once viewed as impossible, can now be successfully achieved in the laboratory, as advances in the synthetic methodologies developed within the previous decades have come to maturity. However, despite these advances the preparation of complex natural products is still a non-trivial matter and the vast majority of syntheses are not efficient from a practical point of view only enabling the preparation of milligram quantities of the target product. If the potentially important therapeutic effects of complex natural products are to be exploited, the focus of total synthesis needs to be shifted from an end unto itself to the procurement of tangible and meaningful quantities of these structures.[1]

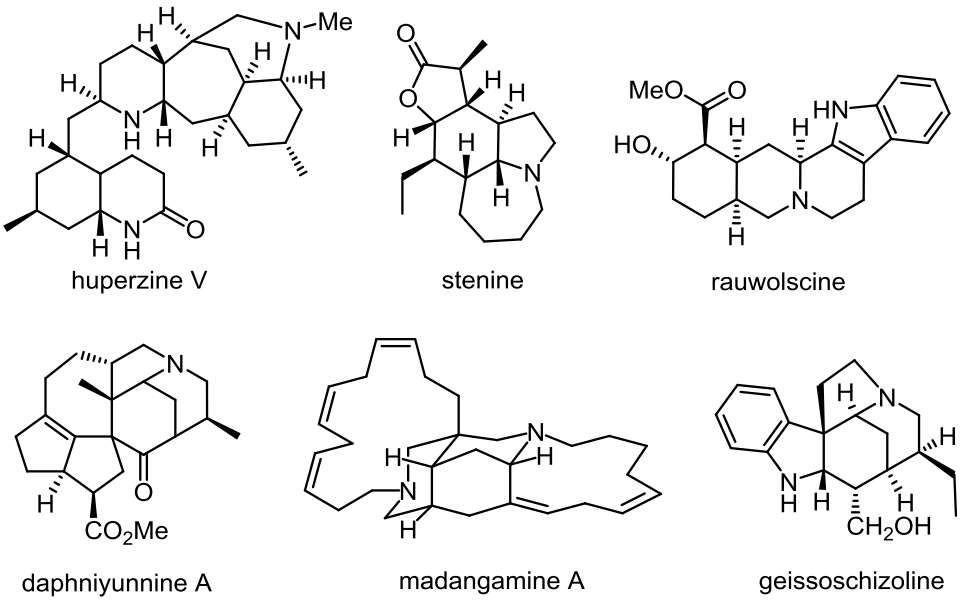


Figure 1.1 Complex biologically active alkaloids

[1] Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. *Nat. Prod. Rep.* **2014**, *31*, 419-432.

1.2 Efficiency in the construction of natural products

1.2.1 Towards the Ideal Synthesis

The following quote from Paul Wender distinctly sums up the situation: "*The challenge now in synthesis is therefore increasingly, not whether a molecule can be made, but whether it can be made in practical fashion, in sufficient quantities for the needs of research and/or society, and in a way that is environmentally friendly if not ideal.*"[2] To achieve this Wender defines[3] the 'ideal synthesis'as follows:

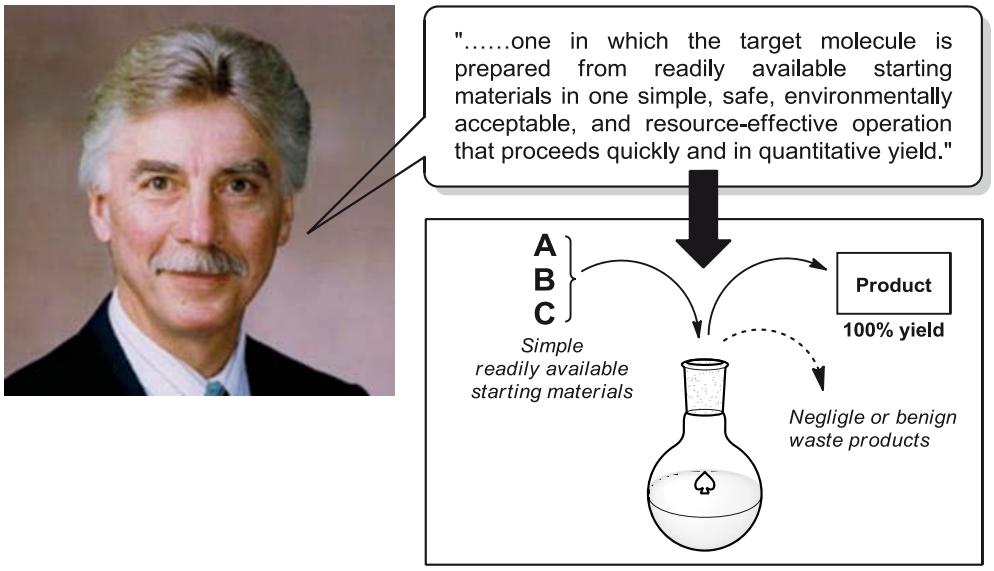


Figure 1.2 Wender´s definition of an ideal synthesis and visual representation of this concept in practice.

1.2.2 Strategies for More Efficient Syntheses

In order to approach the 'ideal synthesis' a number of potential strategies that could be employed are outlined in Figure 1.3 which will be discussed in more detail in later sections. These strategies can be broadly divided into 2 groups:

(i) Synthetic Design strategies: These strategies are based on a number of key design philosophies to arrive at a synthetic route to the target molecule with the minimal amount of steps possible. These include the maximum use of *tandem reactions*[4] thus achieving as many transformations as possible with a minimum of

[2] Quote from Paul Wender see: Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197-201.
[3] (a) Wender, P. A. *Tetrahedron* **2013**, *69*, 7529-7550. (b) Wender, P. A. *Nat. Prod. Rep.* **2014**, *31*, 433-440.
[4] Tandem reaction reviews: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178. (b) Ambrosini, L. M. and Lambert, T. H. *ChemCatChem*, **2010**, *2*, 1373-1380; (c) C. M. R. Volla, I.

effort. Secondly the design must attempt to avoid the use of "*non-productive steps*" by employing as much as possible protecting group-free[5] and redox-free strategies[6] to avoid any of these unnecessary steps. Finally, "*design better targets*" idea encompasses the idea of making simpler targets i.e removing redundant functionalities that are difficult to install and are not essential for function whilst still retaining or possibly increasing the desired effects of the molecule.[7]

(ii) Operational Design strategies: These strategies essentially involve how the synthesis is actually carried out in the real world in a way to avoid the "stop & go" paradigm (see section 1.3) which is a major source of inefficiency with regards to costs, time and wastes. This might include the use of "*solid supported reagents and scavengers"* as well as the use of "*pot-economy"* design. [8]

Finally, the overall design should try to obey green chemistry principals however applying the strategies outlined above the synthesis should automatically adhere to these rules.

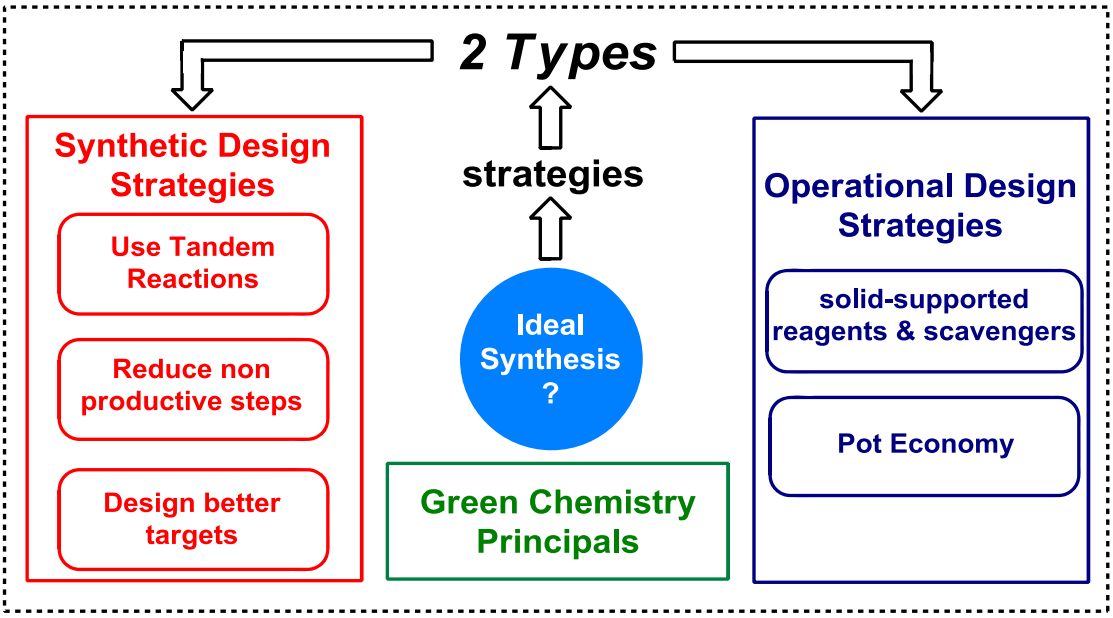


Figure 1.3 Potential strategies to achieve an "ideal syntheses"

Atodiresei and M. Rueping, *Chem.Rev.*, **2014,** *114*, 2390-2461 (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136.
[5] Young, I. S.; Baran, P. S. *Nature Chem.* **2009**, *1*, 193-205.
[6] Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657-4673.
[7] P. A. Wender G. R. Pettit *et al, Proc. Natl. Acad. Sci.* U. S. A., **1998**, *95*, 6624-6629.
[8] Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438-440.

1.3 Synthetic Design strategies in Practice

To highlight the benefits of the previously outlined "synthetic design strategies" methods it may be instructive to compare them to those used in a more traditional synthetic sequence for the construction of a complex pentacyclic product such as that shown in Figure 1.4. To induce the chirality into the molecule the typical approach is to start with a product from the chiral pool or employ a chiral auxiliary in the formation of the first ring. Additional functionality is then added in a stepwise manner that is required for the fusion of the second ring and so on for each additional ring until the target product is completed. An analysis of a typical synthetic sequence like this will generally reveal that the majority of steps that are carried out between each ring forming step can be classed as "unproductive". These include functional group interconversions (FGIs) such as adjustments of the oxidation state of the molecule, protection-deprotection steps, functional group transpositions and the introduction and removal of chiral auxiliaries. Thus much of the work carried out and waste produced is a direct result of transformations that effectively do not forward the construction of the target molecule. Additionally each of these steps operate under the 'stop-and-go' paradigm,[9] in which after each chemical transformation the sequence is stopped whilst a purification step is carried out prior to continuation. This "purification phase" undoubtedly contributes the greatest investment of time and materials in any total synthesis endeavour and is where the major source of waste generation originates. These manipulations also inevitably lead to losses of material at each phase of the process, ultimately lowering the overall yield.[10] Evidently the more steps required the more this problem is exacerbated and becomes a barrier to obtaining the material rapid and efficient manner.

However, through employment of tandem reactions it becomes possible to overcome many of the above problems. Thus, if one can generate from 2 rings to all 5 rings in a single one pot process, one can avoid the multiple steps needed to manipulate the functional groups and protecting groups required en-route to the final product. If these reactions are catalysed by an organocatalyst to initially introduce

[9] Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477-1489.

[10] Even if each step of the process is 100% efficient, some quantities of material will be lost at each phase of the purification process see: Wernerova, M.; Hudlicky, T. *Synlett* **2010**, 2701–2707.

the chirality into the molecules the process becomes even more efficient. Organocatalysis is attractive because it is non-toxic, relatively cheap and easy to carry out (e.g. non anhydrous conditions and open to the air). However, despite the potential and benefits of employing organocatalytic methods this is an area that is still in its infancy especially within the context of target directed total synthesis[11] and general methods to important nitrogen containing nuclei still remain to be developed.

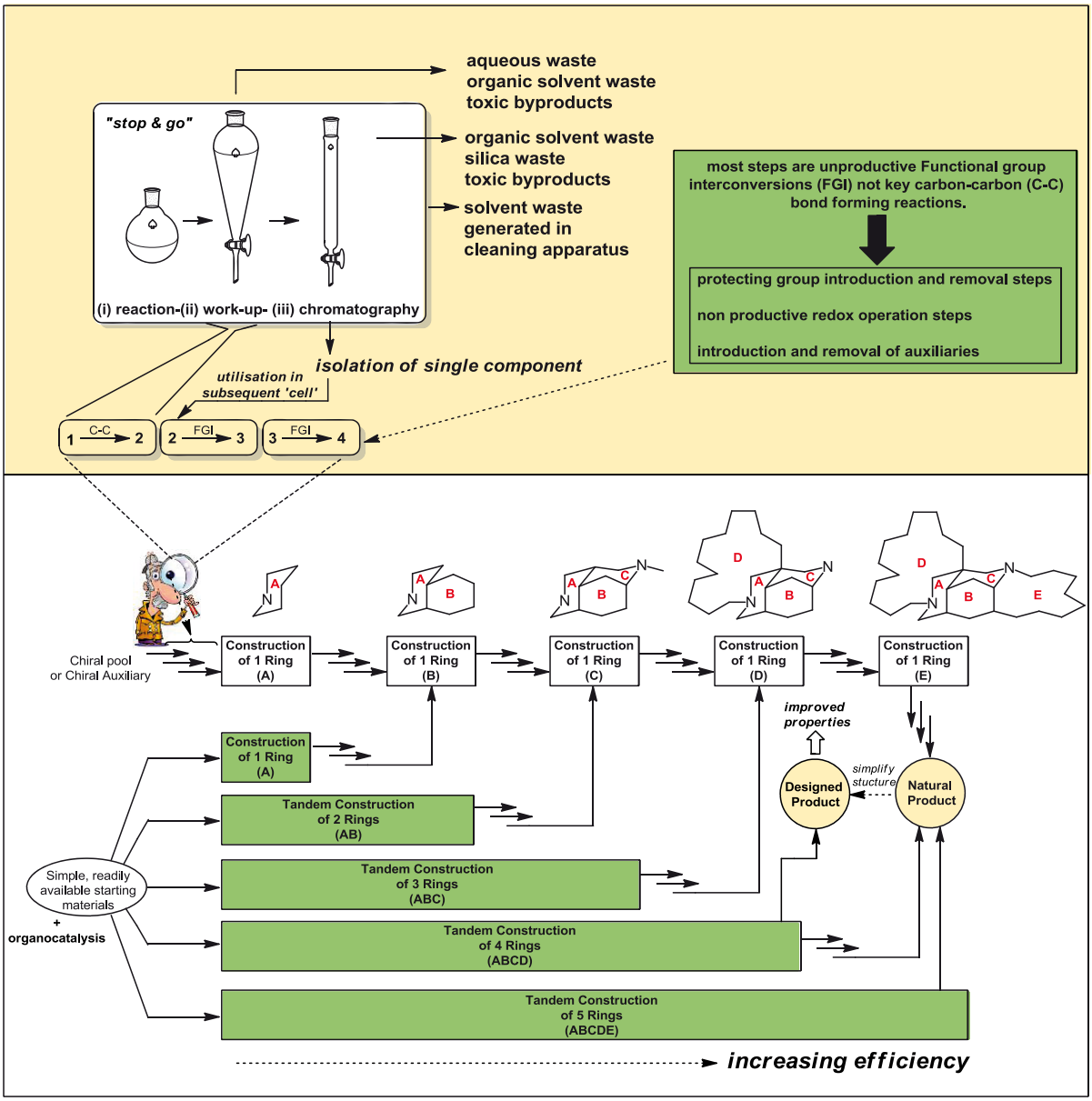


Figure 1.4 Construction of fused polycyclic ring systems – ring by ring using stop & go vs tandem reactions to assemble multiple rings simultaneously.

[11] For a review of organocatalysis in the synthesis of natural products see: Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138–1167.

1.4 Towards the ideal synthesis in practice: Operational Design strategies

The previous section established that one of the main impediments to synthetic efficiency is closely linked with the classical "*stop-and-go"* procedure used in conjunction with employing a large number of non-productive functional group transformations and proposed the best way to avoid these problems is to eliminate as many steps that call for this process in the design phase. Regardless, there will still be some need to undergo some purification steps throughout the synthesis and some alternatives to avoid the laborious and wasteful "*stop-and-go"* process are proposed below.

1.4.1 Alternatives to "*stop-and-go"*

The first possibility is to employ *solid supported reagents*[12] to initiate a reaction sequence and *solid supported scavengers* to clean it up since these can simply be filtered from the reaction mixture at the end of the sequence. They also have the advantage that they can be adapted for flow chemistry methods as well.[13]

A second alternative is the use of pot economy[14] which is somewhat analogous to process chemistry principals. Essentially the design allows for continual addition of reagents to initiate the next reaction without any purifications in between. As much as possible volatile reagents are used which can then be removed by evaporation between adjacent transformations. Finally, if the route is sufficiently short it should be feasible to not have to remove any small quantities of secondary products that are formed from the main product at each step. As much as possible any captured reagents and solvents[15] should be recycled. Here a carefully planned series of tandem reactions in combination with solid supported reagents and 'pot-economy' would offer a potent solution to the problem of how to obtain more efficient synthetic sequences. By eliminating the need for work-up and product isolation between successive synthetic steps, it may become possible to complete an entire multi-step

[12] Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 2194-2197.
[13] Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849–8869.
[14] Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3605-3607.
[15] (a) Drueckhammer, D. G.; Gao, S. Q.; Liang, X.; Liao, J. *ACS Sustainable Chem. Eng.* **2013**, *1*, 87−90. (b) Seyler, C.; Capello, C.; Hellweg, S.; Bruder, C.; Bayne, D.; Huwiler, A.; Hungerbühler, K. *Ind. Eng. Chem. Res.* **2006**, *45*, 7700-7709.

sequence in a single pot,[16] a process that would approach Wender's definition of an 'ideal synthesis' (as outlined in section 1.2.1). Rather than seeing a synthesis as a series of discreet reactions, it is now viewed as a "single reaction process" with every reaction connected into one long synthetic step (Figure 1.5).

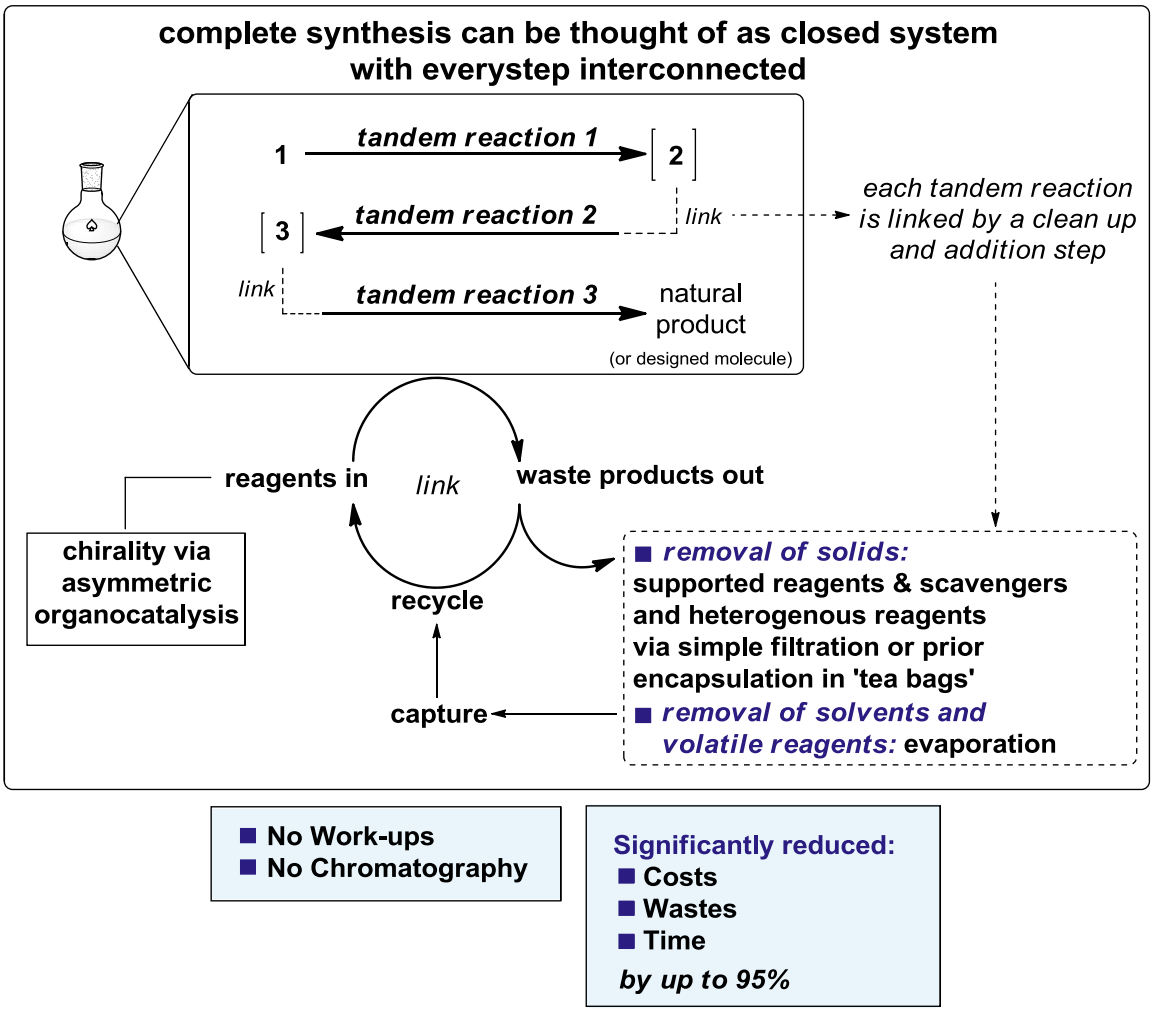


Figure 1.5 Proposed construction of a natural product in a single flask without resorting to work-ups and purifications using a self-contained series of carefully orchestrated of tandem reactions.

[16] The use of solid supported reagents and scavengers requires a simple filtration step to remove resin between steps thus making the reaction not conform to the definition of "one-pot" requiring the use of the word "telescoped reaction" instead. We have demonstrated (unpublished work) that if the resin is enclosed in a "tea-bag" it can be removed from the reaction flask at the end of its use and thus maintain the "one-pot" definition.

1.5 Precedents for Tandem Reactions Developed Within Our Research Group

1.5.1 The Organocatalysed Michael Robinson-aza-Michael reaction

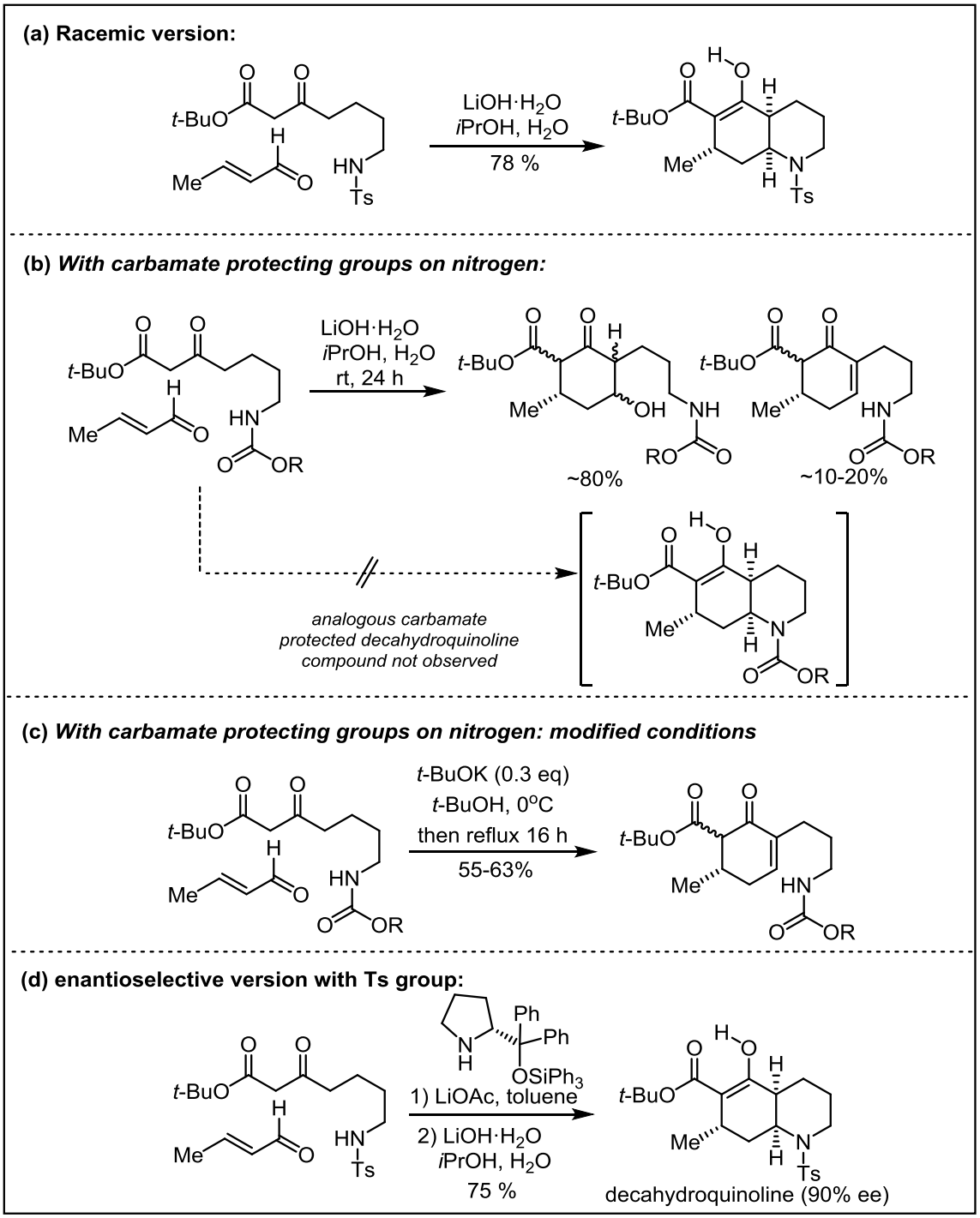
Overview of the reaction: Our research group has developed a "one pot" method that allows us to obtain 5-oxodecahydroquinolines.[17] Starting from a β-keto ester with a tethered sulfonamide group and reacting it with crotonaldehyde in the presence of $LiOH \cdot H_2O$ in *i*PrOH/H_2O led to an intermediate cyclohexenone via a Robinson reaction. This intermediate then undergoes a sequential conjugate addition of the nitrogen onto the cyclic enone giving a decahydroquinoline ring system in a simple, and efficient one-pot reaction whilst at the same time generating three stereocenters in a stereocontrolled manner (see scheme 1.1a).

Some key points to note about the reaction are the following:

- Lithium hydroxide in *i*PrOH with 10 equivalents of water were the optimum reaction conditions. The addition of water increased the aza-Michael product presumably by providing the proton for the aza-Michael step
- One equivalent of base and enal were found to give the best results – the use of excess quantities of either reagent was found to be detrimental to the yield.
- The use of a sulfonamide was found to be essential to effect the Michael reaction – carbamates such as Cbz and Boc did not undergo the aza-Michael reaction (scheme 1.1b). Additionally, the use of $LiOH \cdot H_2O$ only leads to partial cyclisation/elimination with a carbamate protected nitrogen with most material only arriving to the aldol addition product. The use of more forcing conditions *t*-BuOK in *t*-BuOH were required to give the cyclohexenone ring system (scheme 1.1c).
- The ester group functions as a "locking group" since by its proximity to the ketone allows the formation of an enol tautomer with the consequent formation of a hydrogen bond and thus stabilizes the system against retro-aza Michael ring opening processes.
- The bulky *t*-butyl group forces the methyl group to take up the less favourable axial position to avoid unfavourable steric interactions.

[17] Bradshaw, B.; Luque-Corredera, C.; Saborit, G.; Cativiela, C.; Dorel, R.; Bo, C.; Bonjoch, J. *Chemistry* Eur. J. **2013**, *19*, 13881-13892.

- Finally, the reaction with tosyl could be made enantioselective using the modified Hayashi catalyst. LiOAc as additive was essential for good rate and toluene was found to be the best solvent with regards to enantioselectivity (scheme 1.1d).[18]



Scheme 1.1 The Robinson aza Michael Reaction in racemic and enantipure variants

[18] Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326–329.

1.5.2 Overview of the reaction mechanism

Based on the experimental results, we proposed a plausible mechanism for the reaction which was then refined and corroborated by DFT modelling studies[17] (Scheme 1.2). The mechanism can be split into roughly 5 parts:

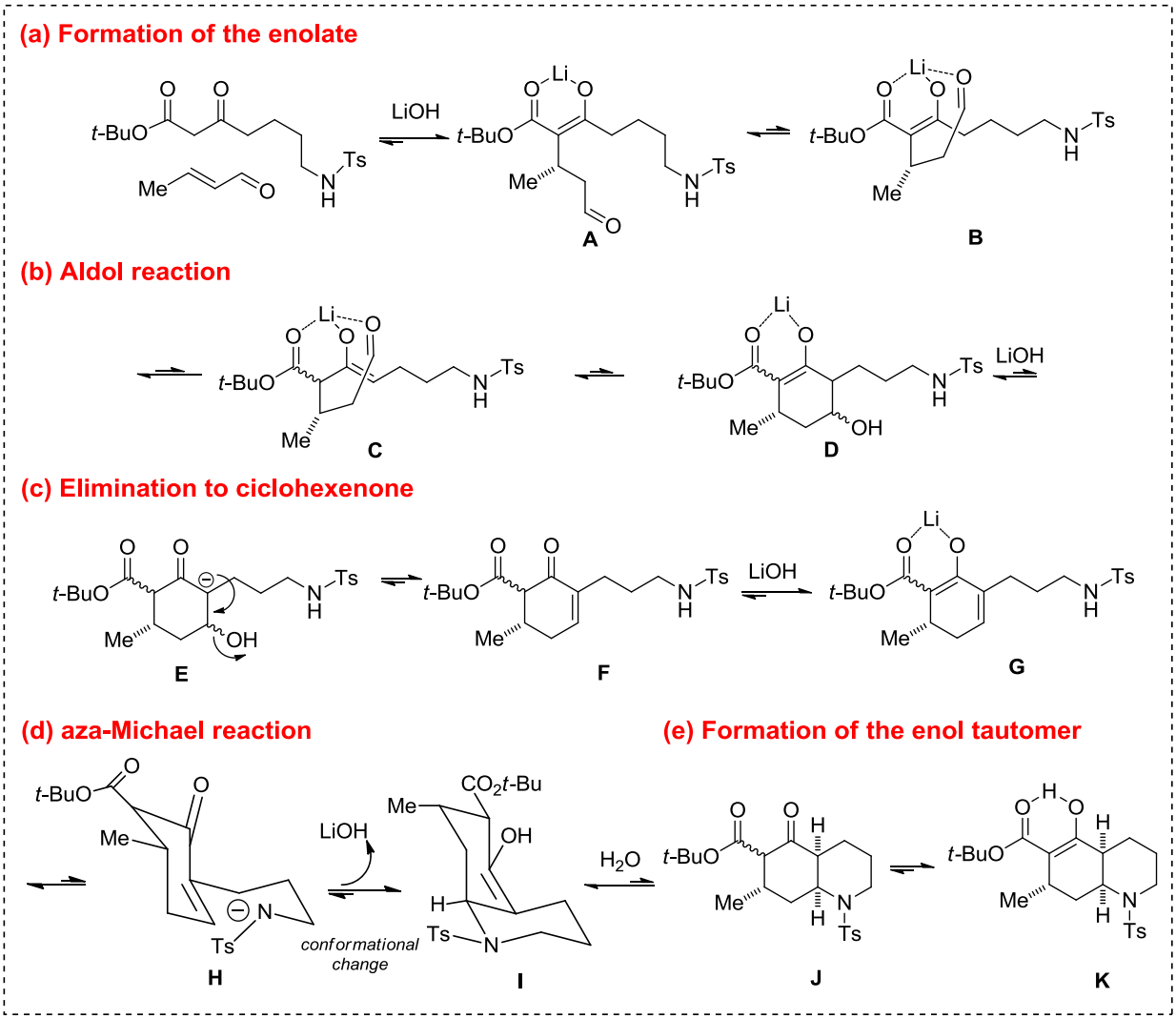
Formation of the correct enolate: Michael reaction between the β-keto ester and crotonaldehyde gave the coupled product, which was further deprotonated to furnish the more stable lithium enolate species **A**, effectively preventing the Robinson annulation from progressing (scheme 1.2a). However, it was thought that the carbonyl group on the side chain could play a role in facilitating the formation of the less stable target enolate by forming a tricoordinated species **B** whose energy difference between the analogous tricoordinated species **C** is reduced. This lowering of energy allows enough of the species **C** to form to allow sequence to continue.

Aldol reaction: Once the required regiospecific enolate is formed, the aldol reaction can take place to give the alkoxide species. However, proton transfer to the alkoxide from the keto ester reforms the more stable enolate **D**, effectively halting the reaction once again (scheme 1.2b).

Elimination to Cyclohexenone: A small quantity of the least stable enolate **E** present at equilibrium undergoes dehydration to give enone **F**. Deprotonation of the keto ester again prevents the reaction from progressing by forming the more stable enolate **G** (scheme 1.2c).

aza-Michael reaction and protonation: A small amount of enone **H** present at equilibrium is attacked from the top face to give aza-Michael addition product intermediate, which immediately undergoes protonation and a ring flip to form **I**. In the changed conformation the methyl group is located in the axial position. The presence of water favours the formation of **I** by providing a ready source of protons to trap intermediate **I** before the retro aza-Michael product can revert back to the ring-opened product **H**. Finally, formation of the hydrogen bond between the enol form and the ester group effectively locks the molecule, driving the reaction to completion and ensuring the stability of **K**. Thus, the tandem reaction would appear to be a series of sequential equilibrium, the vast majority of which are unfavorable. Only the last step, in which the enol of **K** is formed (see scheme 1.2e), is favorable,

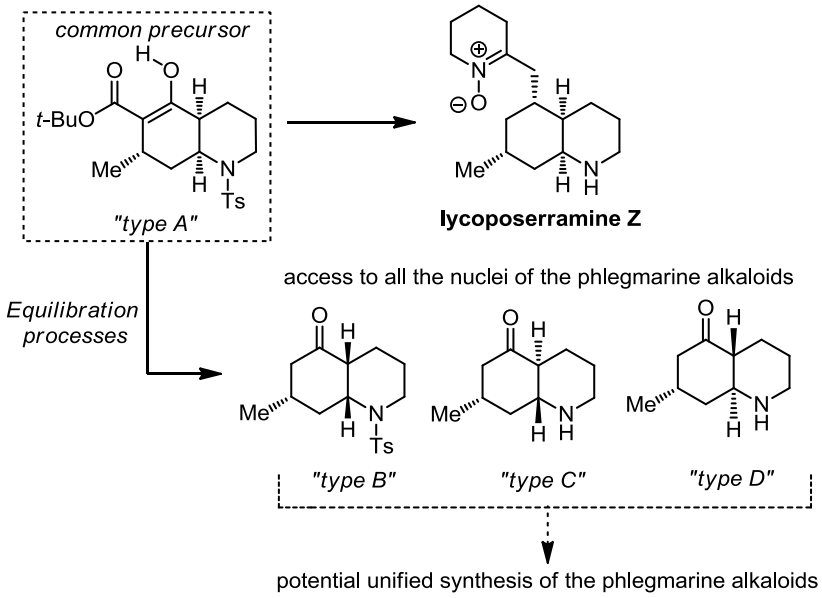
and indeed crucial, because it displaces the various equilibrium over to the right to allow the reaction to reach completion. This overall mechanism would explain why the reactions using carbamate derivatives, which do not undergo the intermolecular aza-Michael reaction, are mostly halted at step (b), giving intermediates analogous to **D**. Only when the unfavourable equilibrium is overcome by using KO*t*-Bu under forcing reflux conditions is the cyclohexenone obtained. However, the poor nucleophilicity of the carbamate is not sufficient to overcome the **H** to **I** step to give the corresponding carbamate protected decahydroquinoline ring system product.



Scheme 1.2 Proposed mechanism for the Robinson aza-Michael reaction

1.5.3 Application of Reaction in the Context of Total Synthesis of Natural Products: The Phlegmarine Alkaloids

It was possible to use the enantiopure decahydroquinoline as an advanced building block for a rapid synthesis of Lycoposerramine Z.[18] It was also shown that this molecule could be converted to all the other possible stereochemistries of this ring system in a controlled manner via equilibration reactions.[17] These other building blocks (labelled A to D to distinguish their respective stereochemistries) are currently under investigation for a unified synthesis of the phlegmarine alkaloids (scheme 1.3).

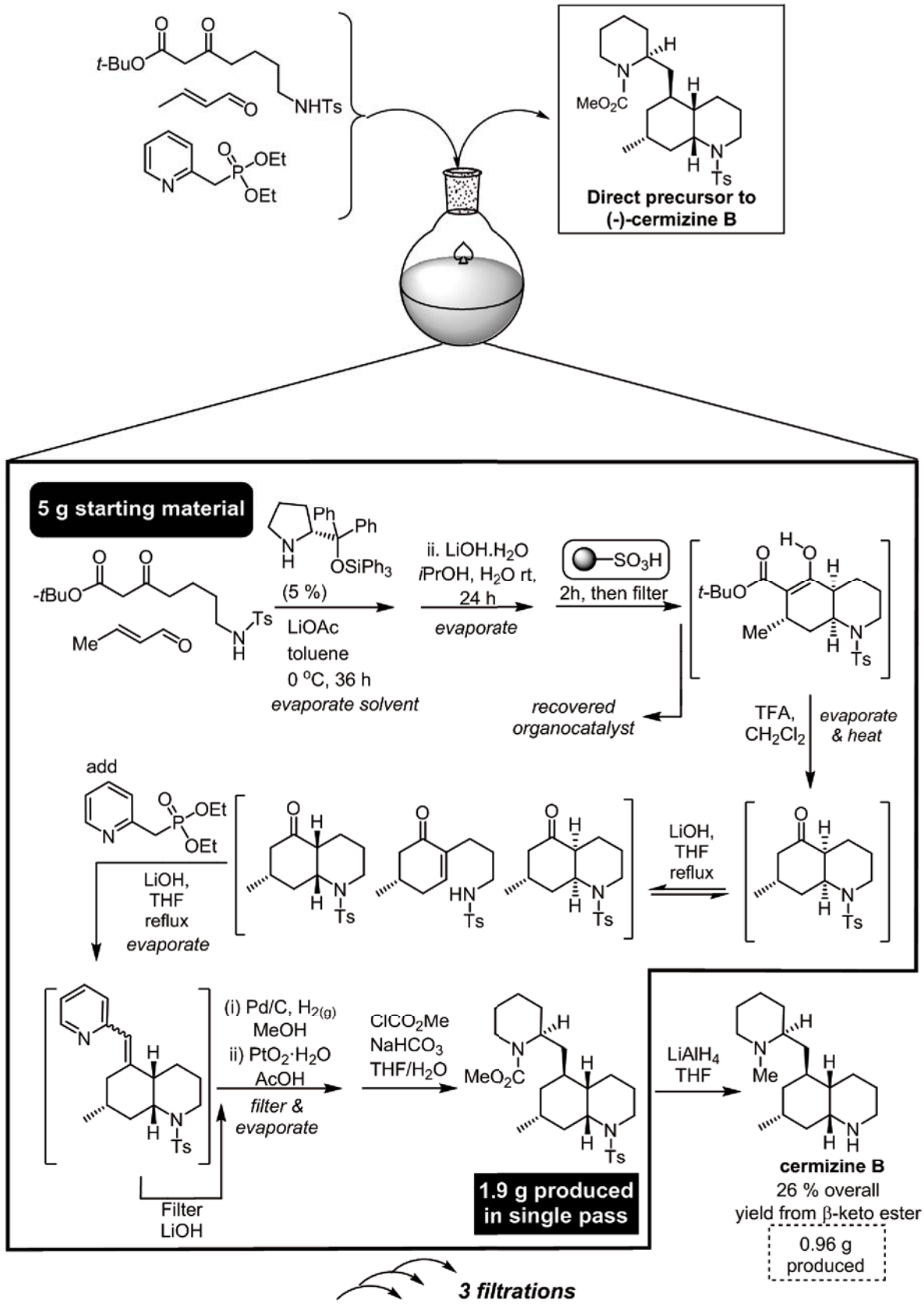


Scheme 1.3 Application of tandem reaction to the total synthesis of lycoposseramine Z and the core nuclei of all the known phlegmarine alkaloids.

1.5.4 Gram-scale total synthesis of cermizine B via *uninterrupted* sequence

This building block was also used in a highly efficient synthesis of cermizine B essentially carrying out all the reactions in a single flask a process which starts to approximate Wender's definition of an ideal synthesis.[19] Notably, this sequence could produce a gram of the final compound from just 5 g of the β-keto ester precursor. This was made possible by using tandem reactions, solid supported scavengers, pot-economy and a synthetic design that avoided any redundant transformations.

[19] Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Chem. Commun.* **2014**, *50*, 7099–7102.



Scheme 1.4 Gram-scale synthesis of cermizine B and all the intermediates formed in the uninterrupted sequence from β-keto ester starting material.

1.6 Objectives of Thesis

As can be seen from the previous section it was possible to construct a natural product essentially in a single flask in a highly efficient manner. Without doubt the key to the success of this process was the easy formation of the core enantiopure decahydroquinoline ring system using a tandem reaction process.

1.6.1 Explore strategies to access multiple nitrogen containing nuclei

To expand this methodology it is proposed to design new organocatalysed tandem reactions to access other important nitrogen containing nuclei embedded in a wide range of different natural product structures.

The application of this core underlying methodology to other structures would open up the way to obtain a large amount of important natural product structures in a similarly effect manner as cermizine B. Moreover since many of polycyclic natural products contain more than one type bicyclic nuclei having access to multiple strategies would allow us to disconnect these molecules from multiple different perspectives giving more flexibility with regards to the positioning of functional groups and stereochemistries.

Such a process would be interesting from a medicinal chemistry point of view as well since multiple ring structures could be accessed from a single methodology but also they could be varied further by using different starting materials due to the multicomponent nature of the reaction.

Finally the most exciting aspect of this approach is that different ring construction modules could potentially be combined to generate complex polycyclic systems in a single reaction as outlined previously in section 1.3.

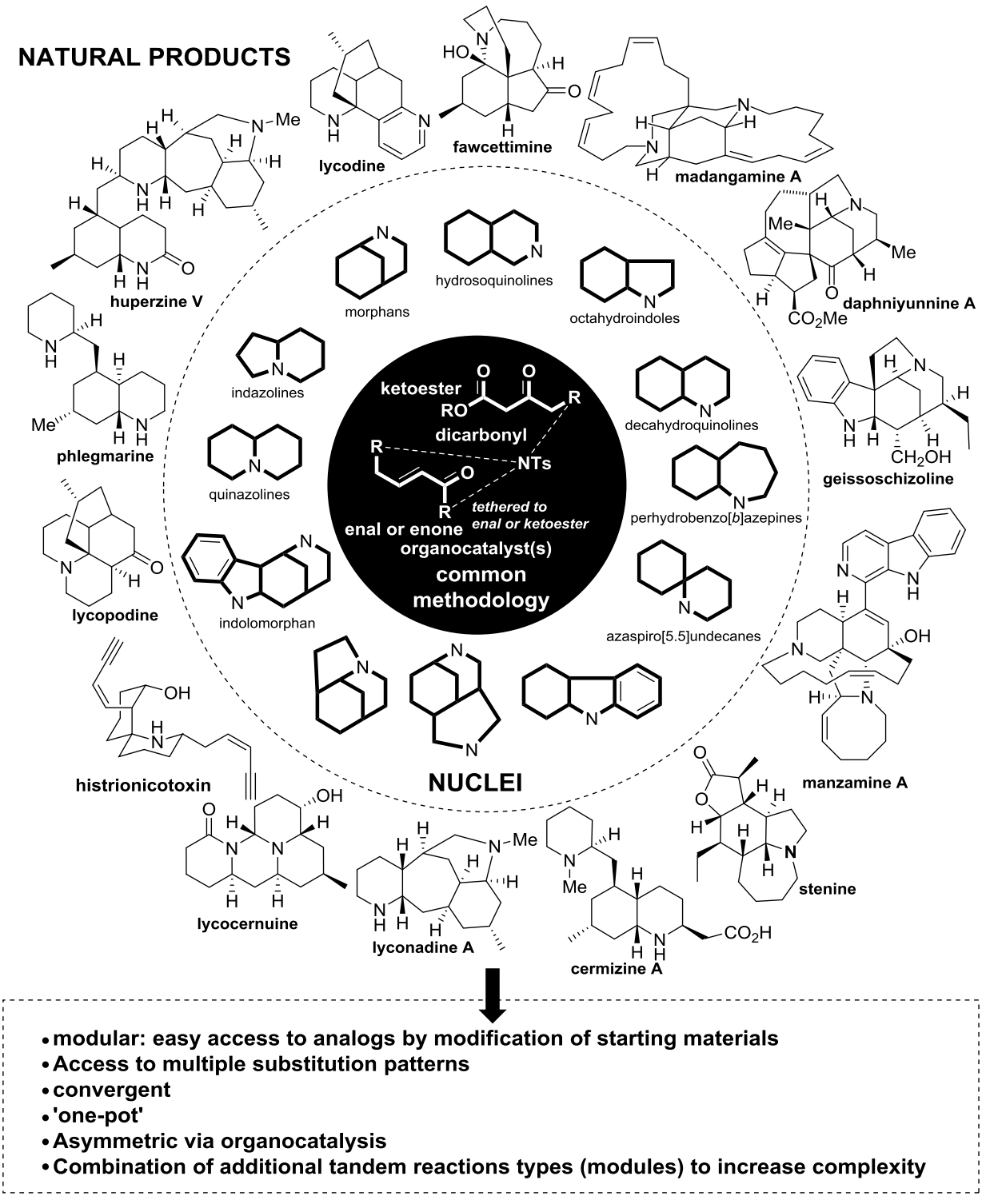


Figure 1.6 Conceptual overview of common methodology to access multiple different heterocycle types embedded in diverse natural product structures and potential advantages of his approach.

1.6.2 Overview of thesis objectives

This thesis is divided into 3 key sections with the objective of each chapter focusing on the construction of one type of bicyclic nitrogen nuclei.

Chapter 2: Strategies to octahydroindole nucleus

The most basic modification of the previously described methodology to decahydroquinolines would be to vary the length of the nitrogen tether to give the corresponding ring contracted or ring expanded products. By shortening the β-keto ester chain by one carbon it should be possible to obtain octahydroindoles (Figure 1.7a) whilst adding one carbon would give access to the perhydrobenzo[*b*]azepine ring system (Figure 1.7b). The use of different Michael acceptors would also expand the potential of the reaction to access many different natural product patterns.

Chapter 3: Strategies to the morphan nucleus

Switching the nitrogen tether from the β-keto ester component to the Michael acceptor should allow the synthesis of morphan ring structures but using the same Robinson-aza-Michael reaction (Figure 1.7c). If successful the study could be expanded for enals with an allylic substituent to give to give 4-substituted morphans which are very common motifs in many morphan containing natural products (Figure 1.7d).

Chapter 4: Strategies to the hydroisoquinoline nucleus

The morphan structure bearing a β-keto ester is essentially a constitutional isomer of the hydroisoquinoline ring system. By switching the mode of attack of the tethered nitrogen from an aza-Michael reaction to a condensation on the ester to form an amide it was proposed to obtain the hydroisoquinoline ring system (Figure 1.7e). The initial scope of this section was expanded during the course of the thesis to incorporate two intramolecular variants: (i) inverting the ring construction order by taking the same starting materials and tethering the nitrogen to the ester prior to the Robinson condensation (Figure 1.7e) (ii) tethering the enal to the opposite end of the β-keto ester and using an indole as the trapping agent (via Pictet-Spengler type reaction) instead of an aza-Michael reaction to give the yohimbane skeleton (Figure 1.7f).

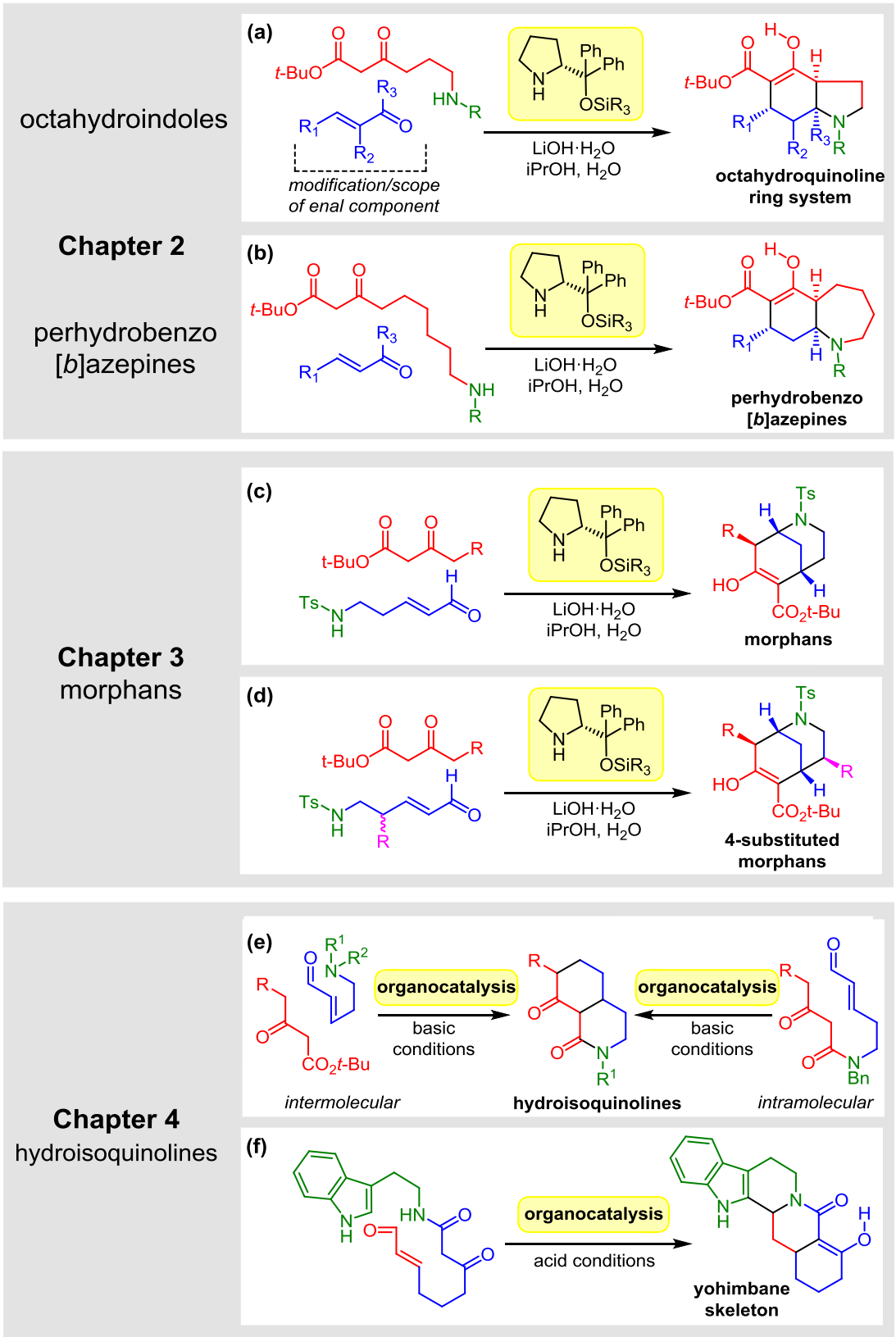
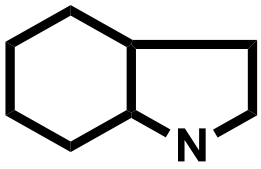


Figure 1.7 *Overview of thesis structure*

CHAPTER 2

SYNTHESIS OF ENANTIOPURE OCTAHYDROINDOLES VIA ORGANOCATALYSIS



2.1 The Octahydroindole Nucleus: Overview of Objectives.

The key focus of this chapter is the application of the Robinson aza-Michael reaction to the synthesis of the octahydroindole ring system. This objective can be sub divided into 3 parts shown in Figure 2.1 below.

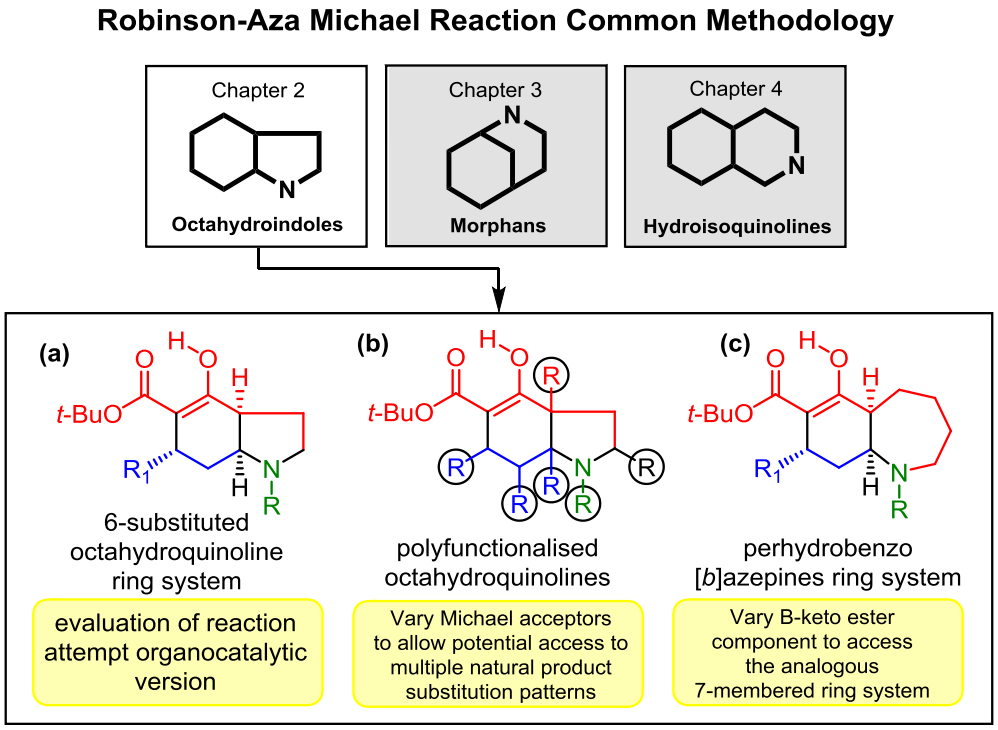


Figure 2.1 Overview of objectives for the synthesis of octahydroindoles.

(a) Carry out proof of concept studies to show that the octahydroindole nucleus can be formed by direct analogy to the decahydroquinoline system using crotonaldehyde as the Michael acceptor in racemic form. If successful the next step would be to evaluate the organocatalysed version of the reaction (b) Once the basic parameters of the Robinson/aza-Michael reaction are determined the modularity and generality of this process would be evaluated by modifying the Michael acceptor to evaluate the potential to access different substitution patterns found in various natural product structures. The possibility to modulate the stereochemistry of the fusion hydrogens to access other *cis* and *trans* stereochemistries could also be carried out at this point.[17] (c) Finally increasing the tether of the β-keto ester would be briefly examined to allow for the synthesis of the ring expanded perhydrobenzo[b]azepine ring structure.

2.2 Octahydroindole Natural Products and Pharmaceuticals

The octahydroindole unit can be considered a privileged ring system in that it is present in an extensive range of compounds (figure 2.2). These include a range of very diverse natural products such as aeruginosine 298-A,[20] mesembrine,[21] daphniyunnine D,[22] melotenine A,[23] pancracine,[24] stenine,[25] albomaculine[26], epicoccin G,[27] tubifoline,[28] tabersonine,[29] deethylibophyllidine,[30] lycorine,[31] A number of pharmaceutical products such as microcin SF608,[32] U93385,[33] S17092[34], perindopril[35] which is one of the top antihypertensive drugs on the market. Mavoglurant[36] which is under active development by Novartis for the treatment of Fragile X Syndrome (phase II-III), Parkinson's disease (phase II), and Huntington's disease (phase II), Finally, octahydroindoles are potentially useful as organocatalysts and have been used as variations of proline analog systems[37] such as the Jorgensen/Hayashi type analog shown which has been used by Melchiorre for the

[20] (a) Valls, N.; Lopez-Canet, M.; Vallribera, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2000**, *122*, 11248–11249. (b) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem. - A Eur. J.* **2001**, *7*, 3446–3460.
[21] Gu, Q.; You, S-L. *Chem. Sci*., **2011**, *2*, 1519–1522.
[22] (a) Kobayashi, J.; Morita, H. *Alkaloids Chem. Biol.* **2003**, *60*, 165–205. (b) Kang, B.; Jakubec, P.; Dixon, D. *Nat. Prod. Rep.* **2014**, *31*, 550–562.
[23] Zhao, S.; Sirasani, G.; Vaddypally, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 8309–8311
[24] (a) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett.* **2010**, *12*, 556. (b) Overman, L. E.; Shim, J. *Society* **1991**, 5005–5007.
[25] (a) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018-6024. (b) Zhang, H.; Chen, J.; Chen, J.; Xie, Y. *Angew. Chem Int. Ed.* **2012**, *51*, 1024-1027.
[26] Jin, Z. *Nat. Prod. Rep*., **2007**, *24*, 886–905.
[27] Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun Y-P.; Sarlah D. *J. Am. Chem. Soc.*, **2011**, *133*, 8150–8153
[28] Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230-7240.
[29] Ziegler, F.E.; Bennett, G. B. *J. Am. Chem. Soc.*, **1973**, *95*, 7458–7464
[30] Bonjoch, J.; Catena, J.; Valls, N *J. Org. Chem.*, **1996**, *61*, 7106–7115.
[31] Schultz, A. G.; Holoboski, M. A.; Smyth, M. S.; York, N. **1993**, 7904–7905.
[32] Valls, N.; Vallribera, M.; Lopéz-Canet, M.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 4945-4950.
[33] Chiu-Hong, L.; Haadsma-Svensson, S. R.; Phillips, G.; McCall, R. B.; Piercey, M. F.; Smith, M. W.; Svensson, K.; Carlsson, A.; Chidester, C. G.; VonVoigtlander, P. F. *J. Med. Chem.* **1993**, *36*, 2208-2218.
[34] J. Lawandi, S. Gerber-Lemaire, L. Juillerat-Jeanneret, N. Moitessier, *J. Med. Chem.* **2010**, *53*, 3423-3438.
[35] K. Alfakih, A. S. Hall, *Expert Opin. Pharmacother.* **2006**, *7*, 63-71. (b) M. Hurst, B. Jarvis, *Drugs* **2001**, *61*, 867-896.
[36] Levenga, J.; Hayashi, S.;de Vrij, F.M.S.; Koekkoek, S.K.; van der Linde, H. C.; Nieuwenhuizen, I.; Song, C.;Buijsen, R. A. M.; Pop, A. S.;GomezMancilla, B.; Nelson, D. L.; Willemsen, R.; Gasparini, F.; Oostra, B. A. AFQ056, a new mGluR5 antagonist for treatment of fragile X syndrome. *Neurobiol. Dis.* **2011**, *42*, 311-317.
[37] Cativiela, C.; Sayago, F. J.; Laborda, P.; Calaza, M. I.; Jiménez, A. I. *Eur. J. Org. Chem.* **2011**, 2011-2028.

alpha alkylation of aldehydes via photocatalysis.[38] In fact, many octahydroindole derivatives have been used as chiral ligands or catalysts.[39]

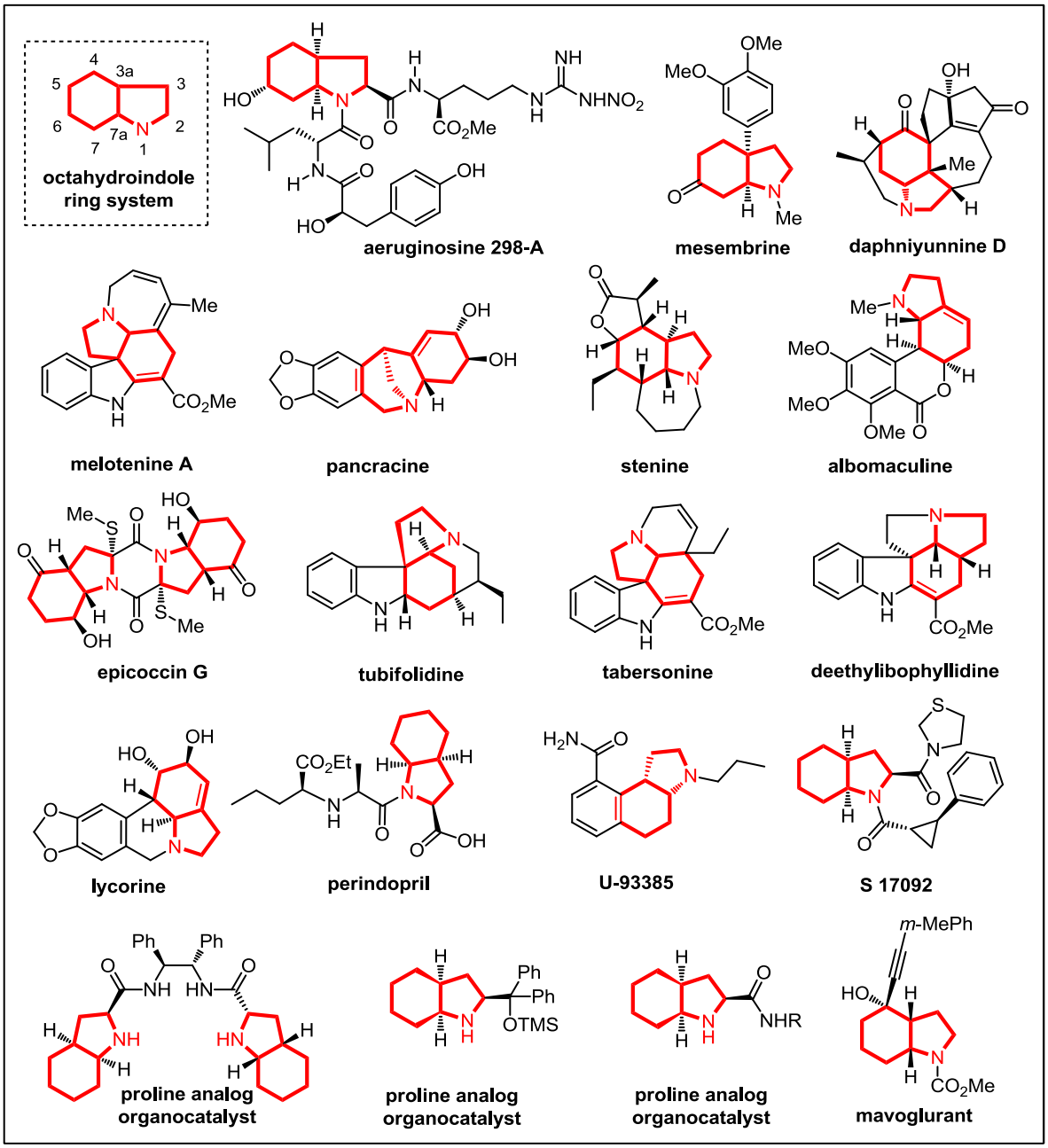


Figure 2.2 Diverse nitrogen-containing heterocycles containing the octahydroindole motif.

[38] Arceo, E.; Jurberg, I. D.; Alvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750–756.
[39] (a) Luo, R. S.; Weng, J.; Ai, H. B.; Lu, G.; Chan, A. S. C.; *Adv. Synth. Catal.* **2009**, *351*, 2449–2459. (b) Wu, Y. Y.; Chai, Z.; Liu, X. Y.; Zhao, G.; Wang, S. W.; *Eur. J. Org. Chem.* **2009**, 904–911. (c) Liégault, B.; Tang, X.; Bruneau, C.; Renaud, J. L.; *Eur. J. Org. Chem.* **2008**, 934–940. (d) Kim, H.; *Acc. Chem. Res.* **2001**, *34*, 955-962. (e) Kim, Y.H.; Kim, S. H.; Park, D. H.; *Tetrahedron Lett* **1993**, *34*, 6063-6066

2.3. Methods for the preparation of enantiopure octahydroindoles

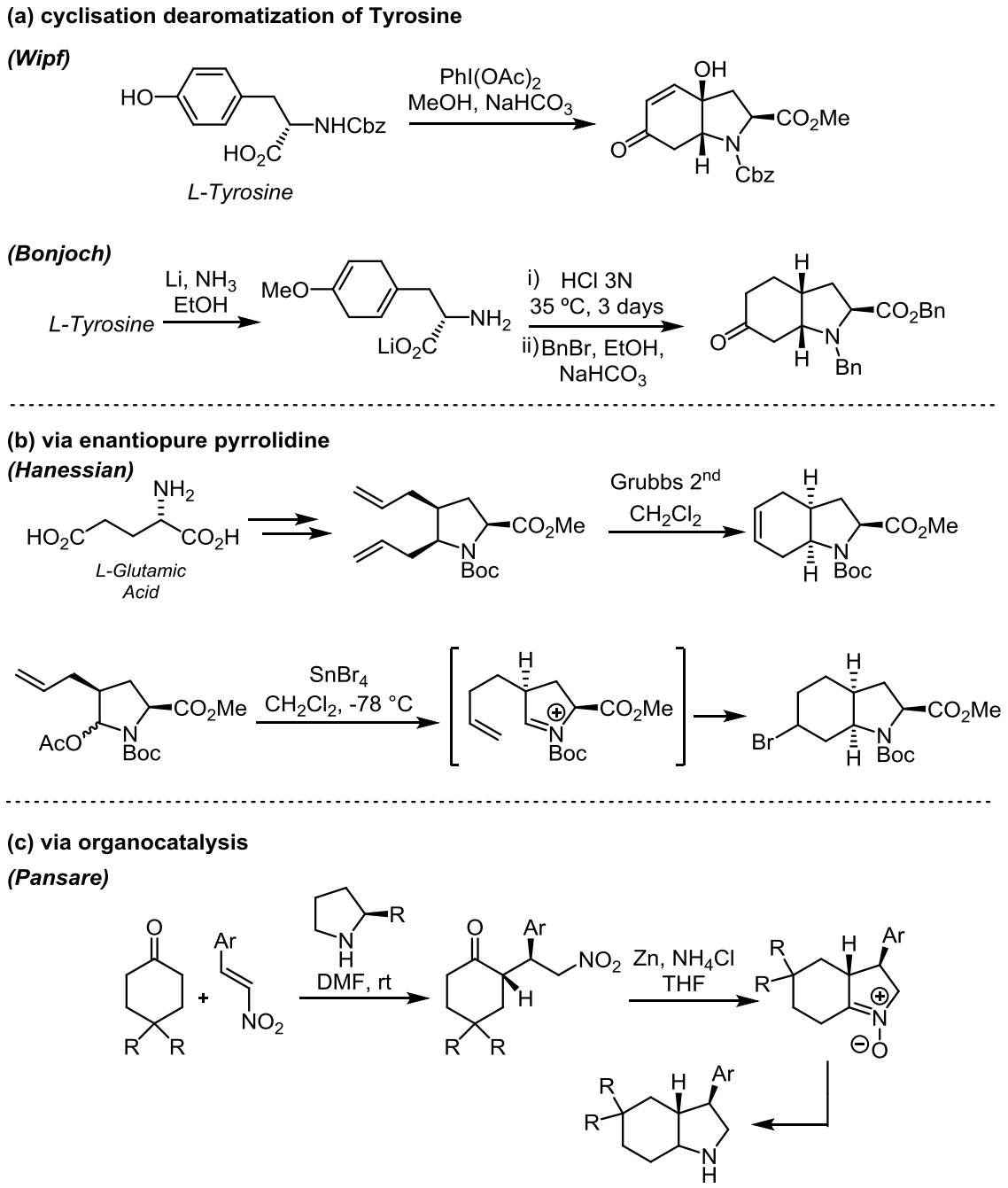
Whilst a number of methods have been developed to synthesize the octahydroindole motif in enantiopure form these strategies use chiral pool approaches[40] and to the best of our knowledge there is only one reported organocatalyzed approach to this nucleus.[41]

In 1995, Wipf et al. developed a concise entry toward the perhydroindole ring system from L-tyrosine via a dearomatising cyclization (Scheme 2.1a). This compound was then employed in the first asymmetric synthesis of (-)-stenine.[40a] Alternatively, Bonjoch et al. described the first synthesis of 6-hydroxyoctahydroindole-2-carboxylic acid derivatives also using *L*-tyrosine as the starting material (Scheme 2.1a). Conversion to the corresponding *O*-methyl derivative, Birch reduction immediately followed by acid treatment of the resulting dihydroanisole led to the diastereomeric α-amino acids, each as a mixture of the keto and hydrate forms. These compounds were converted into the benzylderivatives, which could then be separated.[40b] Notably, these compounds could prepared on a large scale and allowed the first total synthesis of aeruginosine 298-A.[20]

Other synthetic routes to the octahydroindole core were developed by Hanessian starting from *L*-Glutamic Acid (Scheme 2.1b). Conversion to a pyrrolidine ring and a ring-closing metathesis reaction was used as the key step to form the 6–membered ring.[40c] Alternatively, by performing a selective deoxygenation at C-5, a new approach was developed that exploited a seldom used N-acyloxyiminium ion aza-Prins cyclization, which leads directly to 6-halo-octahydroindole 2-carboxylic acids.[40d] Pansare developed a simple stereoselective approach to *cis* or *trans*-3-aryloctahydroindoles from readily available γ-nitroketone precursors (Scheme 2.1c).[41] This strategy was based on the enantioselective organocatalytic synthesis of γ-nitroketones from cyclic ketones and 2-nitrovinyl arenes via an enamine-based, organocatalytic Michael addition reaction. Subsequent reduction of the nitro group formed the 5-membered ring to give the octahydroindole ring system.

[40] (a) Wipf, P; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106-11112. (b) Bonjoch, J.; Catena, J.; Isábal, E.; López-Canet, M.; Valls, N. *Tetrahedron: Asymmetry* **1996**, *7*, 1899-1902. (c) Hanessian, S; Margarita, R.; Hall, A.; Johnstone, M.; Trembay, M; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342-13343. (d) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004,** *126*, 6064-6071.

[41] (a) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett.* **2010**, *12*, 556-559. (b) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624-9625.



Scheme 2.1 Literature syntheses of the enantiopure octahydroindole motif.

2.4 Synthetic studies to octahydroindoles: Evaluation of a One-pot Robinson annulation/intramolecular aza-Michael tandem reaction

2.4.1 Synthesis of starting materials

In order to arrive to the required β-keto ester product three routes were evaluated:

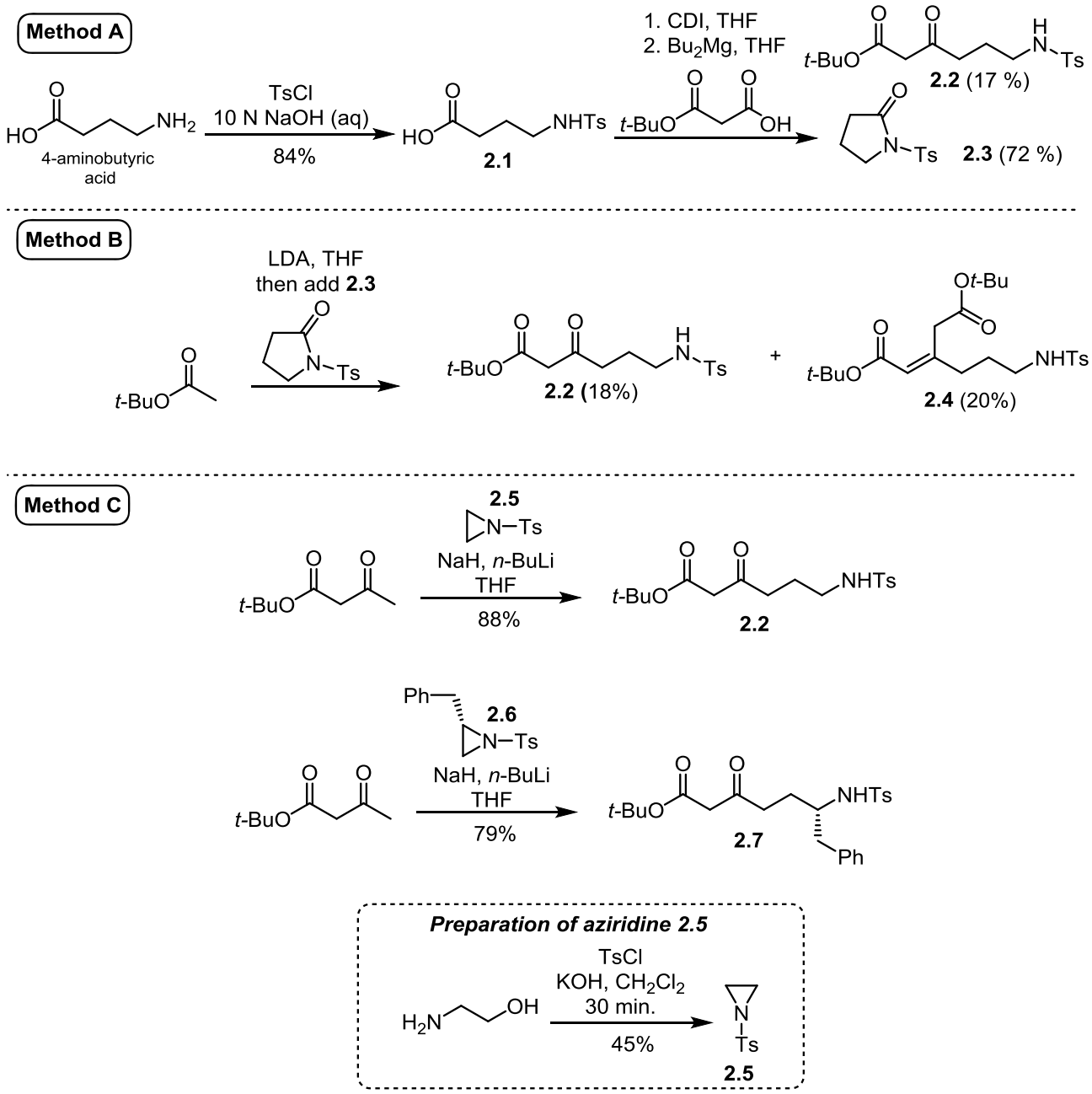
Method A - Masamune Homologation: We began by evaluating the same reaction sequence used for the decahydroquinoline series (Scheme 2.2, Method A). Thus, tosylated aminobutyric acid **2.1** was subjected to a homologation with mono-*tert*-butylmalonate under Masamune-type conditions[42] to give **2.2**. Unfortunately, the undesired cyclization self-condensation pyrrolidone **2.3** was the major product.[43] This side reaction was observed to a small degree in the decahydroquinoline series however the increased propensity to form 5-membered rings now made this the dominant reaction pathway.

Method B - Ring opening of N-tosyl-pyrrolidine: Attempts to use the five-membered pyrrolidone ring[44] product **2.3** and open it with *t*-butyl acetoester[45] were only partially successful give an equimolar mixture of the desired product **2.2** along with the double addition product **2.4** in a 1:1 ratio (Scheme 2.2, Method B).[46] Extensive optimization of this approach was undertaken[47] to attempt to reduce the quantities of the by-product however all trials were complicated by the poor solubility of **2.3** at low temperatures.

Method C - Ring opening of tosyl-aziridine: Finally, ring opening of the tosyl aziridine **2.5**[48] with the dianion of *t*-butyl acetoacetate provided the most effective solution[49] giving **2.2** in 88% yield (Scheme 2.2, Method C). This method could also

[42] Brooks, D. W.; Lu, L. D. L.; Masamune, S.; *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 72-73.
[43] Attempts to limit formation by shortening reaction time had no effect. Control experiments indicated that the cyclisation was not spontaneous only occurring upon addition of the Mg β-keto ester derivative.
[44] Material was prepared by tosylation of commercial 2-pyrrolidinone (Sigma-Aldrich) or by cyclisation of **2.1** with AcCl in 98% yield
[45] For similar method see: Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.*, **2010**, *132*, 9594.-9595.
[46] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
[47] This included varying reaction temperature as well as performing a reverse-addition.
[48] Tosyl aziridine **2.5** could be made easily from ethanolamine via treatment with *p*-toluenesulfonyl chloride or is commercially available from Aldrich though it it is relatively expensive.
[49] For an analogous approach employing the ethyl ester see: Lygo, B. Synlett **1993**, 764-766.

be used to prepare the α-substituted β-keto ester **2.7** from the corresponding commercially available tosyl aziridine **2.6**.



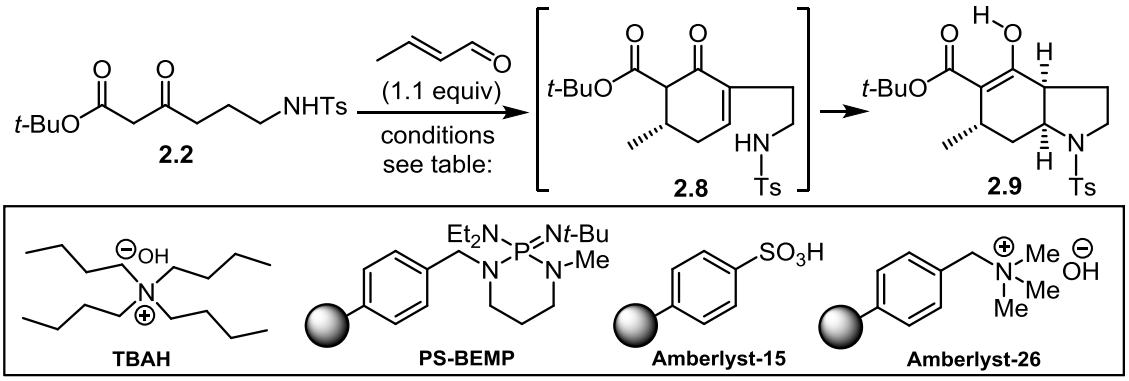
Scheme 2.2 Preparation of β-keto ester starting materials

2.5 Evaluation of the synthesis of octahydroindoles using the Robinson aza-Michael Reaction - racemic version

With the key starting material **2.2** now in hand the non-asymmetric version of the tandem cyclisation reaction was investigated. Gratifyingly, using the optimal conditions (crotonaldehyde $LiOH{\cdot}H_2O$, *i*PrOH, H_2O) developed for the decahydroquinoline series gave the desired analogous octahydroindole product **2.9** which maintained the all *cis* stereochemistry (entry 1). The moderate yield led us to evaluate other conditions such as KO*t*-Bu in *t*-BuOH[50] (entry 2) which gave just 15% of **2.9** with the rest (40%) recovered as the uncyclized cyclohexenone **2.8**. The use nBu_4NOH/KOH[51] gave similar results but was found that if the reaction was lengthened to 72 h the desired product could be obtained in moderately good yield (entry 4). We also evaluated the use of PS-BEMP with amberlyst-15 under the concept of site-isolated reactivity believing that this might enable control of different parts in the catalytic cycle which could be under acid or basic catalysis (see section 1.5.2). However, using the conditions reported by Dixon[52] gave only traces of the Michael product only (entry 5). Increasing the quantity of PS-BEMP to 1 equivalent gave a good yield but was also isolated significant quantities of the transesterification products presumably catalysed by the acid resin (entry 6). Switching the solvent to *t*-BuOH gave slightly less efficient conversion but with no transesterification side-products (entry 7). Lowering the PS-BEMP to catalytic levels and increasing the reaction time however was not feasible giving mainly **2.8** (entry 8). However, using PS-BEMP alone in *i*PrOH gratifyingly gave **2.9** in moderate yield whilst extending the reaction to 72 h gave the best yield so far of 68% (entry 10). The addition of water proved detrimental and also led to destruction of the resin (entry 11). Trying the reaction under catalytic conditions gave a slightly reduced yield (entry 12) however the use of water in this case was more positive thought it did lead to disintegration of the resin as before (entry 13). We also evaluated the more economical Amberlyst-26 resin under a range of conditions (see entries 14-18) however this did not perform as well as PS-BEMP. Of note however are the conditions of entry 17 which while moderate in yield gave pure product in short reaction time. Given the relative

[50] Chong, B.; Ji, Y.; Oh, S.; Yang, J.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323-9325.
[51] Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc. Perkin Trans. 1* **2002**, 895-900.
[52] Pilling, A. W.; Boehmer, J.; Dixon, D. J. *Angew, Chem. Int. Ed.* **2007,** *46*, 5428-5430.

Table 2.1 Screening of conditions for the one-pot Robinson aza-Michael reaction to octahydroindole **2.9**



Entry[a]	Reagents (equiv)	Solvent	t (h)	Product Yield [%])[b]
1	$LiOH·H_2O$ (1)[c]	*i*PrOH	24	44
2	t-BuOK (0.3)	*t*-BuOH	24	15[d]
3	TBAH[e] (0.3), KOH(aq)	Et_2O / THF	24	38
4	TBAH[e] (0.3), KOH(aq)	Et_2O / THF	72	57
5	PS-BEMP (0.1), Amberlyst-15 (2)	CH_2Cl_2	72	--[f]
6	PS-BEMP (1), Amberlyst-15 (2)	*i*PrOH	24	56[g]
7	PS-BEMP (1), Amberlyst-15 (2)	*t*-BuOH	24	45
8	PS-BEMP (0.3), Amberlyst-15 (2)	*t*-BuOH	72	--
9	PS-BEMP (1)	*i*PrOH	24	42
10	PS-BEMP (1)	*i*PrOH	72	68
11	PS-BEMP (1)[c]	*i*PrOH	72	25
12	PS-BEMP (0.3)	*i*PrOH	72	53
13	PS-BEMP (0.3)[c]	*i*PrOH	72	57
14	Amberlyst-26 (1)	*i*PrOH	24	43
15	Amberlyst-26 (1)	*i*PrOH	72	34
16	Amberlyst-26 (1), Amberlyst-15 (2)	*i*PrOH	72	25
17	Amberlyst-26 (1)[c]	*i*PrOH	24	38
18	Amberlyst-26 (0.3)[c]	*i*PrOH	24	19[d]

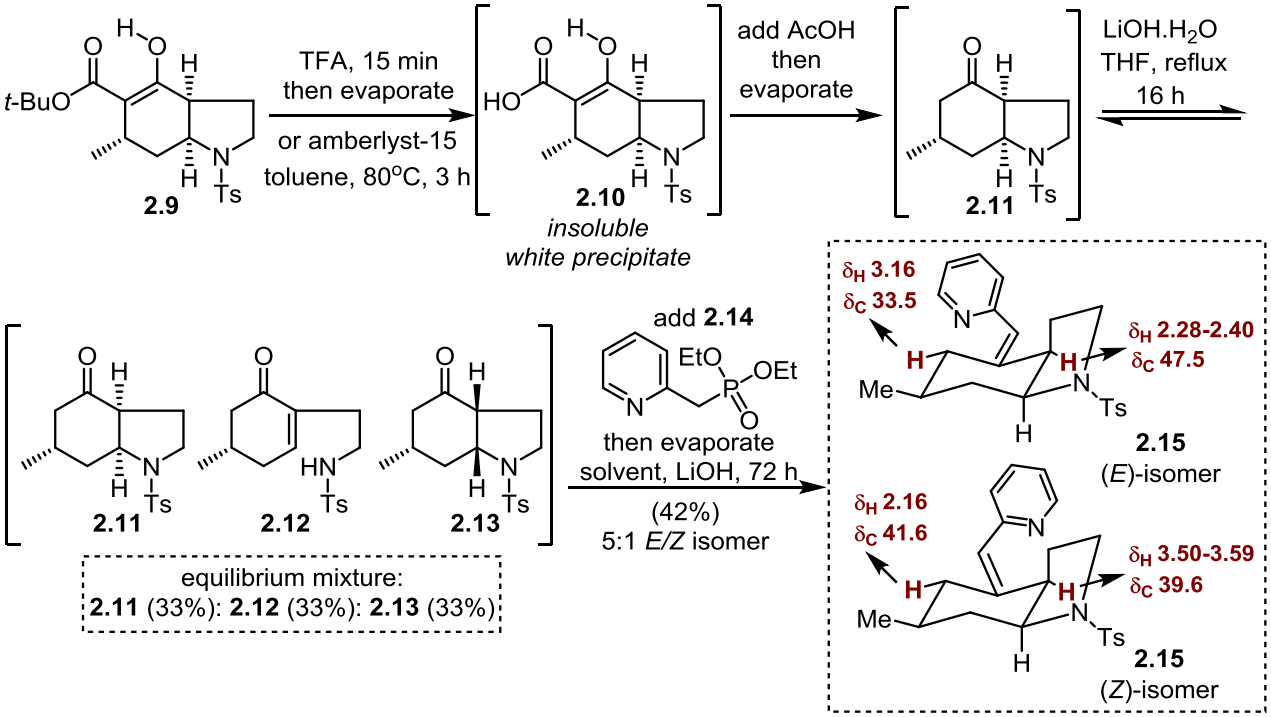
[a] All reactions were carried out at room temperature with 1.1 equiv. of crotonaldehyde **[b]** yield refers to the products isolated by flash chromatography; **[c]** 10 equiv. of H_2O added **[d]** significant amounts of **2.8** were obtained as well (~40%). **[e]** TBAH refers to 40% nBu$_4$NOH in H_2O. **[f]** trace Michael addition product. **[g]** mixture of enone **2.8** along with solvent transesterification products.

cheapness of the A-26 resin optimization of these conditions might prove interesting for scale up.

2.6 Reactivity of octahydroindole nucleus – inversion of ring fusion stereochemistry

To evaluate if in the octahydroindole series it would be possible to invert the ring fusion hydrogens with respect to the substituent at C-6 in an analogous manner to the decahydroquinoline series the *t*-butyl ester group of compound **2.9** was removed with TFA which gave the acid **2.10**. However this compound was highly insoluble so that when toluene was added to effect the thermal decarboxylation/azeotropic sequence developed in the decahydroquinoline series little to no reaction occurred. Therefore the azeotrope had to be done with AcOH to give the octahydroindole **2.11**. Given the success of the use of resins in the cyclisation reaction we considered the use of amberlyst-15 as a more safer and green way to remove the butyl group.[53] Addition of the resin to **2.9** in toluene and heating caused removal of the *t*-butyl group to the acid **2.10** which was then processed as before. Subsequent treatment of **2.11** with LiOH in refluxing THF gave the expected retro aza-Michael ring opened product as well as the inverted product **2.13**. However unlike the decahydroquinoline series this equilibrium was a 1:1:1 equimolar mixture (decahydroquinoline series: 1:4:4). This can be attributed to the thermodynamic stability of **2.11** and **2.13** being equivalent (see subsequent section 2.7 for analysis). However when exposed to pyridine phosphonate **2.14** in the presence of LiOH under solvent free conditions the desired coupled product **2.15** was observed as a 5:1 *E*:*Z* mixture. Given the good reactivity of PS-BEMP in the cyclisation reaction we also evaluated it as a base in this reaction however no coupling was observed under solvent or solvent free conditions.

[53] Ploypradith, P.; Cheryklin, P.; Niyomtham, N.; Bertoni, D. R.; Ruchirawat, S. *Org. Lett.*, **2007**, *9*, 2637–2640.



Scheme 2.3 Ring opening of **2.11** via retro aza-Michael and selective closure to **2.15** with inverted fusion stereochemistry and assignment of configuration.

2.6.1 Stereochemical assignment of exocyclic alkenes 2.15

Scheme 2.3 shows the products corresponding to the selective closure with inverted fusion stereochemistry. The comparison of the ^{13}C NMR data of **2.15-*E*** and **2.15-*Z*** allowed the assignment of the alkene configuration. In the minor isomer **2.15-*Z*** a crowding interaction is found between the pyridyl group and H-3a, which results in an upfield shift (8 ppm) of C-3a (δ 39.6) with respect to the isomer **2.15-*E*** (δ47.5). A similar interaction between the pyridyl group and H-5eq appears in the *E*-isomer **2.15-*E***, causing an upfield (8 ppm) of C-5 (δ 33.5) as compared with **2.15-*Z*** (δ 41.6). Furthermore, both isomers could be differentiated by ^{1}H NMR by considering the deshielding effect exerted by the pyridyl group upon the H-3a in the *Z* isomer (δ 3.50-3.59); compare with δ 2.28-2.40 in **2.15-*E*** and upon the H-5eq methine proton in the *E*-isomer (δ 3.16); compare with δ 2.16 in **2.15-*Z***.

2.7 NMR structural and conformational elucidation of octahydroindole compounds synthesized

2.7.1 Determination of stereostructure in β-keto ester compounds

The relative stereochemistry of the synthesized azabicyclic compound rac-**2.9**, which is the same for all compounds synthesized in this series, was elucidated by 2D NMR spectra (COSY, HSQC). It is well known that for *cis*-hydroindoles, when the nitrogen atom is embedded in a carbamate, carboxamide or sulfonamide group, it shows a preferred conformation in which the C7-C7a bond of the carbocyclic ring adopts an axial disposition with respect to the nitrogen-containing ring to avoid the allylic strain. Thus, the chair conformation in the carbocyclic ring with the nitrogen equatorially substituting the carbocyclic ring should be the lowest energy conformation for this compound if a *cis*-hydroindole was formed (see Figure 2.3).

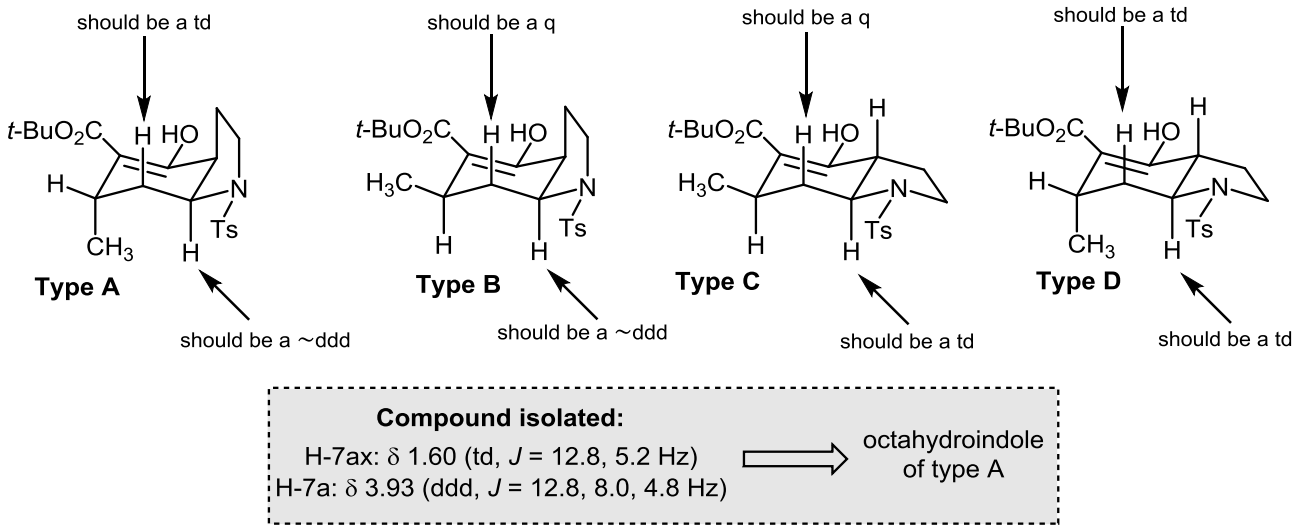


Figure 2.3 NMR determination of stereochemistry of hydroindole **2.9**.

Between the two possible *cis*-hydroindoles (A or B), the key evidence for discarding B was found in the ^{1}H NMR coupling pattern for the H-7ax, which appears as triplet of doublets (J = 12.8, 5.2 Hz). This coupling pattern only is compatible with a location of the methyl group at C-7 in an axial disposition. However, this argument doesn't allow discernment between compound type A and a configuration of type D, in which there is a *trans* ring fusion. In this case, the diagnostic signal is the coupling constant pattern of H-7a. The axial proton H-7a is strongly coupled only with one adjacent

axial proton. Hence, its resonance signal appears as a deceptively doublet (J = 12.8 Hz) of other doublets (J = 8.0, 4.8 Hz) (see Figure 2.3).

2.7.2. Determination of stereochemistries in 4-oxooctahydroindoles

Figure 2.4 depicts the structures (relative configuration and preferred conformation) of the synthesized diastereomeric *cis*-octahydroindoles **2.11** (type A) and **2.13** (type B), with their stereochemistry elucidated on the basis of 2D NMR spectra (COSY, HSQC).

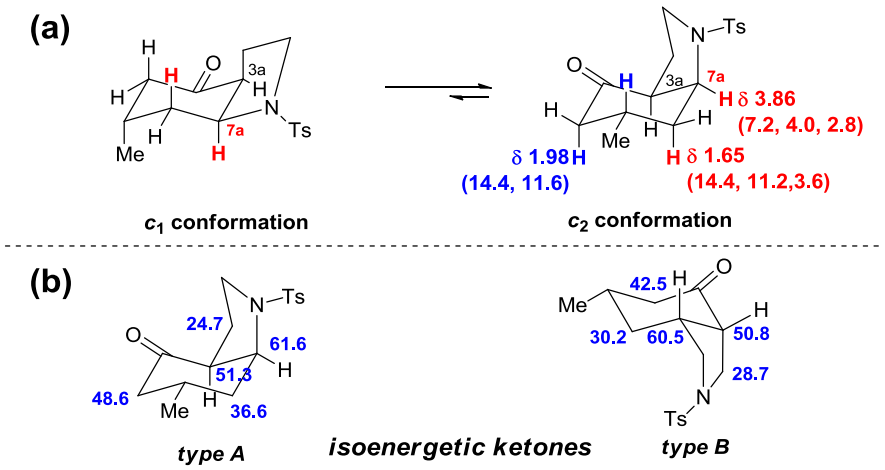


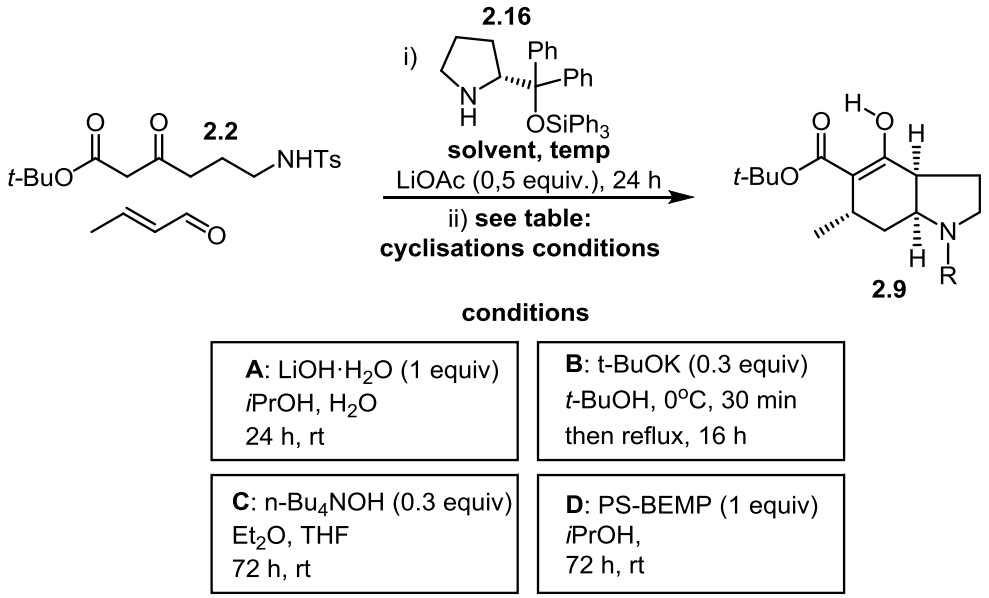
Figure 2.4 Conformational preferences of octahydroindoles **2.11** and **2.13** determined on the basis of NMR spectroscopic data.

For compound **2.11** the nitrogen substituent occupying an axial position on the carbocyclic ring is the lowest energy conformation for this N-Ts substituted *cis*-octahydroindole (Figure 2.3, entry a). On the other hand, in this conformation the axial proton H-7 and axial proton H-5 are strongly coupled to axial H-6. The multiplicity ensures the *cis* ring fusion in both isomers and also corresponds to a *cis* 1,3-relationship between H-7a and the equatorial methyl group at C-6 in **type A**, deshielding the chemical shift of H-7a (Figure 2.4a). When treated with equilibration conditions, we obtained an equimolar mixture of **type A**, **type B** compounds and uncyclized cyclohexenone. The OHI are clearly differentiated by ^{13}C NMR where the chemical shift of C-5 and C-7, which are shifted more upfield (δ 42.5 and 30.6) in **type B** than in **type A** (δ 48.6 and 36.6), due the strong effect of the C3-C3a bond upon the axial C-H bonds at C-5 and C-7 in the octahydroindole with a type B configuration (Figure 2.4b).

2.8 Synthesis of octahydroindoles – enantioselective version

In order to render the initial Michael addition step in the tandem Robinson/aza-Michael reaction enantioselective we used an organocatalyst in the initial Michael step followed by application of a various basic conditions developed in the previous section. Initially we applied the conditions for the decahydroquinoline series (Hayashi-Palomo catalyst **2.16**, LiOAc additive, solvent) to see if the octahydroindole series followed the same reactivity pattern. A brief solvent screen for the organocatalytic step proved this to be the case (entries 1-4) therefore we selected toluene as again the solvent of choice based on ee and yield. Carrying out the reaction at reduced temperature for the organocatalytic step resulted in a slightly increased ee (entry 5). With the organocatalytic step sufficiently optimized the use of different cyclisation conditions for the tandem reaction were then evaluated. However, in addition to differences in yield, which was expected given the previous screening carried out in table 2.1, we observed slight discrepancies in the enantioselectivity. The use of *t*-BuOK resulted in a lowering of the ee (entry 6) quite significantly whilst the use of TBAH in biphasic conditions gave an improved ee of 94% (entry 7). The treatment with PS-BEMP obtained a similar outcome to TBAH with 90% ee (entry 8). These observations indicate that the initial Michael adduct must be to some degree reversible (since they are all prepared in the same manner with the more vigorous *t*-BuOK conditions giving more retro Michael product which then undergoes a competitive parallel conversion to **rac-2.9**. On the other hand the TBAH conditions (conditions C) are quite mild since the base is phase separated from the Michael adduct intermediate. Whilst the TBAH conditions gave a slight superiority in ee over the other conditions we chose PS-BEMP as the standard conditions to move forward with for a number of important criteria: (i) the TBAH can only be removed by chromatography (ii) the reaction setup was more complicated requiring more components and multiple solvents – the PS-BEMP could be added and removed by filtration simplifying both the set-up an purification conditions. (iii) The TBAH conditions were subsequently found to be not so effective in terms of reactivity when we used other enals resulting in low yields of the corresponding cyclisation products. On the other hand PS-BEMP performed more consistently giving good reactivity with a wide range of substrates (see section 2.10).

Table 2.2 Screening of conditions for organocatalyzed asymmetric synthesis of octahydroindole **2.9**.



Entry	Organocatalytic Step Solvent	T (°C)	Cyclisation Conditions	Yield (%)	ee (%)
1	toluene	rt	A	51	82
2	Free	rt	A	--[a]	14
3	MeOH	rt	A	40	77
4	CH_2Cl_2	rt	A	27	85
5	toluene	0	A	55	87
6	toluene	0	B	61	73
7	toluene	0	C	51	94
8	toluene	0	D	50	90

[a] only very low yield observed which was not quantified

2.9 Organocatalysed Synthesis of octahydroindoles using non-volatile enals – strategies to avoid racemic pathway

One of the key problems we encountered in preliminary work on the use of alternative enals to crotonaldehyde was their lack of volatility. At the end of the organocatalysed step any excess remaining crotonaldehyde could be removed by evaporation due to its low boiling point. Thus, on addition of a base to effect the tandem cyclisation step there was no possibility of carrying out a background Michael reaction between unreacted β-keto ester and residual enal thus lowering the ee. In the cases where the R_1 group was significantly larger than methyl the larger molecular weight of the enal meant it could not be easily removed by evaporation. This was more problematic since when the group was larger than methyl the coupling reaction did not go 100% to completion meaning there was increasing amount of both components present at the end of the organocatalytic step. We therefore looked at 2 alternative ways to remove the excess enal from the reaction mixture (a) hydrogenation of the crude mixture (b) capture of the enal using a solid supported thiol based scavenger. The conditions were initially evaluated for the reaction of **2.2** with cinnamaldehyde (scheme 2.4).

2.9.1 Method A: Hydrogenation

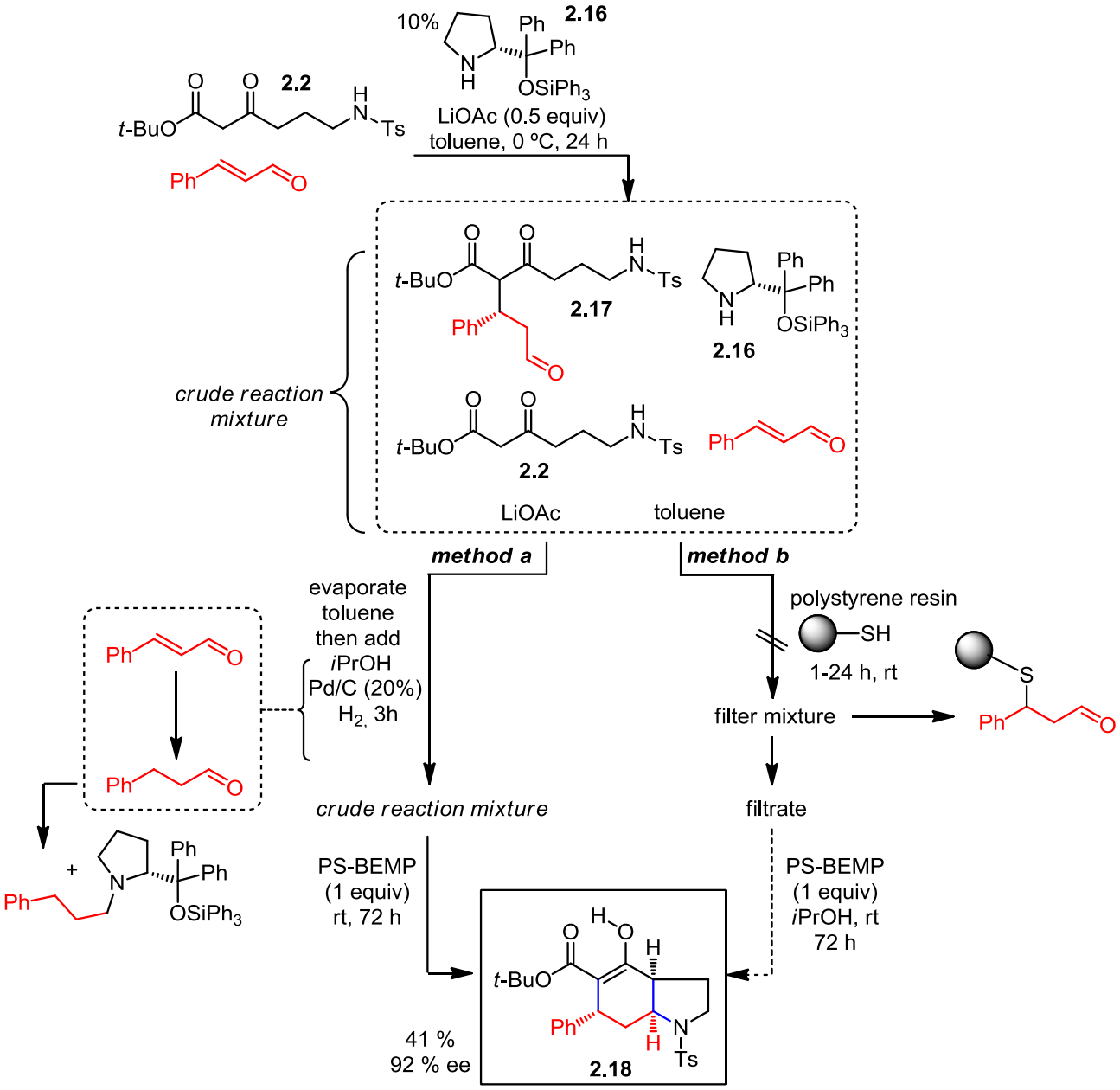
After the initial organocatalysed Michael step the crude mixture was treated directly with 20% Pd/C and a hydrogenation balloon and the mixture was hydrogenated for 3 h. At the end of this time when TLC analysis showed that no cinnamaldehyde remained, PS-BEMP was added and the mixture stirred for 72 h to give the desired product **2.18** in 41% yield and excellent 92% ee.

2.9.2 Method B: Thiol based scavenger method

Alternatively, after the initial organocatalysed Michael step the crude mixture was treated with a commercially available thiol based scavenger.[54] This method would have the advantage of being able to recover the organocatalyst which presumably under the hydrogenation conditions of method A would undergo a reductive amination with the reduced enal. After completion of the initial Michael reaction the resin was added and the reaction was monitored by TLC. However,

[54] Thiol resin was purchased from Aldrich.

despite prolonged stirring the resin did not scavenge the cinnamaldehyde in an efficient manner and this method was not pursued further.



Scheme 2.4 Strategies to remove remaining non-volatile enals from crude organocatalytic reaction mixture prior to base catalysed tandem reaction step.

2.10 Evaluation of the scope of the reaction

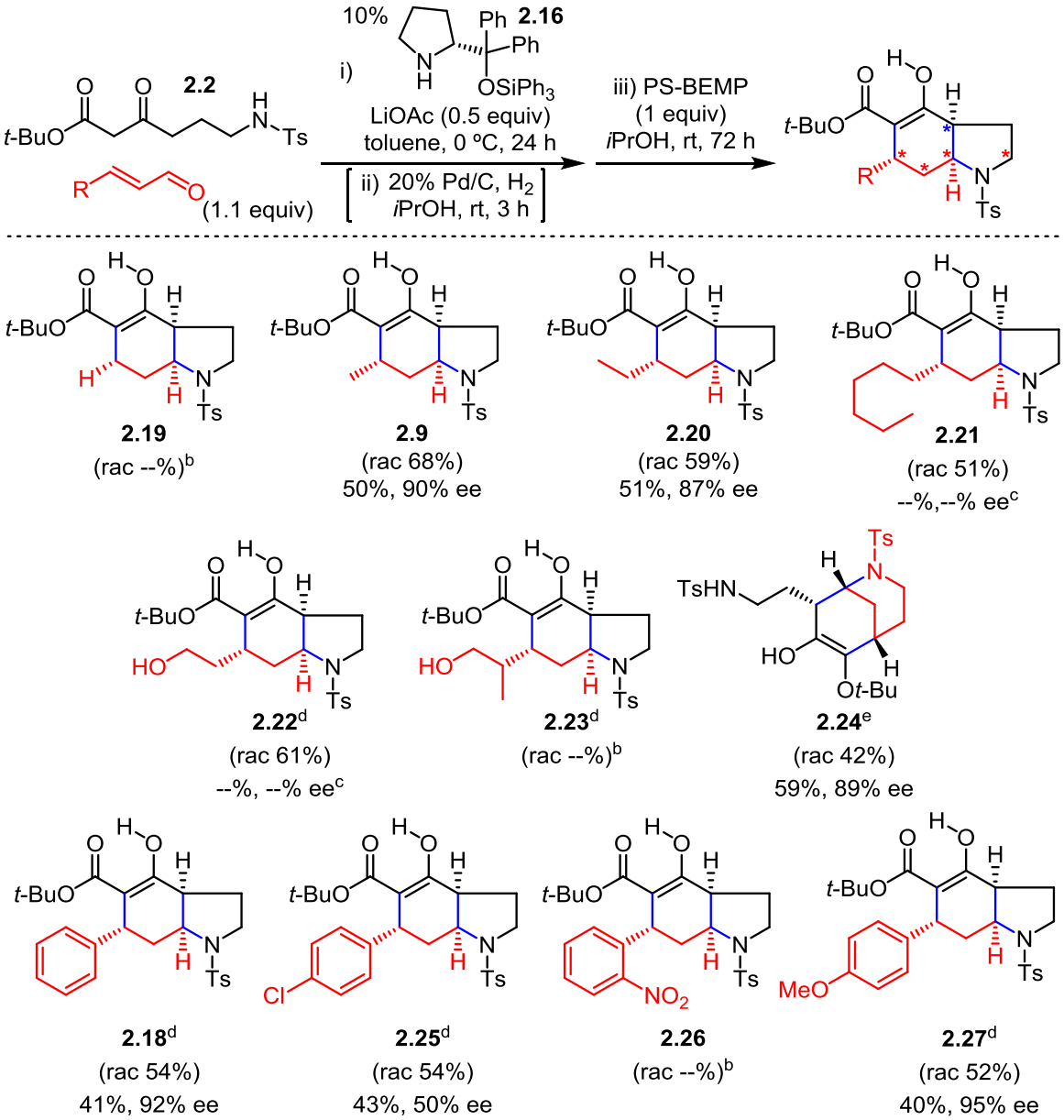
2.10.1 Synthesis of 6-substituted octahydroindoles.

With proof of concept of the feasibility of the tandem reaction we set about exploring the potential of other Michael acceptors which would potential allow entry to numerous natural product system core structures (Table 2.3). Each compound was initially synthesized in racemic form to test the viability of the different enals and as well to obtain racemic reference material for HPLC analysis. The use of acrolein was evaluated but was found to give poor results and only traces of **2.19** were observed in the crude spectra. Reaction with other aliphatic enals such as crotonaldehyde and *trans*-2-pentenal gave good results and good enantioselectivities to the corresponding octahydrondoles **2.9** and **2.20** respectively. However, the use of *trans*-2-nonenal whilst giving good formation of the octahydroindole **2.21** under racemic conditions did not undergo the corresponding organocatalysed reaction with the enal only coupling in very minor amounts in the initial Michael step. The use of *trans*-5-hydroxy-2-pentenal (that could be potentially used to form the morphan ring of daphniyunnine D by cyclisation of the alcohol onto the nitrogen) readily underwent the reaction to give **2.22** under racemic conditions but only partially under organocatalysis where it existed as its hemiacetal form that did not readily progress upon addition of base. The corresponding methyl substituted enal compound that would give **2.23** did not undergo the reaction in racemic or asymmetric form.[55] Interestingly the use of the N-Ts tethered enal **3.4** developed for the morphan series (see chapter 3 for more details) led exclusively to the formation of the morphan product **2.24** despite the expectation that the formation of the 5-membered ring to the octahydroindole would be expected to be more favourable.[56] The use of enals with aromatic substituents generally performed well in both racemic and organocatalysed versions. Formation of octahydroindoles with cinnamaldehyde (**2.18**) or an electron donating substituent as *p*-OMe phenyl group (**2.27**) worked well and with excellent enantioselectivities. The use of a *p*-Chloro substituent (**2.25**) led to only moderate ee but this may be due to lack of complete removal of the excess enal

[55] A similiar enal was used in chapter 3 for the synthesis of substituted morphan synthesis and its synthesis and an explanation of its poor reactivity is outlined there.
[56] See chapter 3 for in depth study on the formation of morphan ring system.

before the tandem reaction and would need repeating to verify if this an experimental problem or related to the substrate itself. The ortho nitro analog of cinnamaldehyde to potentially give **2.26** did not react to any great extent even under racemic conditions.

Table 2.3 Screening of different Michael acceptors.[a]



[a] Each compound was prepared initially in racemic form using only the conditions of part iii of the scheme. **[b]** no appreciable quantity of product was obtained under racemic conditions. **[c]** organocatalytic conditions did not lead to any significant quantity of coupled product **[d]** excess unreacted non-volatile enal was converted by hydrogenation to corresponding aldehyde **[e]** LiOH was used as the base instead of PS-BEMP.

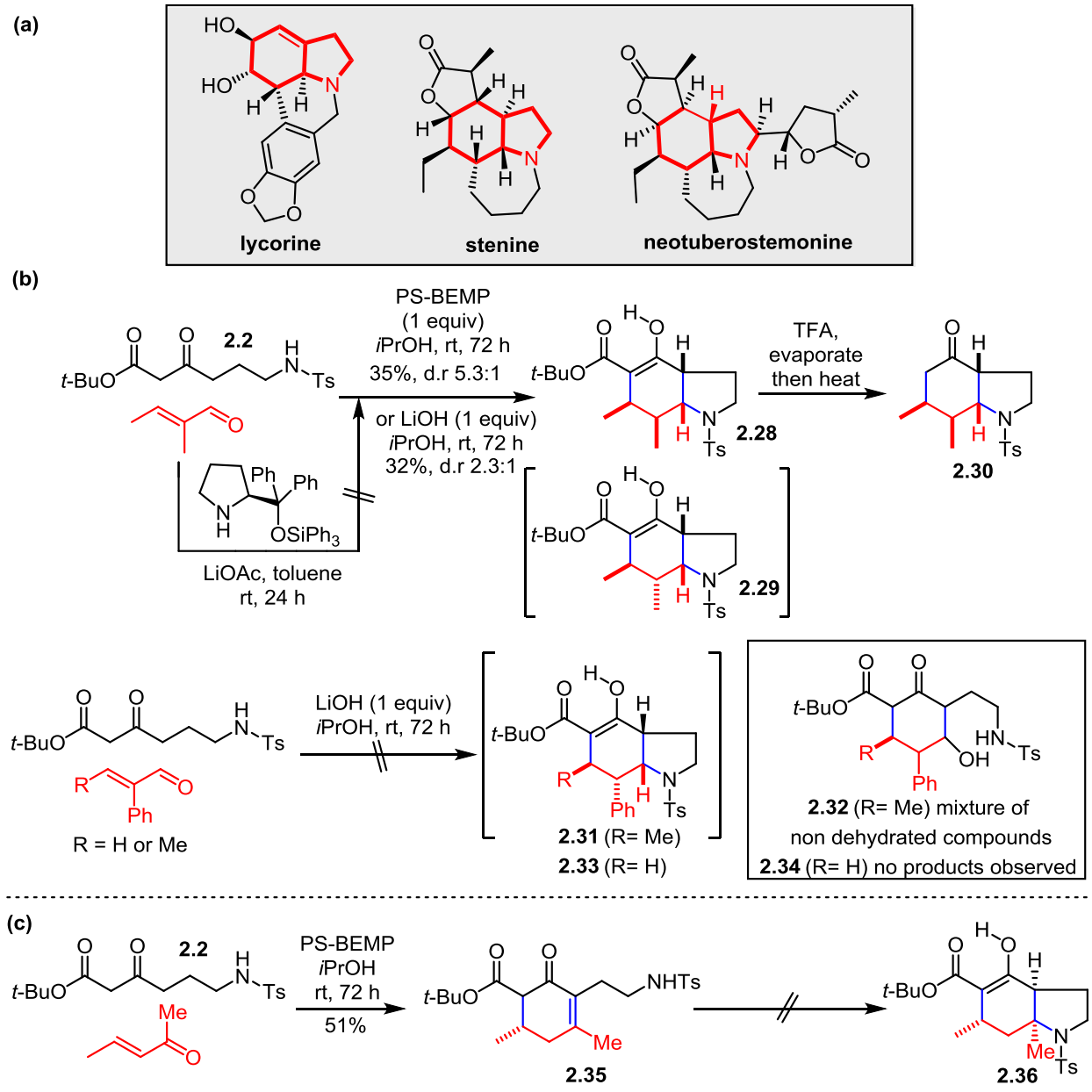
2.10.2 Synthesis of 6, 7-disubstituted octahydroindoles.

The use of enals with an additional α-substituent could in theory allow the synthesis of 7-substituted octahydroindoles with structures analogous to the natural products stenine,[25] lycorine[31] and neotuberostemonine[57] (scheme 2.5a). To test this approach the standard β-keto ester **2.2** was reacted with *trans*-2-Methyl-2-butenal in the presence of both PS-BEMP according to the standard developed conditions giving **2.28** and **2.29** in a moderate 35% yield as a 5.3:1 mix of epimers at C-7. NMR analysis (see next section for detailed interpretation) of the resulting product **2.28** indicated that the 6 and 7 substituents were unfortunately located *cis* to each other with only the minor compound **2.29** having the same relative stereochemistry as a natural product (e.g. neotuberostemonine). Interestingly, switching the base to LiOH led to a reduced ratio of epimers at C-7 (2.3:1) indicating that it may be possible to selectively access the *cis* or the *trans* 6,7 substituted compounds via modification of the reaction conditions. Of further note under the conditions of LiOH the product was isolated as a mixture of keto/enol forms which made it necessary to remove the butyl ester group with TFA to simplify the NMR spectra to determine the ratio of products. Attempts to render the reaction asymmetric were carried out by applying the previously developed organocatalytic conditions prior to the base cyclisation step.[58] Unfortunately, the enal only underwent very little coupling and this was not pursued further. Other enals with a α-phenyl substituent were evaluated to give structures analogous to lycorine, unfortunately however in both cases examined under racemic conditions very little formation of the bicyclic product was observed when R = Me and little Michael coupling was observed when R = H. Presumably the steric bulk and potential deactivation of the enal prevent the reaction from occurring. We also decided to look at the use of enones as the Michael acceptor to see if an alkyl substituent could be placed at the 7a position of the octahydroindole ring system. Reaction of β-keto ester **2.2** with 3-penten-2-one in the presence of PS-BEMP did

[57] Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, **17**, 117–127.

[58] It should be noted that the use of α-substituted enal in organocatalytic Michael reactions are scarce. For one of the few examples of an α-substituted enal being used in organocatalysed Michael reactions using imine catalysis see: Terrasson, V.; Van Der Lee, A.; De Figueiredo, R. M.; Campagne, J. M. *Chem. - A Eur. J.* **2010**, *16*, 7875–7880. For solution to organocatalysis using α,β substituted enals see: Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7892–7894.

not lead to the fully cyclised product **2.36** but instead to the Robinson adduct **2.35**. Further attempts to induce the aza-Michael reaction were attempted but in all cases the molecule stubbornly refused to cyclise.



Scheme 2.5 (a) Examples of 6,7 disubstituted octahydroindole natural products (b) Synthesis of 6,7-substituted octahydroindoles via use of α,β-substituted enals (c) Attempted synthesis of 7a-substituted octahydroindoles via use of an enone as the Michael acceptor.

2.10.3 Structural determination of 6,7-substituted octahydroindoles and proposed mechanism to account for the observed stereochemistry

The relative stereochemistry of the compound **2.28** was elucidated by ^{1}H and ^{13}C NMR spectra (figure 2.5). The key evidence for the assignment of **2.28** was found in the coupling pattern for the H-7ax, which appears as double quadruplet of doublets (J = 11.0, 6.8, 4.4 Hz). This coupling pattern only is compatible with a location of the methyl group at C-6 in an axial disposition and a *trans* relationship between H-7 and H-7a (both in an axial disposition). The chemical shift of H-6 (δ 2.56) agrees with a coplanar disposition with the β-keto ester unit

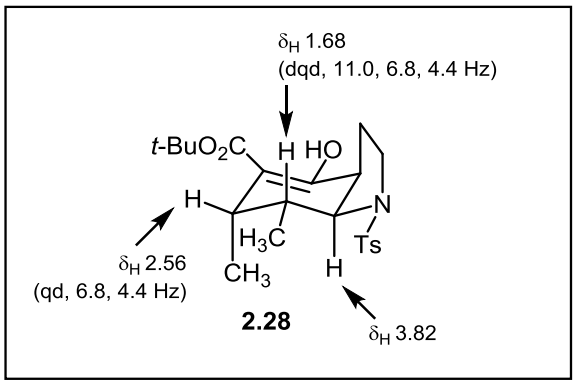


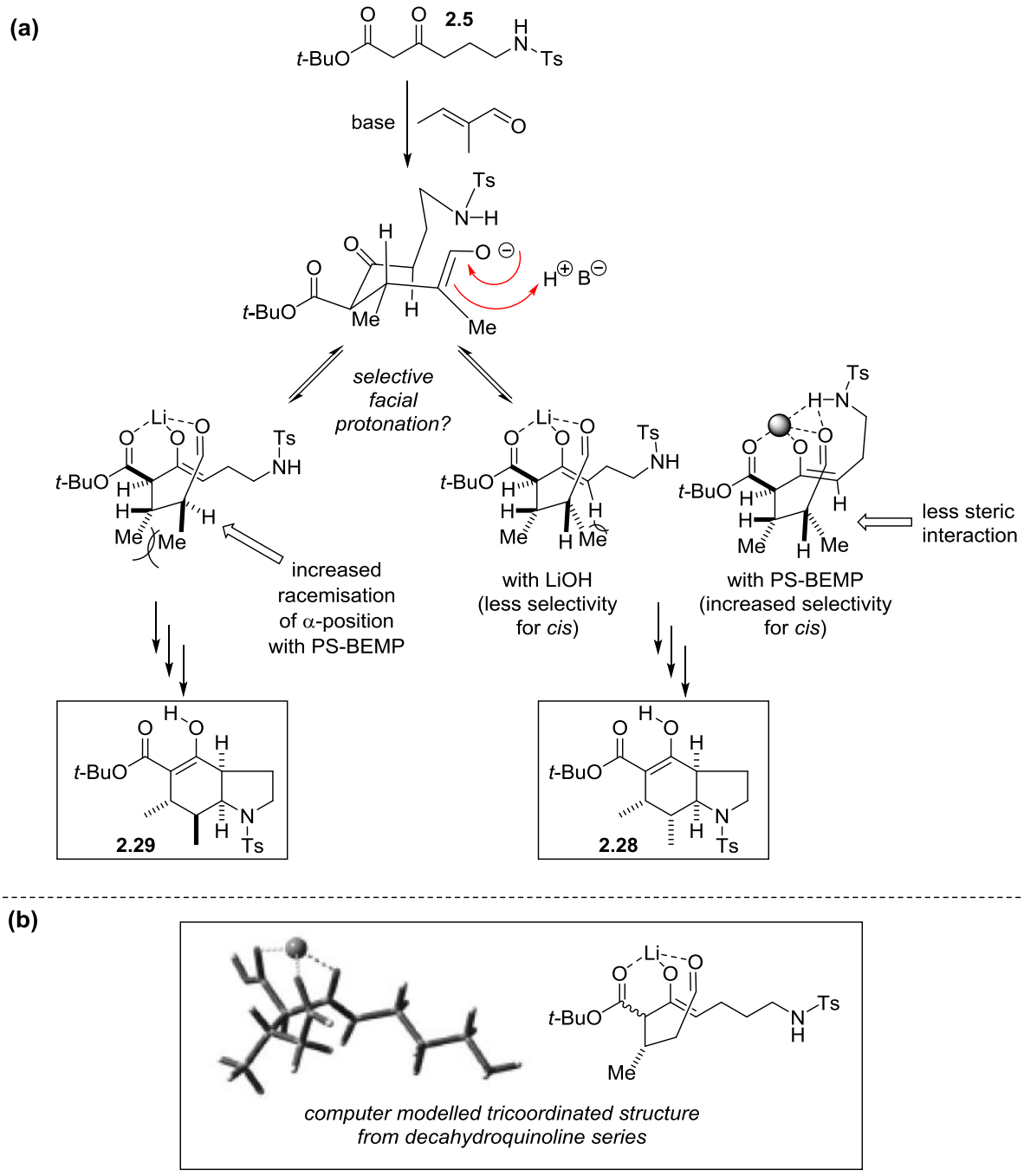
Figure 2.5 Spectral assignment of octahydroindole **2.28**.

To account for the selectivity in the reaction it is assumed that the formation of the first stereocentre (6-position) follows the same course as before. However the 7-position is likely not controlled (although this cannot be ruled altogether – there may be a selective facial protonation which leads to the observed product **2.28**).

Examining the intermediates en route to the compounds **2.28** and **2.29** (scheme 2.6a) and comparing them with the intermediate predicted by computer modelling studies in the decahydroquinoiline series[17] (scheme 2.6b) it seems likely that en route to the *trans* compound the two methyls are arranged in an unfavourable manner whereas in the *cis* compound this interaction is avoided.

The increased selectivity of PS-BEMP over LiOH may be due to various factors: the stronger base PS-BEMP may more readily epimerise the unfavourable intermediate letting it convert to the *cis* intermediate compound. There also may be significant coordination effects of the diferent bases – in particular PS-BEMP may coordinate

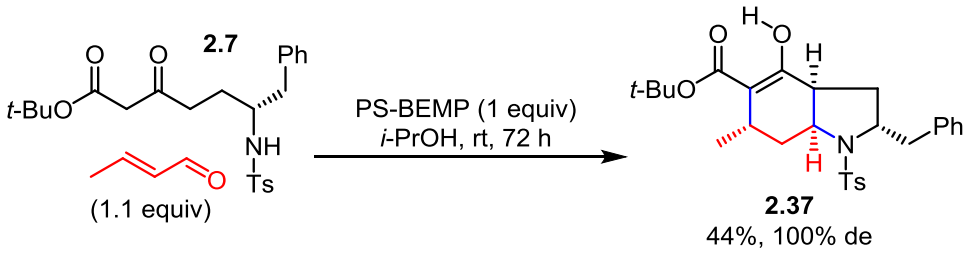
the side chain to the β-keto ester group (see subsequent section for a similar effect) which could relieve a slightly unfavourable steric interaction of the 7-methyl with the hydrogen of the enolate.



Scheme 2.6 (a) Proposed mechanistic proposals to account for the formation *cis* stereochemistry of the 6,7 substituents of octahydroindole **2.28** (b) Modelling studies in the decahydroquinoline series showing spatial orientation of an analogous intermediate under tricoordination.

2.10.4 Using β-keto esters bearing a chiral α-substituent - Synthesis of 2-substituted octahydroindoles

We began by taking α-substituted β-keto ester **2.7** (see section 2.41 for preparation) and reacting it under the racemic conditions (PS-BEMP, *i*-PrOH). Surprisingly the reaction was completely diastereoselective as evidenced from the crude reaction mixture where we observed only one set of signals by NMR allowing us to isolate compound **2.37** as a unique diastereoisomer (scheme 2.7).

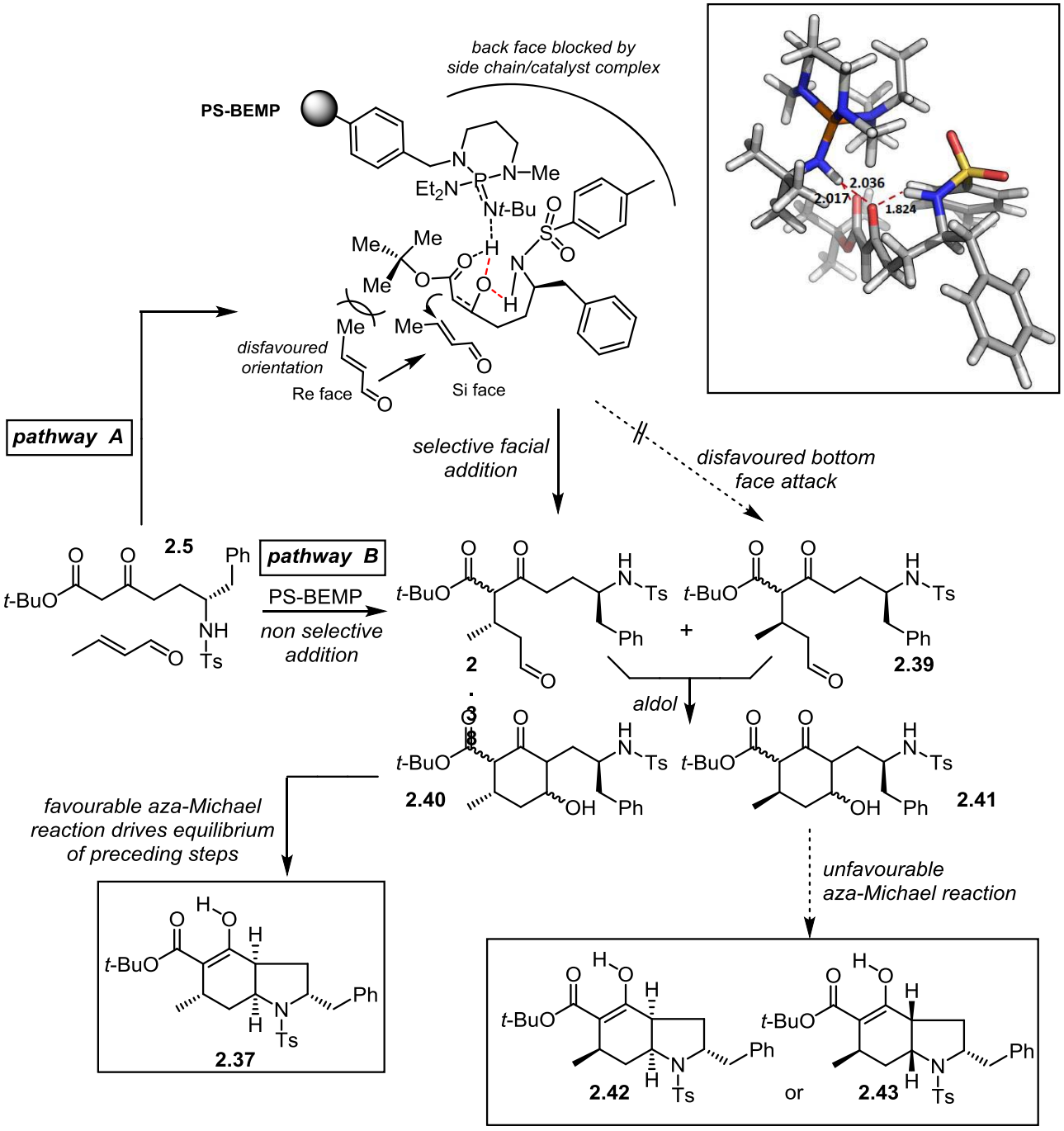


Scheme 2.7 Synthesis of 2-substituted octahydroindole **2.37**

The set of signals showed a great correlation with that observed in compound lacking the benzyl substituent at C-2 (with the clear exception that the signals for methine at C-2 and methylene at C-3 are different). Thus considering the same pattern of chemical shifts and coupling constants for H-3a, H-6, H-7, and H-7a, in **2.37** with respect to that described for **2.9**, the stereostructure depicted in scheme 2.7 was assigned to **2.37**.

Whilst we expected the substituent to have an effect on the aza-Michael reaction it was not immediately evident how the control of the C-6 chiral centre of the octahydroindole came about due to its remote nature from the benzyl group. We proposed two possibilities based our experience of the mechanism of the reaction (see section 1.5.2) which are illustrated in scheme 2.8. (i) *By remote induction*: the β-keto ester relays the stereochemistry of the C-2 position by forming a cyclic H-bonding type intermediate which blocks the back face of the molecule. When the crotonoaldehyde approaches it must do so from the Si face to avoid steric clash with the *t*-butyl group (pathway A). (ii) *kinetic resolution*: both C-6 epimers form and arrive at the aldol addition products **2.40** and **2.41**. However, the benzyl substituent may favour the aza-Michael reaction of only the intermediates that lead to the observed

product **2.37** whilst leaving the other epimer as cyclohexenone intermediate **2.41** (pathway B).



Scheme 2.8 Proposed mechanistic proposals to account for the formation of only one 2-substituted octahydroindole diastereoisomer

The first theory seemed more favourable after we demonstrated depending on the base used the diastereocontrol was complete (PS-BEMP) or non-existent (as in the case of the A-26 resin) see figure 2.6. As can be seen the 6-methyl peaks of the other diasteroisomer **2.43** are not observed with PS-BEMP whilst A-26 gives a 1:1 diastereomeric mixture. Lithium hydroxide due to its coordinating ability gives some control but the other diastereoisomer is still produced.

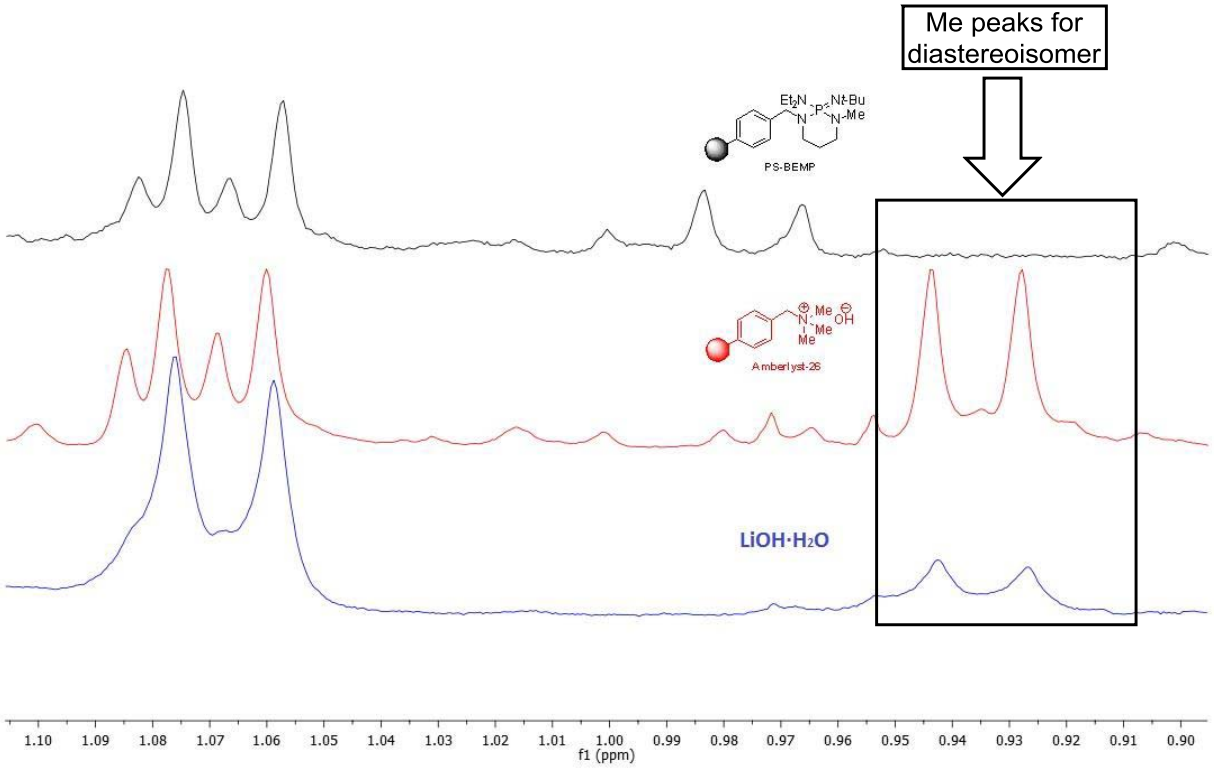


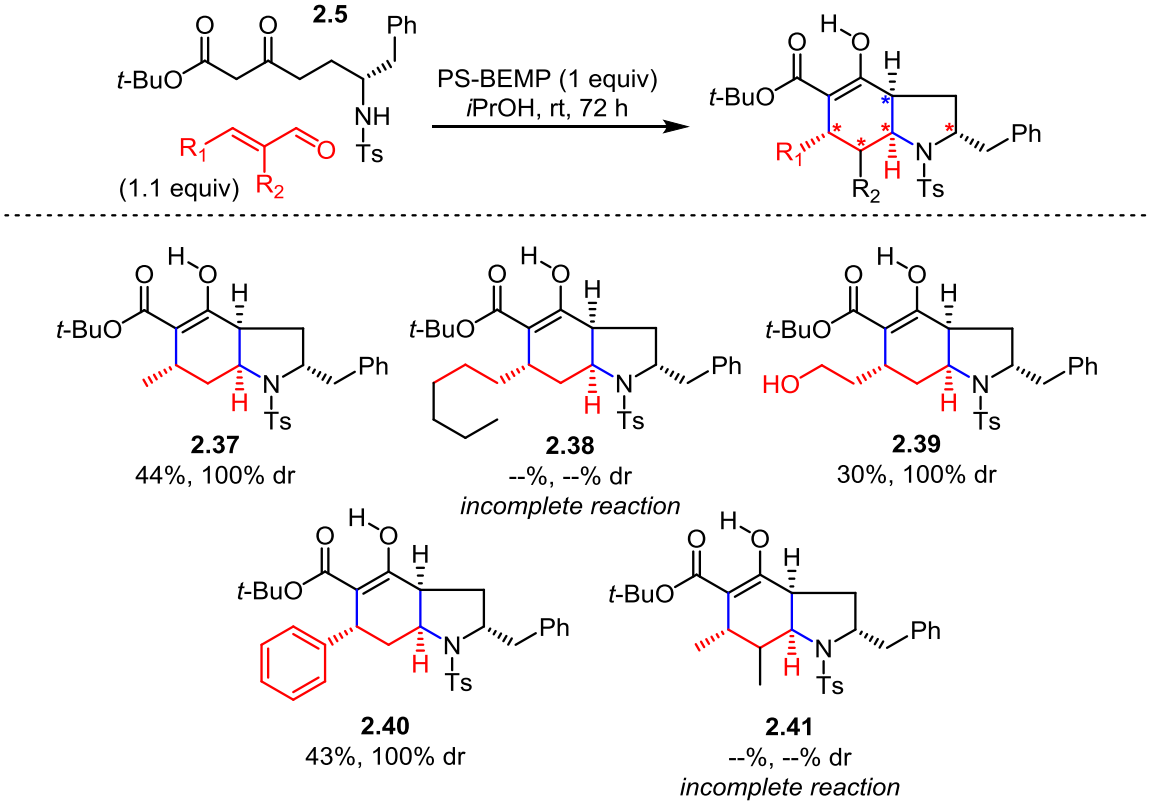
Figure 2.6 Crude 1H NMR spectra for the reaction to **2.37** with 3 sets of basic conditions – no methyl peaks for other the diastereoisomer are observed at 0.935 for PS-BEMP conditions.

As has been seen in the organocatalytic coupling step if the enal component was aliphatic >Et then the organocatalysed reaction was not successful. We believe this failure may be attributed to the formation of dienamine intermediates which are unstable and undergo side reactions. This is a general phenomenon observed throughout the literature on organocatalysis – one which often leads to the use of aromatic substituents in the reaction.[59] For a more in depth discussion of this

[59] For a recent example see: Quintard, A.; Rodriguez, J. *Chem. Comm.* **2015**, *51*, 9523-9526.

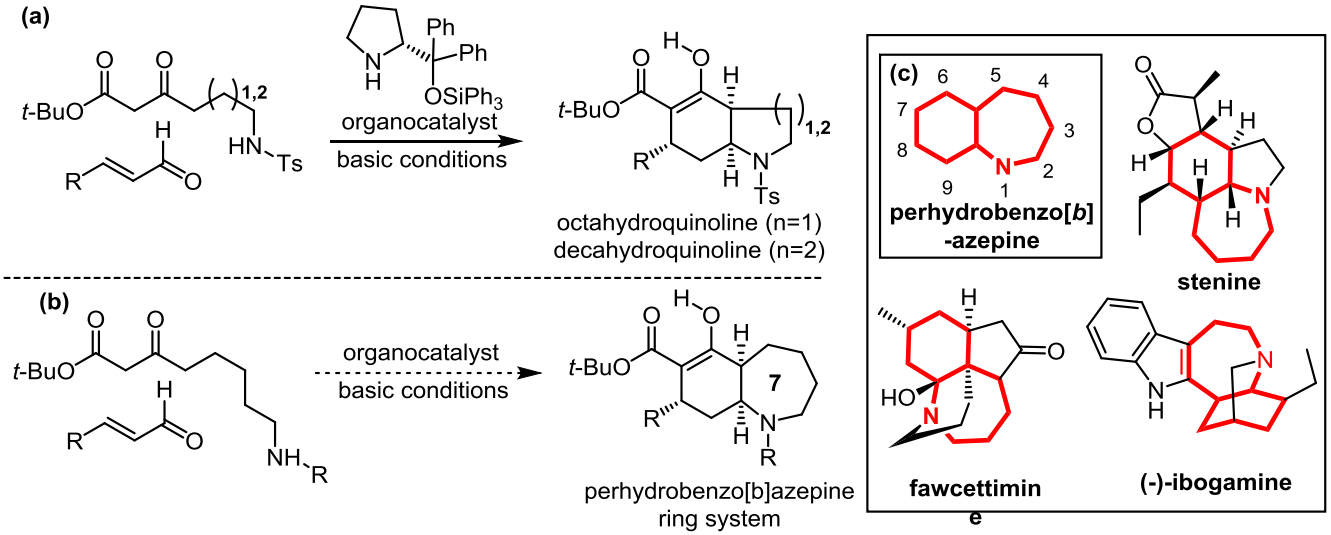
phenomenon see section 3.9.2. We thought that those enals that had proven to be unsuccessful under organocatalytic conditions but worked well under racemic conditions could be employed using this new method. As can be seen from table 2.4 below this proved to be the case allowing for the synthesis of various complex octahydroindole structures with 4 stereocentres. In the case of **2.38** the reaction was incomplete and no more enal material was available to repeat the reaction. In the case of **2.41** the reaction was incomplete probably due to the increased steric congestion of the molecule. Whilst it is likely that optimization of the reaction conditions should be able to give **2.38** and **2.41** this work was carried out at the end of this thesis and no time or material was available to carry out further studies.

Table 2.4 Screening of different Michael acceptors with an α-substituted β-keto ester



2.11 Adaptation of methodology to access Perhydrobenzo[*b*]azepines.

Using the underlying philosophy and principles developed for the octahydroindoles and decahydroquinolines series (scheme 2.9a) we believed it should be possible to access the analogous 7-membered azepines ring containing structures by lengthening the tethered NH-Ts of the β-keto ester side chain (scheme 2.9b). The adaptation of our strategy to these heterocycles whilst straightforward in concept was at the outset envisaged to be more challenging due to the difficulties in forming 7-membered rings. Indeed, there is very little precedent[60] for 7-membered azepine formation and no literature precedent existed for their synthesis using an aza-Michael reaction. Access to this nucleus would be interesting because many pharmaceuticals are based on the azepine ring structure as well as a number of natural products such as stenine,[25] ibogamine[61] and the lycopodium alkaloid fawcettimine[62] (Scheme 2.9c).

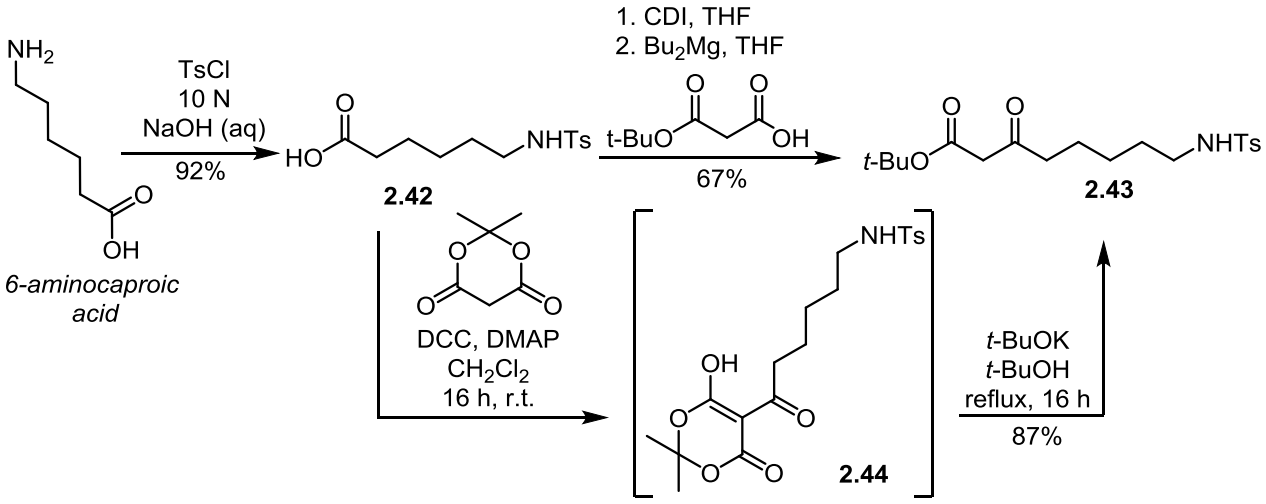


Scheme 2.9 (a) Strategy to octahydroquinoline and decahydroquinoline ring systems (b) Strategy to access perhydroazepine ring structure using same principles (c) Selected natural products containing nucleus.

[60] Kim, H. D.; Kim, G. *Tetrahedron Lett.* **2013**, *54*, 1765–1767.
[61] Kuehne, M. E.; Reider., P. J. *J. Org. Chem.* **1985**, *50*, 1464–1467.
[62] Lei, X.; Li, H.; Wang, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 491-495.

2.11.1 Synthesis of starting material

Two methods were evaluated for the synthesis of the required β-keto ester (scheme 2.10) **(i)** Protection of 6-aminohexanoic acid with tosyl chloride to give **2.42** followed by using Masamune conditions[42] (analogous to the decahydroquinoline series) to give **2.43 (ii).** Alternatively, treatment of **2.42** with Meldrum's acid to generate **2.44** which was refluxed with *t*-BuOH to give **2.43**. The second method was both better yielding, more economical and easier to carry out.

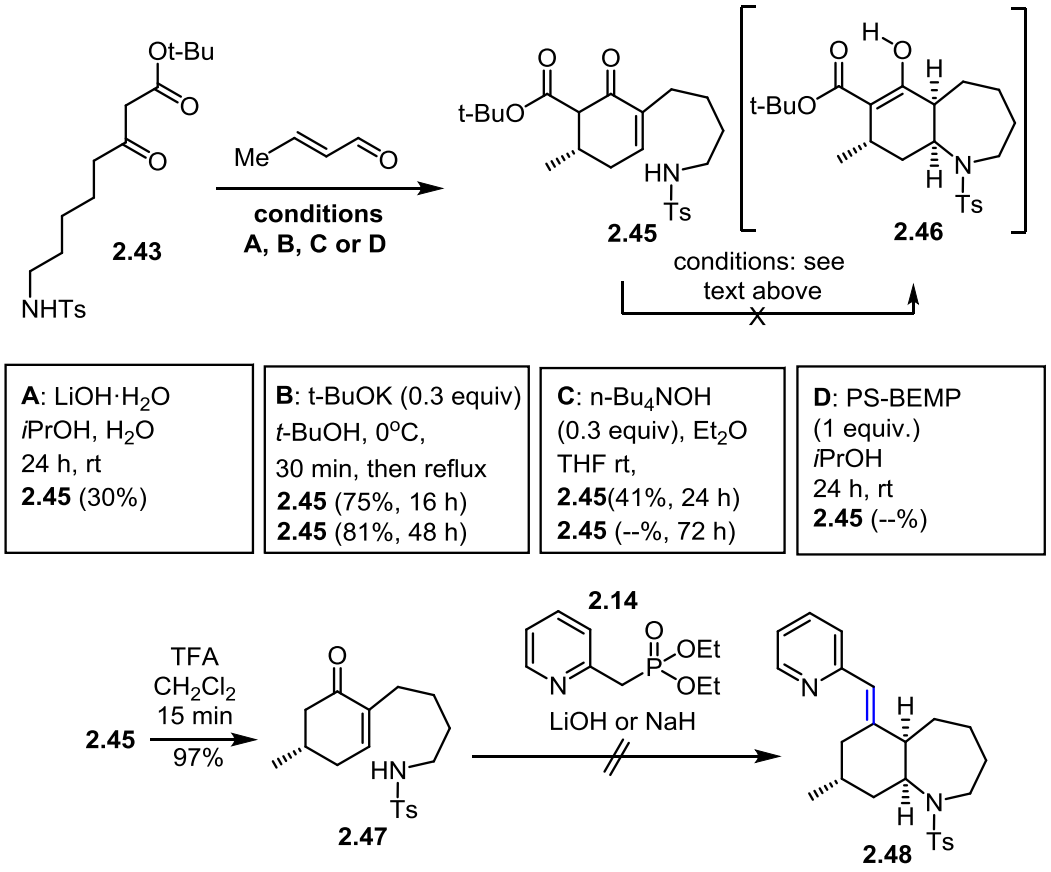


Scheme 2.10 Preparation of β-keto ester starting material **2.26**

2.11.2 Attempted synthesis of perhydrobenzo[b]azepine ring system

Screening the range of basic conditions (A-D) that functioned well for the previous series in all cases led only to the cyclohexenone product **2.45** (scheme 2.11). Not surprisingly given the lack of aza-Michael reaction to drive the reaction forward the best results were obtained with *t*-BuOK (conditions B) with 81% yield. Attempts to induce **2.45** to undergo the aza-Michael reaction with use more forcing conditions such as LiOH/THF/reflux, NaH, BuLi, LDA, CsF/DMF, K_2CO_3/DMF were all met with failure. To investigate if the reaction would be more favorable without the ester the *t*-butyl ester group it was removed from **2.45** (TFA, then heat, 97% yield) to give **2.47**. Evaluation of the conditions outlined above in addition to PS-BEMP, HCl

or TfOH[63] did not give any azepine ring formation. Since the reaction is evidently unfavourable we thought that if a small amount of aza-Michael is formed at equilibrium then trapping the ketone with a suitable nucleophile we might be able to push the reaction to completion in an analogous manner to our cermizine B synthesis (see section 1.5.4). However all attempts to trap **2.47** with vinyl pyridine **2.14** in the presence of LiOH/solvent free, LiOH/THF/reflux or NaH/THF were met with no reaction to **2.48** even after prolonged reaction times.



Scheme 2.11 Attempted cyclisations of β-keto ester **2.43** to the perhydrobenzo[*b*]azepine ring system.

[63] Haskins, C. M.; Knight, D. W. *Chem. Commun.* **2002**, *6*, 2724–2725.

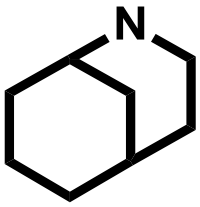
2.12 Summary of Chapter 2

An effective synthesis of variously 6-substituted enantiopure octahydroindoles was developed in up to 95% ee using an organocatalysed Michael, aldol, aza-Michael reaction and PS-BEMP as the base. The procedure could be used successfully to give 6 and 6, 7-disubstituted octahydroindoles. Attempts to adapt the reaction to the 7a substituted octahydroindoles compounds and 7-membered ring azepine analogs were unsuccessful with the reaction forming the corresponding cyclohexenones but not evolving further to the aza-Michael ring closed products.

Incorporation of a chiral substituent alpha to the nitrogen of the β-keto ester starting material allowed for the synthesis of diastereoselectivity pure octahydroindoles via proposed cyclic transition state which only allowed the enal to approach the β-keto ester from one face only. This reaction presented an alternative to the organocatalysed version allowing the use of enals bearing aliphatic groups when the analogous organocatalytic reaction fails.

CHAPTER 3:

SYNTHESIS OF ENANTIOPURE MORPHANS VIA ORGANOCATALYSIS



3.1 The Morphan Nucleus: Objectives and Chapter Overview

So far in chapter 2 we have described modifications of the original decahydroquinoline methodology by shortening or lengthening the tethered N-Ts side chain to give octahydroindoles and perhydrobenzo[b]azepines respectively. Another important nitrogen containing nucleus which our research group has dedicated significant effort towards is the 2-azabicyclo[3.3.1]nonane (2-ABN) or morphan framework. Before discussion of our adaptation of the common methodology to this structure a brief overview of this nucleus presented divided into 3 parts: (i) natural products containing the morphan nucleus (ii) previous general strategies that have been employed (iii) a brief survey of the asymmetric methods. It is then described the synthetic plan to obtain this nucleus based on the Robinson/aza-Michael reaction. The results section then covers 3 main areas (figure 3.1) (a) Synthesis of 8-substituted morphan ring system in racemic form and enantiopure form via organocatalysis using the Robinson/aza-Michael reaction (b) variations to incorporate a substituent in the 4-position a motif found in many morphan natural products systems and (c) incorporation of an indole nucleus to access indolomorphan natural products.

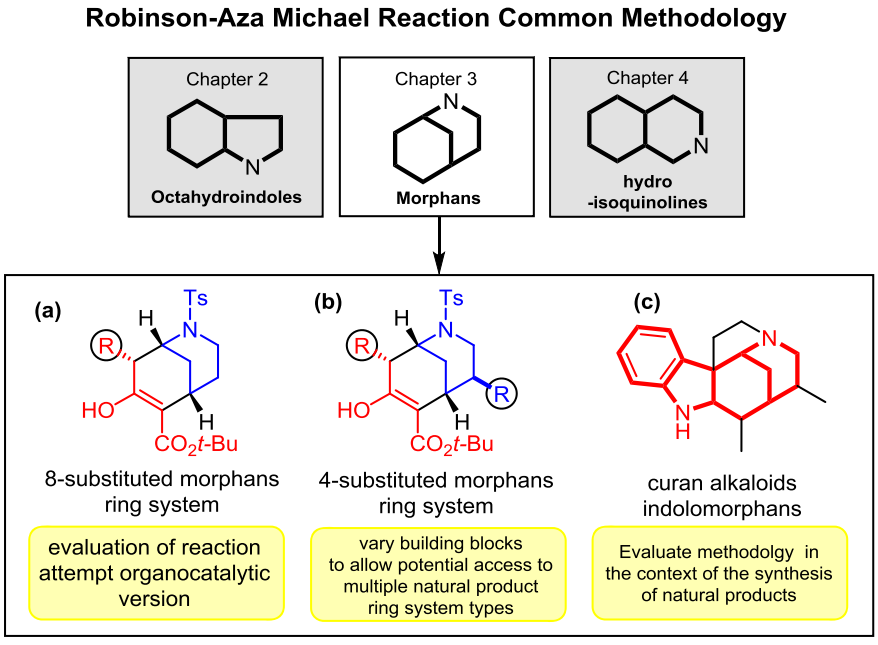


Figure 3.1 The morphan nucleus and chapter overview.

3.2 Morphan Natural Products and Pharmaceuticals

The 2-azabicyclo[3.3.1]nonane framework (morphan) features prominently in many complex and biologically active natural products as well as medicinal compounds of significant interest (Figure 3.2). Natural products include morphine[64] (potent analgesic), kopsone,[65] himgaline[66] (potent muscarinicantagonistic properties), secu'amamine A,[67] aspernomine,[68] (activity against 3 human solid tumour cell lines), suomilide[69] (serine protease inhibitor), strychnos alkaloids (e.g.akuammicine, strychnochromine, geissoschizoline),[70] madangamines,[71] (activity against various cancer cell lines), and some types of Daphniphyllum alkaloids[72] such as calyclphylline A (cytotoxicity against murine lymphoma L1210 cells *in vitro*) and daphniyunnine D (cytotoxicity against tumor cell lines, P-388 and A-549). This nuclei is also present in many pharmaceutical products such as toxiferine[73] (muscle relaxant, paralysis of skeletal muscle), dextromethorphan,[74] (an antitussive from the morphinan class with sedative and disassociative properties) and FR901483[75] (immunosuppressant activity).

[64] (a) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388-405. (b) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358-362.
[65] Kan-Fan, C.; Sevenet, T.; Had, H. A.; Bonin, M.; Quirion, J. C.; Husson, H.-P. *Nat. Prod. Lett.* **1995**, *7*, 283-290.
[66] Evans, D. A.; Adams, D. J.; *J. Am. Chem. Soc.*, **2007**, *129*, 1048–1049.
[67] Magnus, P.; Padilla, A. I. *Org. Lett.* **2006**, *8*, 3569-3571.
[68] Staub, G. M.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Am. Chem. Soc.* **1992**, *114*, 1015-1017.
[69] Schindler, C. S.; Stephenson, C. R. J.; Carreira E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 8852-8855.
[70] (a) Bosch, J.; Bonjoch, J.; Amat, M. *The Alkaloids: Chemistry and Pharmacology* **1996**, *48*, 75-189. (b) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455-3482.
[71] (a) Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267-271. (b) Ballette, R.; Perez, M. Proto, S.; Amat, M.; Bosch, J *Angew. Chem. Int. Ed.* **2014**, *53*, 6202-6205.
[72] Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936-962.
[73] Zlotos, D. P.; Buller, S.; Stiefl, N.; Baumann, K.; Mohr, K. *J. Med. Chem.* **2004**, *47,* 3561-3571.
[74] Heinkele, G.; Schanzle, G.; Murdter, T. M.; *J Label Compd Radiopharm* **2002**; *45*, 1153-1158.
[75] Bonjoch, J.; Diaba, F. *Stud. Nat. Prod. Chem.* **2005**, *32*, 3-60.

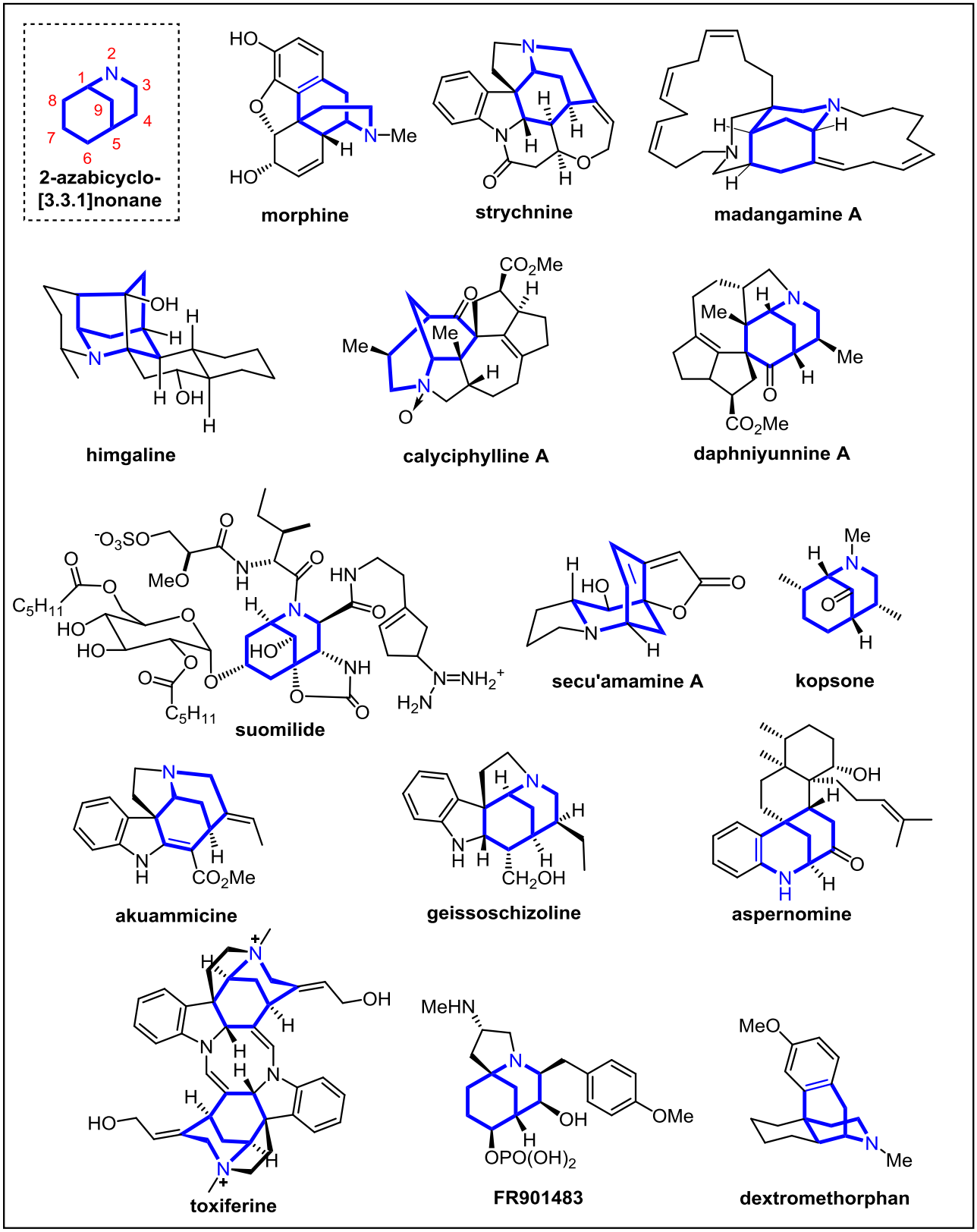


Figure 3.2 Natural products and pharmaceuticals containing the morphan nucleus.

3.3 Literature precedents for the preparation of morphans

The strategies to access the morphan nucleus developed so far can be roughly split into 2 distinct types (a) those that start from a carbocycle ring system and construct the nitrogen ring on top of it and (b) those strategies that start with a piperidine ring and construct the carbocycle. A brief overview of these methods are now presented but for a more detailed discussion the reader is directed to an extensive review on the subject and the references cited therein.[76]

3.3.1 Synthetic approaches from carbocyclic compounds

Most of the approaches involve the C(1) or C(5) atom in the ring forming step, usually with an sp^2 hybridization, which evolve to a bridgehead atom. The N–C(1) bond is strategically important in the morphan nucleus formation, since, as well as being a carbon–heteroatom bond, it is directly attached to another ring. One of the most successful approaches involves the formation of the C(4)–C(5) bond in the key step. This can be achieved by enolate alkylation, aldol reaction, metal promoted procedures such as the Heck reaction and palladium-catalyzed alkenylation of enolates, radical procedures, as well as some other miscellaneous processes. The disconnection involving the N–C(3) bond is rather uncommon since synthetically it requires a previous *cis*-stereochemical relationship between the nitrogen and the involved side-chain of the cyclohexane derivative precursor (figure 3.3, left)

3.3.2 Synthetic approaches from piperidine derivatives

The synthesis of the 2-ABN ring by carbocyclic ring formation from a piperidine has been less frequent than the aforementioned approaches, in which the heterocyclic ring is elaborated in the final step. Again, the most common procedures involve the formation of a bond, either C(1)–C(8) or C(5)–C(6), that generates a bridgehead (figure 3.3, right). The former usually involves an iminium or acyliminium salt as a counterpart of a nucleophilic species, while several routes exist for the latter. In contrast, there are only two procedures involving the C(6)–C(7) bond, using

[76] For a detailed review of approaches to morphan-containing natural products, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, *7*, 993-1018.

either a Dieckmann cyclization or a ring-closing metathesis process and none to induce the ring closure by formation of the C(7)–C(8) bond in the last thirty years.[77]

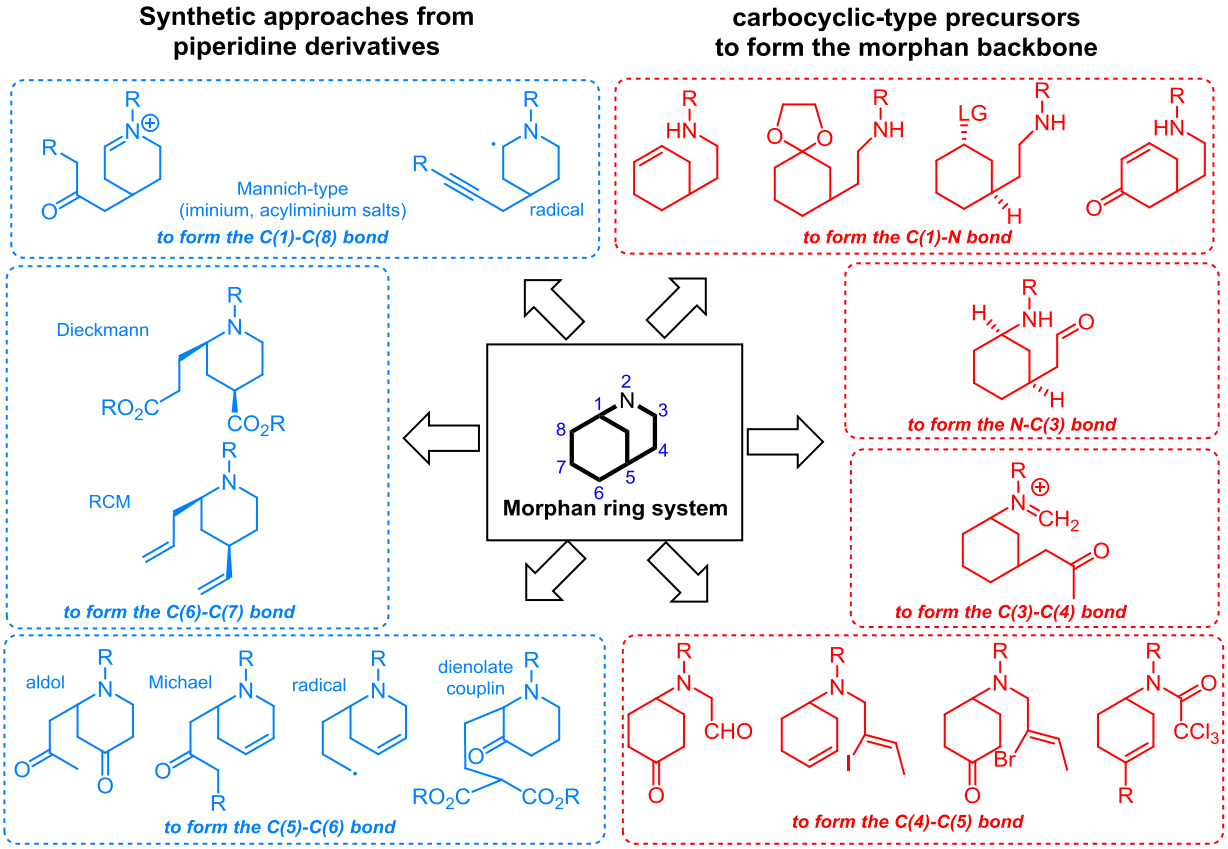


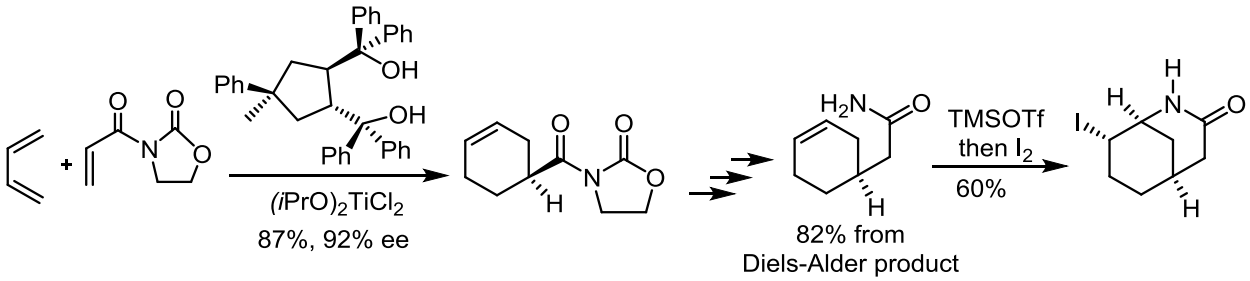
Figure 3.3 Methods for synthesis of ring morphan system.

3.3.3 Synthesis of enantiopure morphans

Despite the plethora of methods that have been developed for the formation of the morphan nucleus, to date few catalytic asymmetric strategies to polyfunctionalized enantiopure morphan ring systems has been developed. The first was reported by Eschenmoser in 2000 (Scheme 3.1)[78] where the enantio-enriched starting material was prepared by an asymmetric Diels–Alder reaction catalyzed by a TADDOL catalyst complexed in situ with dichlorodiisopropoxytitanium (IV). This was

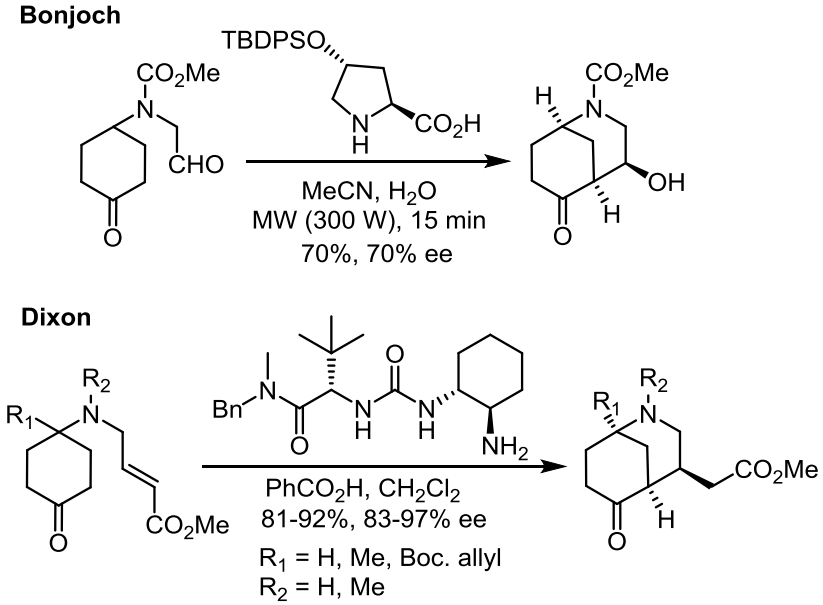
[77] For the only morphan synthesis implying the C7–C8 bond formation in the last step that uses a Dieckmann cyclization, see: Adachi, J.; Nomura, K.; Shiraki, S.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1974**, *22*, 658-662.
[78] G. Karig, A. Fuchs, A. Büsing, T. Brandstetter, S. Scherer, J. W. Bats, A. Eschenmoser and G. Quinkert, *Helv. Chim. Acta*, **2000**, 83, 1049-1078.

then converted into an amide which formed the morphan nucleus via an iodolactonization reaction.



Scheme 3.1 Asymmetric Diels-Alder reaction/iodolactamization approach to enantiopure morphans.

The first asymmetric aldol-based synthesis of the morphan moiety using organocatalysis was achieved by our research group through the desymmetrization of the prochiral 4-*N*-protected aminocyclohexanone via organocatalyzed intramolecular aldolization under microwave activation to give the morphan product in 70% yield and 70% ee.[79] Subsequent to this work an adaptation was published by the Dixon group utilizing a Michael reaction catalysed by a primary amine urea catalyst.[80]

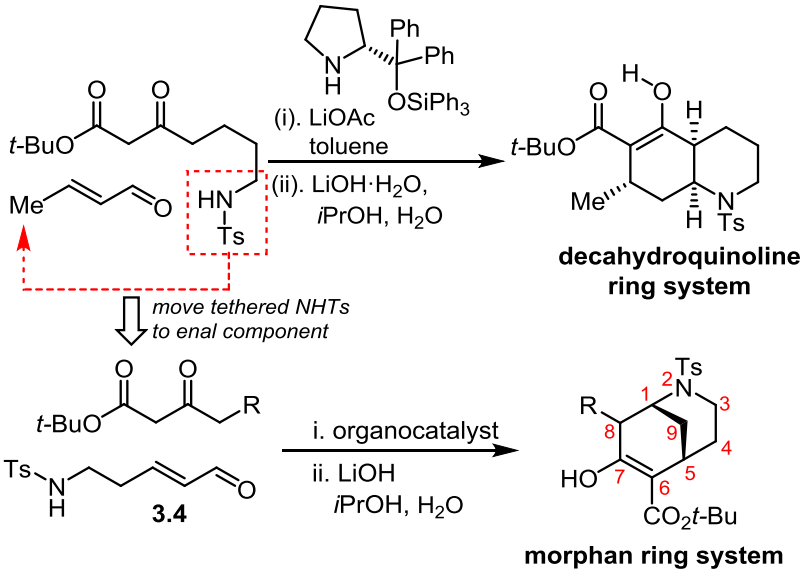


Scheme 3.2 Asymmetric organocatalyzed aldol reaction to form morphan ring system via desymmetrization.

[79] Bonjoch, J.; Diaba, F.; *Org. Biomol. Chem.*, **2009**, *7*, 2517-2519.
[80] Yamagata, D.G.; Datta, S.; Jackson, K.E.; Stegbauer, L.; Paton, R.S.; Dixon, D.J.; *Angew. Chem. Int. Ed.* 2015, *54*, 4899-4903.

3.4 Overview of strategy to access morphans via the Robinson aza-Michael reaction

We postulated that the Robinson aza-Michael reaction could be adapted to access the morphan ring system by moving the tethered nucleophillic *N*-Tosyl group from the β-keto ester to the enal component (Scheme 3.3). However, it was not clear at the outset that the direct application of the original method would be feasible, since the resulting enal **3.4** would now bear both nucleophilic and electrophilic centers. Indeed, similar compounds separated by additional carbons have been used in organocatalyzed intramolecular aza-Michael reactions.[81] We hoped that in our case the formation of the azetidine ring by intramolecular cyclization would be sufficiently disfavoured to allow the intermolecular Michael reaction.



Scheme 3.3 Strategy to access morphan nucleus based on a modified version of the organocatalyzed Michael Robinson aza-Michael reaction developed for decahydroquinolines.

As has been seen in section 3.3 all methods developed so far to form the morphan ring system rely on the preformed construction of one of the 2 rings present in the parent morphan ring system. Additionally there is a scarcity of catalytic asymmetric methods. The above mentioned strategy would not only be catalytic but would be the first to start from completely acyclic starting materials. Additionally the highly

[81] For the use of this type of compound for the formation of piperidines via organocatalysis, see: Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283-5286. For a general review on organocatalytic asymmetric aza-Michael reactions, see: Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur J.* **2009**, *15*, 11058-11076.

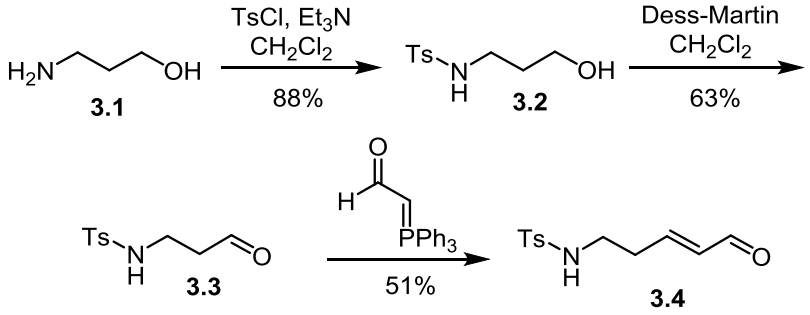
convergent nature of this strategy should make it highly flexible in order to access multiple diverse natural product systems based on this nucleus.

3.5 Synthesis of starting material(s)

The synthesis of the required enal **3.4** coupling partner was carried out via two methods:

3.5.1 Wittig approach

Starting from 3-aminopropanol **3.1**, protecting as the tosylamide **3.2**, oxidation with the Dess Martin reagent gave the aldehyde **3.3** which was then reacted with the wittig reagent to give the desired enal **3.4** in moderate yield (Scheme 3.4).



Scheme 3.4 Synthesis of tethered N-Ts enal **3.4** via wittig homologation.

The relatively high cost of the Wittig reagent combined with the requirement for the use of the reagent in excess led us to investigate an alternative route which might be more amenable to scale-up.[82]

3.5.2 Cross metathesis approach

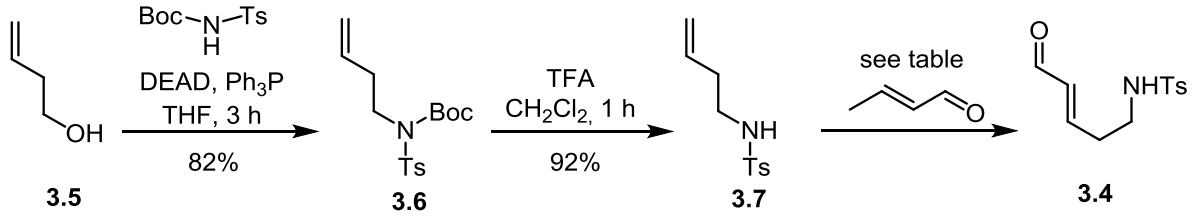
Alternatively **3.4** could be prepared from 3-buten-1-ol via Mitsonobu coupling with *tert*-butyl tosylcarbamate[83] to give **3.6** followed by removal of the Boc group with TFA. The resulting alkene **3.7** underwent a cross metathesis reaction to give the desired alkene **3.4** with a range of conditions (table 3.1). Initially 2.5% of Hoveyda-

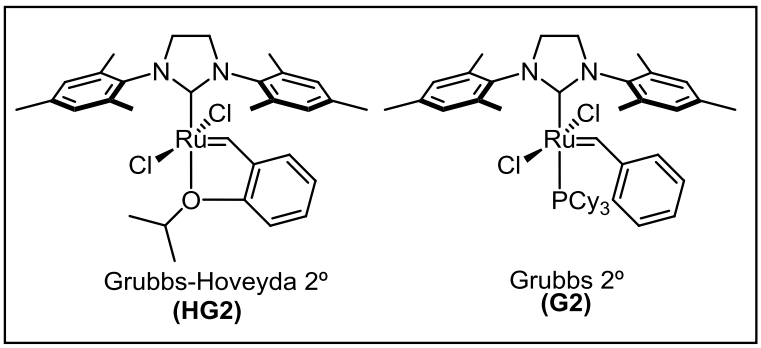
[82] It should be noted that **3.4** could also be prepared from aldehyde **3.3** more economically via a Wittig reaction with the corresponding ester Wittig reagent however this provides the compound in the wrong oxidation state requiring additional 2 steps (DIBALH reduction to allyl alcohol followed by reoxidation to the aldehyde).

[83] Teichert, J. F.; Zhang, S.; Zijl, A. W. V.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658-4660.

Grubbs 2nd generation catalyst and crotonaldehyde[84] was found to be best (entry 2). However we later found that the method of Lipshutz[85] using Grubbs 2nd generation catalyst with CuI as additive was superior with respect to catalyst loading (just 1%), time and reproducibility of yields (entry 7).

Table 3.1 Synthesis of tethered N-Ts enal **3.4** via cross metathesis.





Entry[a]	**catalyst**	***Catalyst loading***	***Conditions***	***Temp***	***Time***	***Yield***
1	HG2	2.5%	CH_2Cl_2	rt	16 h	59%
2	HG2	2.5%	CH_2Cl_2	reflux	16 h	85%
3	HG2	1%	CH_2Cl_2	reflux	16 h	67%
4	HG2	1%	CH_2Cl_2	reflux	48 h	36%
5	G2	2.5%	CH_2Cl_2	reflux	16 h	51%
6	G2	2.5%	Et_2O, CuI (4%)	reflux	4 h	85%
7	G2	1%	Et_2O, CuI (1.5%)	reflux	4 h	85%

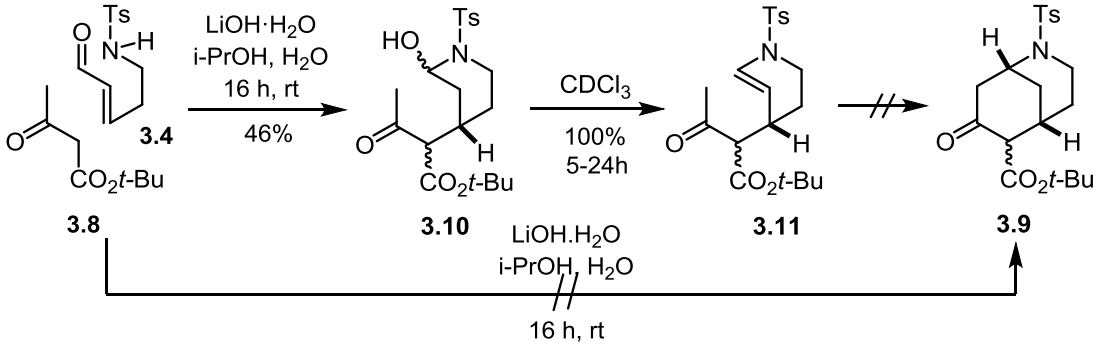
[a]5 equivalents of enal were used in all cases

[84] For a related procedure, see: Chen, JR.; Li, CF.; An, XL.; Zhang, JJ.; Zhu, XY.; Xiao, WJ.; *Angew. Chem. Int. Ed.* **2008**, *47*, 2489-2492.
[85] Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697–4702.

3.6 Synthesis of morphans – racemic version

3.6.1 Initial evaluation of the tandem Robison aza-Michael reaction

With enal **3.4** in hand, we began our studies by investigating the coupling reaction in non-asymmetric form. We initially chose *tert*-butyl acetoacetate as the β-keto ester component since this would give resulting products without substitution at the 8-position which would avoid the potential formation of diastereoisomers and thus simplify the analysis and characterisation of the resulting product. However, upon treatment of an equimolar mixture of **3.4** and the β-keto ester **3.8** with $LiOH{\cdot}H_2O$ in *i*PrOH/H_2O resulted not in the formation of the desired morphan **3.9** but the heminal **3.10**.



Scheme 3.5 Initial attempt to synthesize the morphan nucleus via tandem reaction

It was noted that when kept in $CDCl_3$ solution to run the ^1H NMR spectra that this compound would readily eliminate to the piperidine compound **3.11**.

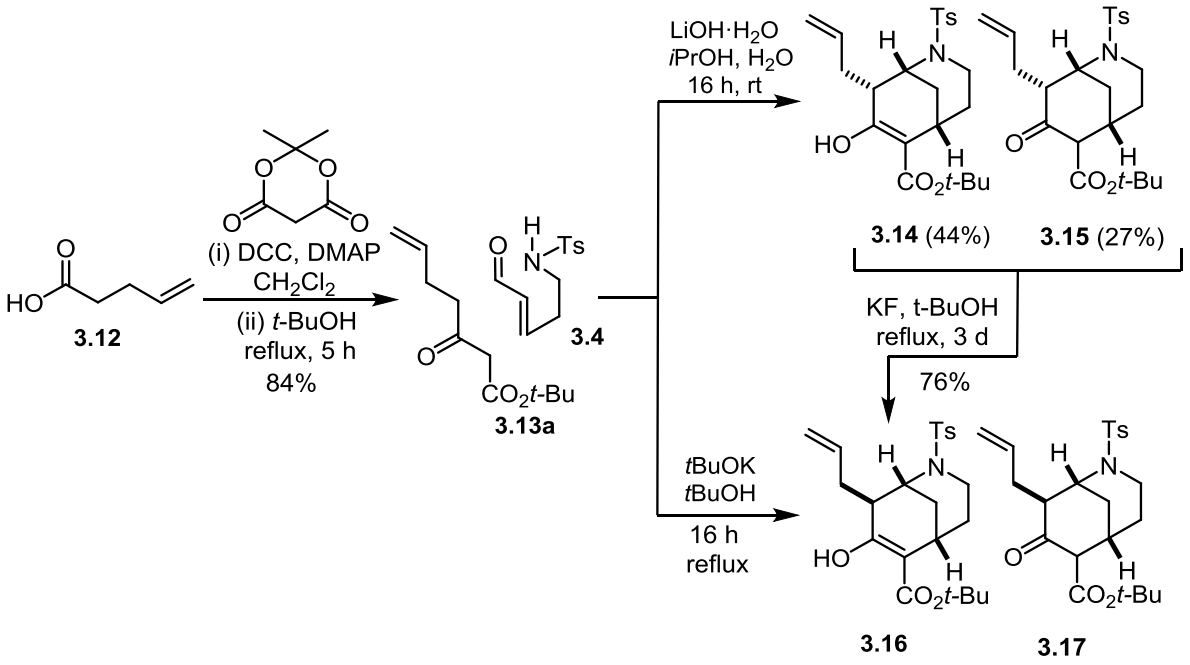
3.6.2 Revaluation of the synthesis to give 8-substituted morphans

Believing that substitution at the 8-position would favour the formation of the cyclohexenone ring system we took acid **3.12** and homologated it to β-keto ester **3.13a** using Meldrum`s acid.[86] Upon treatment of an equimolar mixture of **3.4** and the β-keto ester **3.13a** with $LiOH{\cdot}H_2O$[87] in *i*PrOH/H_2O, we were pleased to observe the formation of the desired morphan **3.14** (Scheme 3.6). A second, more polar

[86] Kralj, D.; Friedrich, M.; Grošelj, U.; Kiraly-Potpara, S.; Meden, A.; Wagger, J.; Dahmann, G.; Stanovnik, B.; Svete, J. *Tetrahedron* **2009**, *65*, 7151–7162.

[87] It should be noted that this work was carried out prior to the majority of the work on octahydroindoles presented in the previous chapter. The beneficial effects of using PS-BEMP to effect the cyclisation reactions were not known at this time. Regardless, attempts to effect the tandem sequence with PS-BEMP in the above reaction were not successful and the product did not evolve much beyond the hemiaminal intermediate **3.18**.

compound **3.15** was also isolated and identified as the same cyclized product in its keto tautomeric form.



Scheme 3.6 Synthesis of the morphan nucleus via tandem reaction

Surprisingly, it was possible to separate these two compounds by column chromatography, and once isolated they did not undergo equilibration in solution,[88] allowing their NMR structures to be determined. In both cases, the allyl substituent was determined to be equatorial (see section 3.6.3 for structural determination analysis). Access to the axially positioned substituent product **3.16** was achieved by refluxing the mixture of **3.14** and **3.15** with KF in *t*-BuOH for 3 days.[89] Notably under these conditions the enol form of the keto ester was the dominant species isolated. It was also possible to go directly to the kinetic product by carrying out the cyclisation reaction with *t*-BuOK in *t*-BuOH at reflux. To rationalize the observed stereochemistry of the allyl substituent, it was presumed that upon attack of the *N*-Tosyl group, the resulting enolate protonates from the less hindered top face to give **3.14** and **3.15**, with the allyl in the equatorial position (kinetic products).

[88] It should be noted, however, that upon prolonged standing the pure compounds would revert to mixtures of the enol/keto forms.
[89] For thermodynamic isomerization of α-substituted cycloalkanones using KF, see: Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010***, 132,* 5966-5967.

3.6.3 Determination of stereochemistry by NMR

The structures of **3.14** and **3.16** were determined by NMR analysis (see figure 3.5). The resulting steric compression suffered by the allyl substituent with the tosyl group[90] was minimized in the kinetic isomer **3.14** by nitrogen inversion. The axial orientation of the *N*-tosyl group relieved the steric crowding with the equatorial side chain at C-8. This effect was observed comparing ^{1}H NMR of both isomers, where are clearly differentiated in the chemical shift of H-1_{eq}, which appears more deshielded (δ 4.40) in **3.14** than in **3.16** (δ 4.12), due to which promotes a compression, is shifted more upfield, an effect that is also observed in H-8 (δ 2.59 and 2.00 respectively) and H-3_{ax} (δ 3.11 and 2.96 respectively).

This conformational change was deduced from a shielding at C-4 observed when comparing the ^{13}C NMR spectra of **3.14** (δ 26.5) and the thermodynamic isomer **3.16** (δ 29.0)**.** The chemical shift of the C-8 substituent, which is shifted more upfield (δ 44.1) in **3.14** that in **3.16** (δ 42.6). In the latter, the allyl group axially located at C-8 allowed the *N*-tosyl to adopt an equatorial disposition.

[90] For a related 1,3-syn interaction within the *N*-substituent and alkyl side chain in C-8 in morphan compounds, see: Bonjoch, J.; Casamitjana, N.; Quirante, J.; Torrens, A.; Paniello, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 377-381.

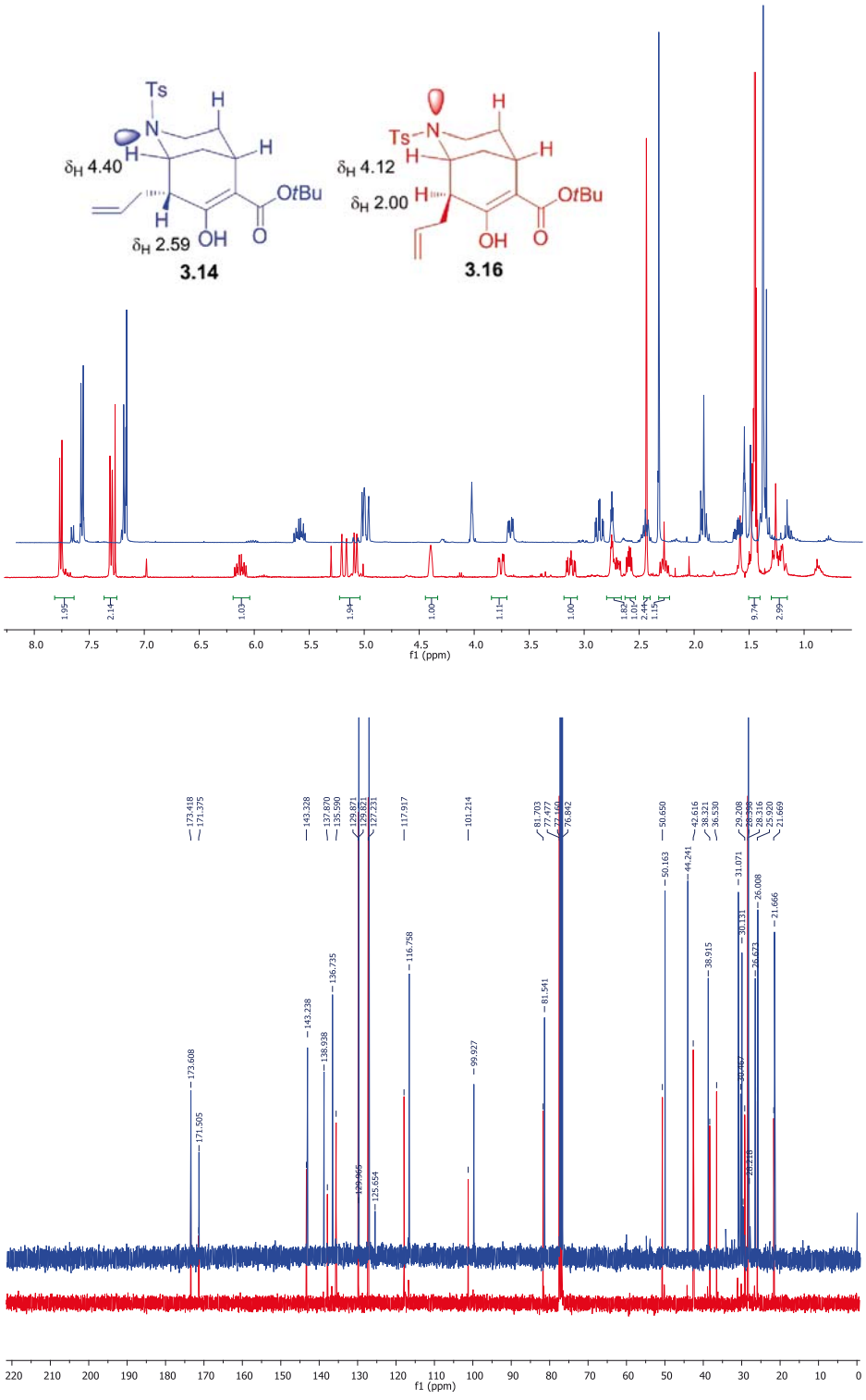
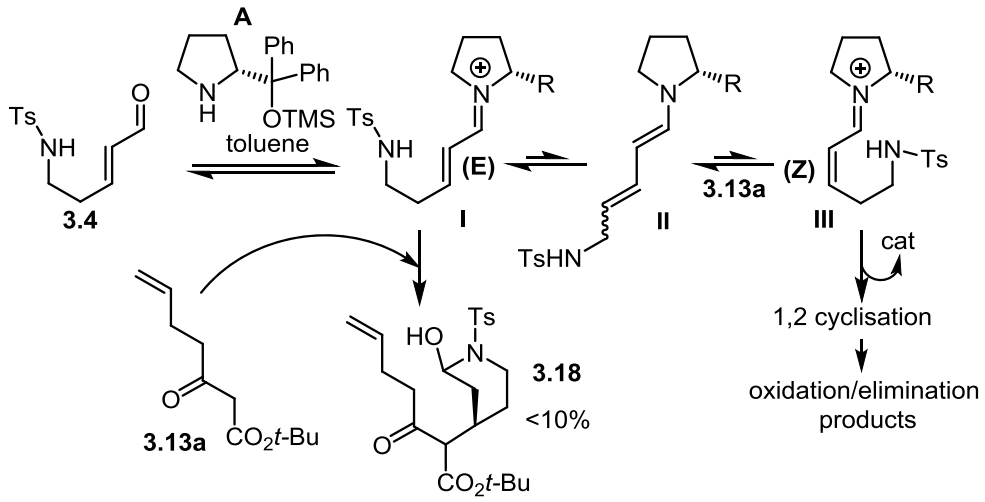


Figure 3.5 Assignation of morphan structures/diastereoisomers.

3.7 Synthesis of morphans – enantioselective version

3.7.1 Initial attempts

Having proof of concept, we then turned to investigate the reaction in asymmetric form. Unfortunately, upon treatment of β-keto ester **3.13a** with enal **3.4** in the presence of the Hayashi-Jorgensen catalyst **A**[91] in a range of organic solvents,[92] we observed only trace amounts of the Michael addition product **3.18**, which existed exclusively in its hemiaminal form (Scheme 3.7). While the β-keto ester **3.13a** was stable under the reaction conditions, enal **3.4** was slowly consumed into an unidentified product. We believe that the side reaction is a result of an isomerization of the double bond of **I** via the dienamine **II**[93] to form the cis isomer **III**, which then cyclizes to form a 6-membered ring, followed by subsequent oxidation.[94] It should be noted that this side reaction did not occur in the absence of **3.13a**, indicating that the β-keto ester must somehow facilitate the isomerization by proton transfer processes (see section 3.8 for full mechanism outline).



Scheme 3.7 Initial attempt to effect organocatalysed coupling reaction.

[91] (a) Hayashi, Y., Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem Int. Ed*. **2005**, *44*, 4212-4215. (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797

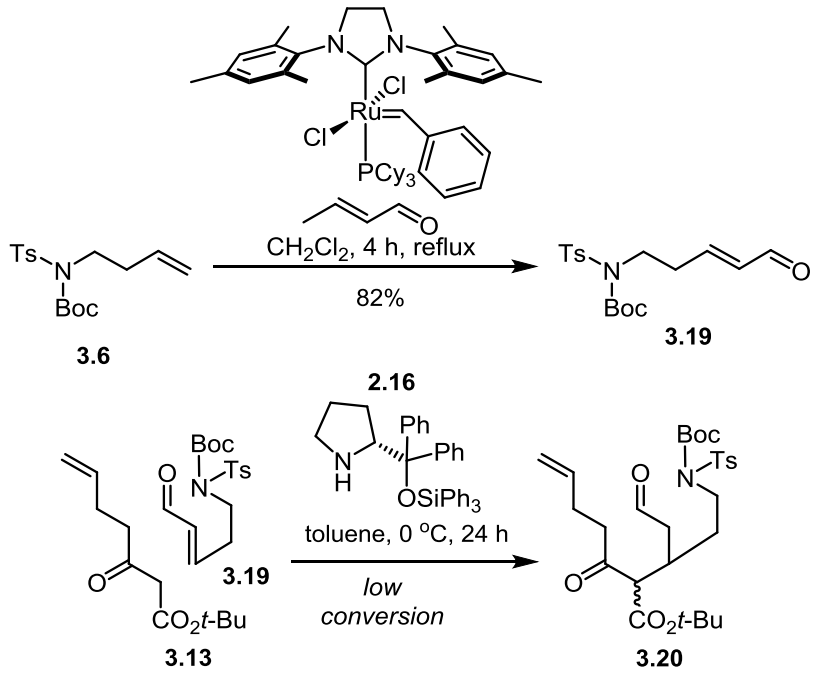
[92] Solvents screened were toluene, CH_2Cl_2, and MeOH; all gave equally poor results so a detailed solvent screen was not undertaken

[93] For isomerization of enals to dienamines via organocatalysis, see: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973-12980.

[94] For related intramolecular cyclization of N-Ts derivatives to form pyridines, see: Donohoe, T. J.; Bower, J. F.; Baker, D. B.; Basutto, J. A.; Chan, L. K. M.; Gallagher, P. *Chem. Commun.* **2011***, 47*, 10611-10613.

3.7.2 Coupling attempt with N blocking group

To prevent the undesired intramolecular reaction of the free NH group of enal **3.4** the Boc protected analog was investigated.[95] The previously prepared compound **3.6** was used in a cross metathesis reaction to give enal **3.19**. This compound was treated under the same reaction organocatalytic conditions as before to determine the importance of free nitrogen in the first coupling step. Unfortunately, only trace quantities of the coupled product were observed, indicating that the Michael reaction is generally unfavourable without the formation of the heminal form (e.g **3.18**) driving the reaction to completion.[96]



Scheme 3.8 Attempted coupling of bisprotected enal.

[95] Since N-Ts acetamides can be cleaved under mildly basic conditions, it was planned to substitute the Boc group for an acetamide. Under the basic cyclization conditions it would in theory be cleaved in-situ thus eliminating the need for a separate deprotection step.

[96] Presumably the formation of the hemiaminal is important since it helps drive the reaction forward by removing the formed aldehyde from competition with the organocatalyst, as well as preventing a possible retro Michael reaction.

3.7.3 Optimization of conditions

Returning to the coupling reaction of **3.4** and **3.13a** we observed that if the reaction was carried out in the absence of any solvent, it was noticeably accelerated and we were able to obtain moderate quantities of the coupled product **3.18**. Treatment of the crude mixture with $LiOH \cdot H_2O$ in *i*PrOH/H_2O led to the cyclized product in 79% ee and moderate 38% overall yield for the two steps (Table 3.2, entry 1). Again, the product was isolated as a mixture of enol/keto forms (~3:1 ratio, only the enol form is shown for clarity). To improve the reaction, a series of additives (BzOH, TBAB,[97] $NaHCO_3$, LiOAc) were investigated, with significantly improved yields being obtained with LiOAc (entry 3). The use of water as an additive (10 equiv) led to both an increase in yield and ee (entry 7). Carrying out the reaction at reduced temperature, however, proved to be detrimental (entry 9). Switching to the more impeded catalyst **2.16**[98] gave similar results to the Hayashi catalyst when water was used as the additive (Table 1, entry 10), but it proved to be superior when LiOAc was used (compare entries 3 *vs* 11). Again, reducing the temperature resulted in significantly inferior results (entry 12). The use of both additives together, as opposed to individually, proved to be superior (entry 14), with the enantioselectivity increasing to 92%.[99]

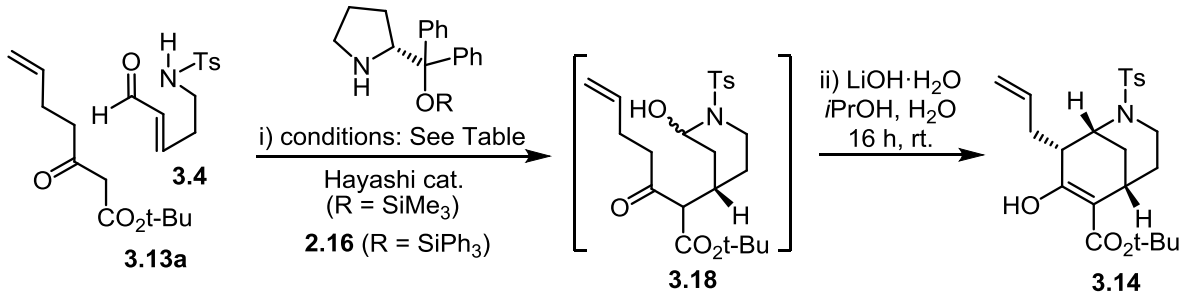
Based on the variations of enantioselectivity observed for other bases in the octahydroindole series we tried Bu_4NOH under phase transfer conditions but noted no improvement in ee. As commented before (see reference 87) the use of PS-BEMP was innefective at driving the cyclisation of the morphan ring system and was therefore not evaluated in the asymmetric version.

[97] TBAB refers to tetrabutylammonium bromide. For its use, see: Duce, S.; Mateo, A.; Alonso, I.; Garcia Ruano, J. L.; Cid, M. B. *Chem. Commun.* **2012***, 48*, 5184-5186.

[98] Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci* **2011**, *2*, 353-357. The more expensive *R* form of the catalyst was used since the major morphan enantiomer formed eluted second by HPLC and gave a better separation. If the major compound eluted first the tail from the HPLC peak overlapped with the minor enantiomer formed and the ee could not be accurately detemined.

[99] The absolute configuration proposed for morphan **3.14** is based on the accepted mechanism of organocatalyzed Michael addition of β-keto esters upon enals: Jensen, K. L.; G. Dickmeiss, G.; Jiang, H.; Albrecht, L.; K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248-264.

Table 3.2 Screening of conditions[a] for organocatalyzed synthesis of morphans.



entry	additive (equiv)	R	temp	yield (%)[b]	ee (%)
1	--	TMS	rt	38	79
2	BzOH (0.1)	TMS	rt	34	51
3	LiOAc (0.1)	TMS	rt	61	79
4	$NaHCO_3$ (0.1)	TMS	rt	37	81
5	TBAB (0.1)	TMS	rt	43	75
6	H_2O (0.1)	TMS	rt	28	83
7	H_2O (10)	TMS	rt	69	88
8[c]	H_2O (10)	TMS	rt	41	80
9	H_2O (10)	TMS	0 °C	52	73
10	H_2O (10)	$SiPh_3$	rt	67	88
11	LiOAc (0.1)	$SiPh_3$	rt	66	86
12	LiOAc (0.1)	$SiPh_3$	0 °C	62	64
13	LiOAc(0.1)/H_2O(10)	$SiPh_3$	rt	52	90
14[d]	LiOAc(0.1)/H_2O(10)	$SiPh_3$	rt	55	92

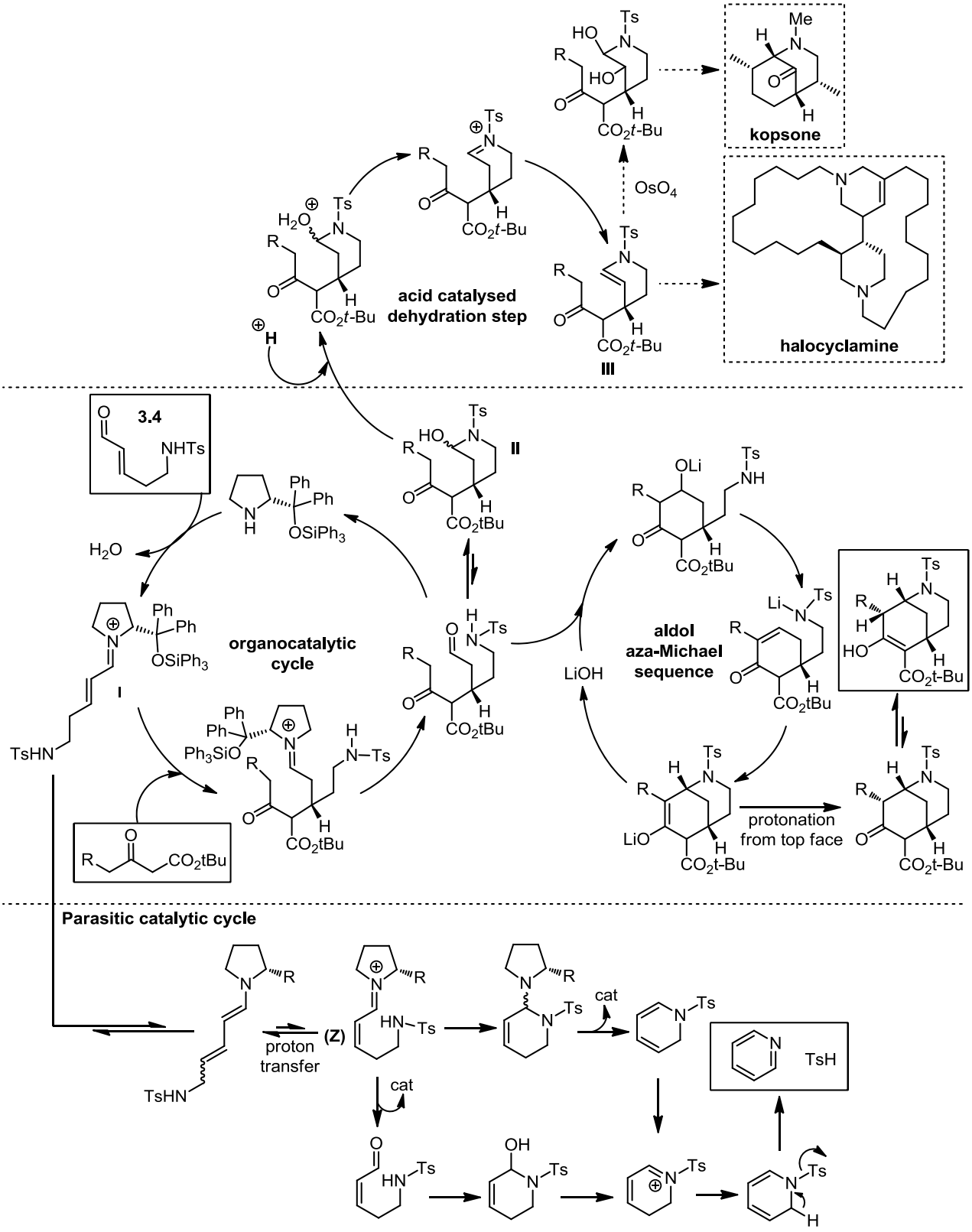
[a] Conditions 2 equiv β-keto ester **3.13a**, 1 equiv enal **3.4**, 10% catalyst, 3 h then add *i*PrOH (4 mL/mmol of enal), LiOH.H_2O (3 equiv), H_2O (10 equiv), 16 h. [b] Yield is given for enol and keto forms combined. [c] 1:1 Ratio of keto ester and enal used. [d] Reaction time 24 h for the initial step.

3.8 Proposed reaction mechanism

The proposed mechanism of the reaction is outlined in Scheme 3.9. The enal **3.4** forms the organocatalyst imine species **I** which can undergo two possible reactions. Under the desired pathway a Michael addition reaction with the β-keto ester compound occurs from the top face due to the catalyst blocking the lower face of the molecule. The resulting product spontaneously forms the hemiaminal compound intermediate **II** which then allows the catalyst to re-enter the catalytic cycle. Notably the formation of the hemiaminal by removing the aldehyde from the cycle prevents its interaction with the catalyst driving this sequence forward. It should be noted that the hemiaminal compound is extremely acid sensitive - readily dehydrating to the piperidine ring system in the presence of trace acid. However it is worth noting that such compounds might offer a potential access to 4-substituted piperidine natural products in an enantiopure form such as halocyclamine. On the other hand dihydroxylation of the enamine followed by base cyclisation could potential generate bridged C-9 oxy morphans such as kopsone. Alternatively a second undesired pathway can consume **I** where via the formation of a dienamine intermediate (see section 3.9.2 for more details) the *trans* enal passes to the *cis* form in small quantities. This compound can then cyclise to a 6-membered intermediate which then dehydrates and oxidizes with elimination of the sulfamide group. It should be noted that the postulated by-products formed are speculative based on analysis of crude NMR spectra.

After completion of the organocatalyzed phase of the reaction the formation of the morphan ring system is initiated by the addition of base which causes a small amount of the hemiaminal **II** to revert to the aldehyde form.[100] This then undergoes an aldol reaction with the ketone followed by a dehydration reaction. The sulfonamide group then undergoes an aza-Michael reaction to give the morphan ring system which is protonated from the less hindered top face to give the observed product which can then tautomerise to the enol form.

[100] Since only a small amount of aldehyde is formed at any one time during the reaction it is less susceptible to lowering of the *ee* by retro Michael processes which are observed in the octahydroindole series.



Scheme 3.9 Proposed mechanism for reaction and side reactions.

3.9 Evaluation of the scope of the reaction

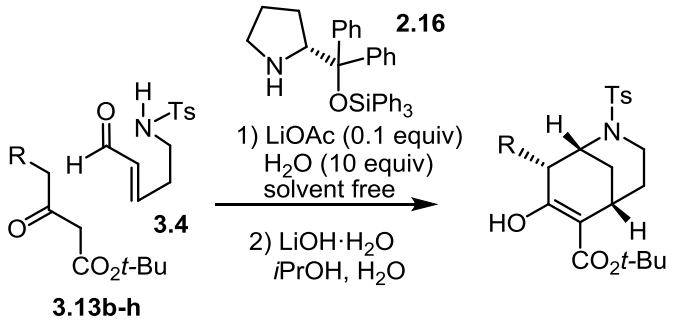
3.9.1 Modifying the β-keto ester component

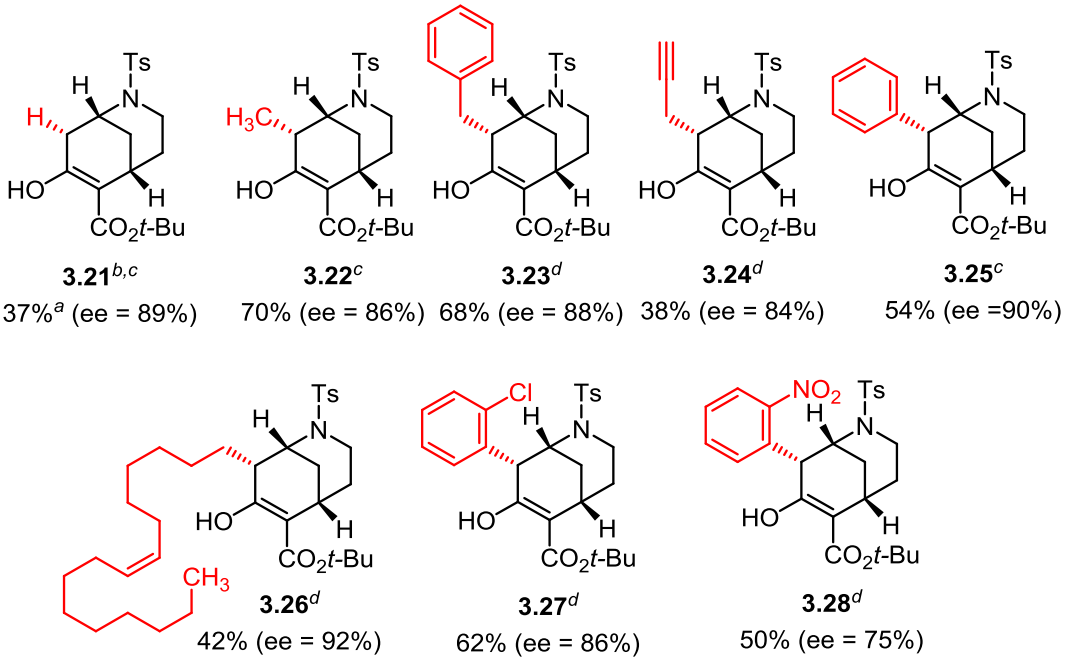
To explore the scope of the reaction, a number of varied β-keto ester substrates (**3.13b-h**)[101] were used in the coupling reaction. As can be seen in Table 3.3, the reaction works with a wide range of substrates, including both aliphatic and aromatic substituents. Mainly the compounds were isolated as the enol tautomeric form but depending on the substrate varying proportions of the keto were also obtained (only the enol form is shown for clarity). The 8-substituents formed are potential precursors for various natural products such as morphine (**3.21**, R = H,), kopsone and daphniyunnine A (**3.22**, R = Me) or the madangamine alkaloids (**3.26**, R = alkyl). Compounds bearing a propargyl substituent (**3.24**) or allyl (**3.14**) could be used to form five membered ring systems with the nitrogen to give tricyclic moieties as found in strychnos alkaloids, daphyniphyllum alkaloids. On other hand, aromatic group with a suitable *o*-phenyl substituent are potential precursors such as **3.27** and **3.28**[102] to tetracyclic indolemorphans structures present in many interesting products such as strychnos alkaloids (e.g. strychnine, akuammicine, geissoschizoline).

Although in some cases the yields were moderate, we believe this reflects difficulties in mixing the reagents under solvent-free conditions on a small scale. Additionally, the reactions were not extensively optimized and it is likely that they could be improved on a case by case manner.

[101] β-keto esters were prepared by coupling the correpsponding carboxylic acid with Meldrum's acid using DCC, followed by refluxing in *t*-BuOH. For an early use of this methodology, see: Li, B.; Franck, R. W: *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629-2634.
[102] For commentary on the reduced ee for this compound see section 3.9.3.

Table 3.3 Synthesis of C-8 substituted morphans





[a]Conditions 2 equiv β-keto ester **3**, 1 equiv enal, 10% catalyst , 24 h then add *i*PrOH (4 mL/mmol of enal), LiOH.H_2O (3 equiv), H_2O (10 equiv), 24 h. [b] step ii required 48 h to reach completion. [c] Forms predominantly or exclusively as the enolic form. [d] Forms as a mixture of enol/keto forms, yields are given for both forms combined. For the tautomer ratio, see experimental section.

3.9.2 Introducing substituents on the enal unit: synthesis of 4-substituted morphans

Substituents at the 4-position of the morphan ring (which can be present in both epimeric forms) feature in a large number of morphan natural products[76] (figure 3.5). The introduction of this substituent is particularly non-trivial and as such is often a determinant in the design of these types of compounds.

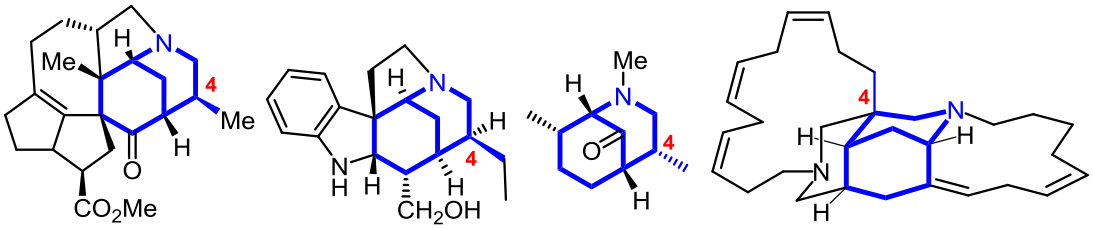
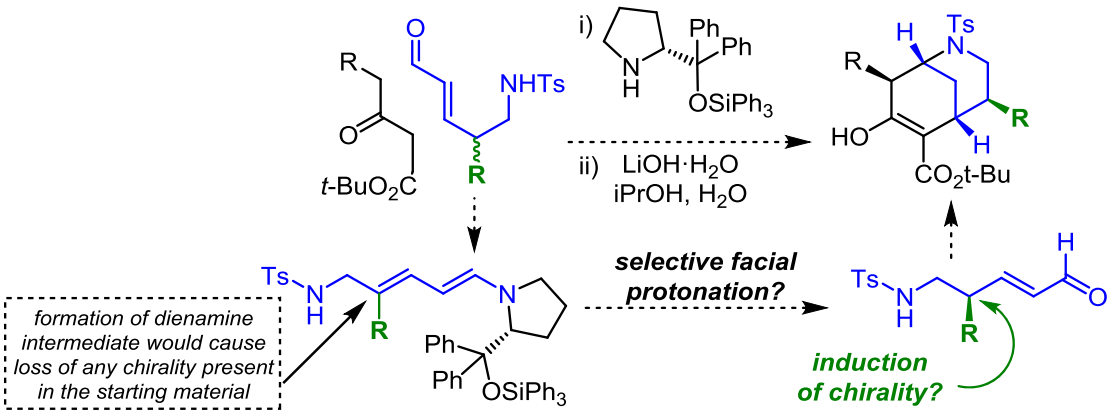


Figure 3.5 Morphan containing natural products subtituted at the 4 position.

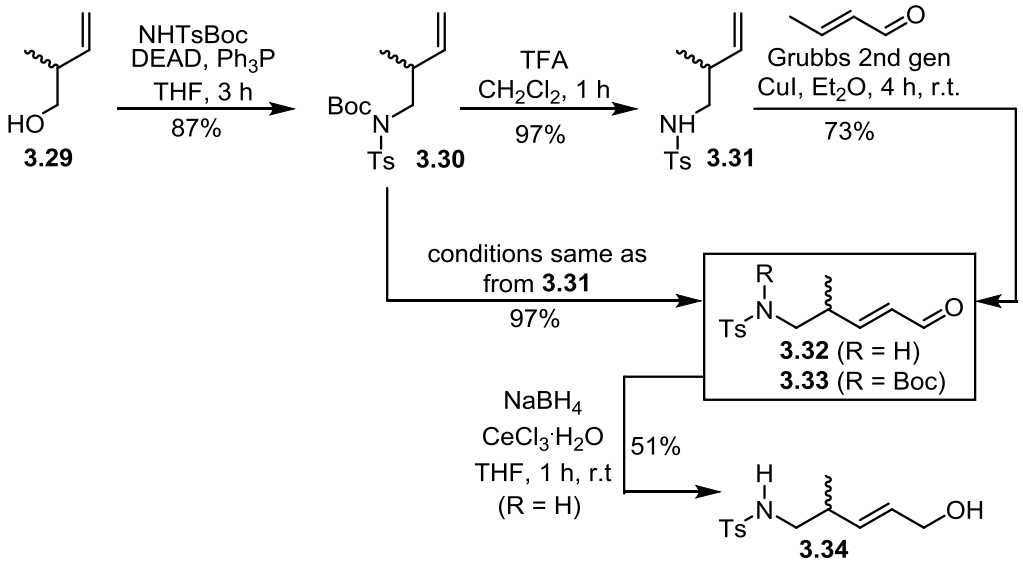
To adapt our methodology to incorporate this substituent would imply the use of an enal with an allylic substituent. The synthesis of this type of compound is particularly non trivial[103] and moreover we faced the likely possibility that under the reaction conditions the chiral centre would likely undergo racemization via the dienamine intermediate (scheme 3.10). Alternatively we thought this might work in our favour via a selective facial protonation reaction in which transfer of chirality from the organocatalyst could induce the required chiral centre.[104] There presented 2 possible approaches (i) induce the chirality and then cyclise under basic conditions via a diastereoselective reaction (ii) use organocatalysis conditions to form the required enal and couple the β-keto ester giving double stereo control.

[103] For an example of preparation of an alkene precursor to these compounds which could then be used in a cross metathesis reaction to form the enal see: Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. **1993**, *115*, 6997–6998.
[104] For an excellent review on use of dienamine catalysis see: Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869–4883.



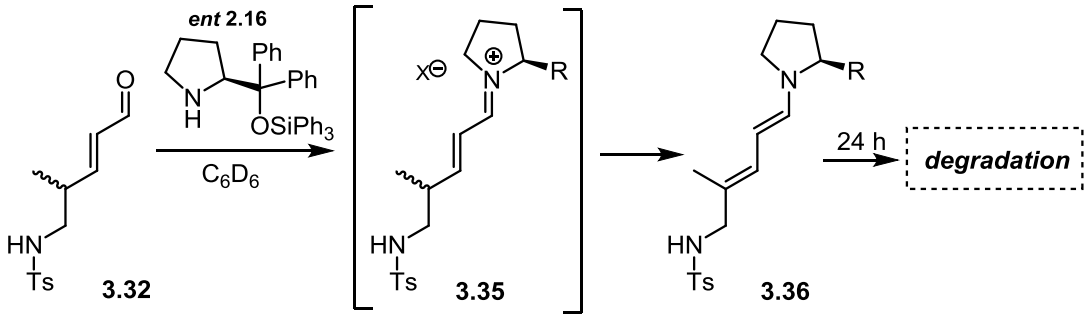
Scheme 3.10 Strategy to 4-substituted morphans

To evaluate this strategy we began by synthesizing the enals **3.32** and **3.33** which we wanted to expose to organocatalyst **2.16** to see if we observed any enantioenrichment of the racemic enal. Commercially available alkene **3.29** was converted via Mitsonobu reaction to **3.30**. Removal of the Boc group with TFA followed by cross metathesis reaction with Grubbs 2[nd] gen catalyst with CuI as additive under the conditions developed by Lipshutz[85] gave the enal **3.32**. The enal **3.33** was prepared in an analogous manner but omitting the Boc deprotection step. Luche reduction of **3.32** gave **3.34** which was expected to be more easier to analyse by HPLC.



Scheme 3.11 Synthesis of starting material

We began by trying to observe the formation of the dienamine intermediate **3.35** in a solution C_6D_6 analogous to the experiments carried out by Jorgensen[93] who observed that more than 50% of the catalyst was present in the form of the dienamine with next to no imine being present despite this being the reactive species. Thus, to a solution of **3.32** in C_6D_6 was added catalyst *ent*-**2.16**. Immediately a rapid change in the enal was observed which underwent progressive degradation made evident by the rapid loss of all the signals in the alkene region (figure 3.8).



Scheme 3.12. NMR analysis of organocatalyst and enal **3.32** in benzene

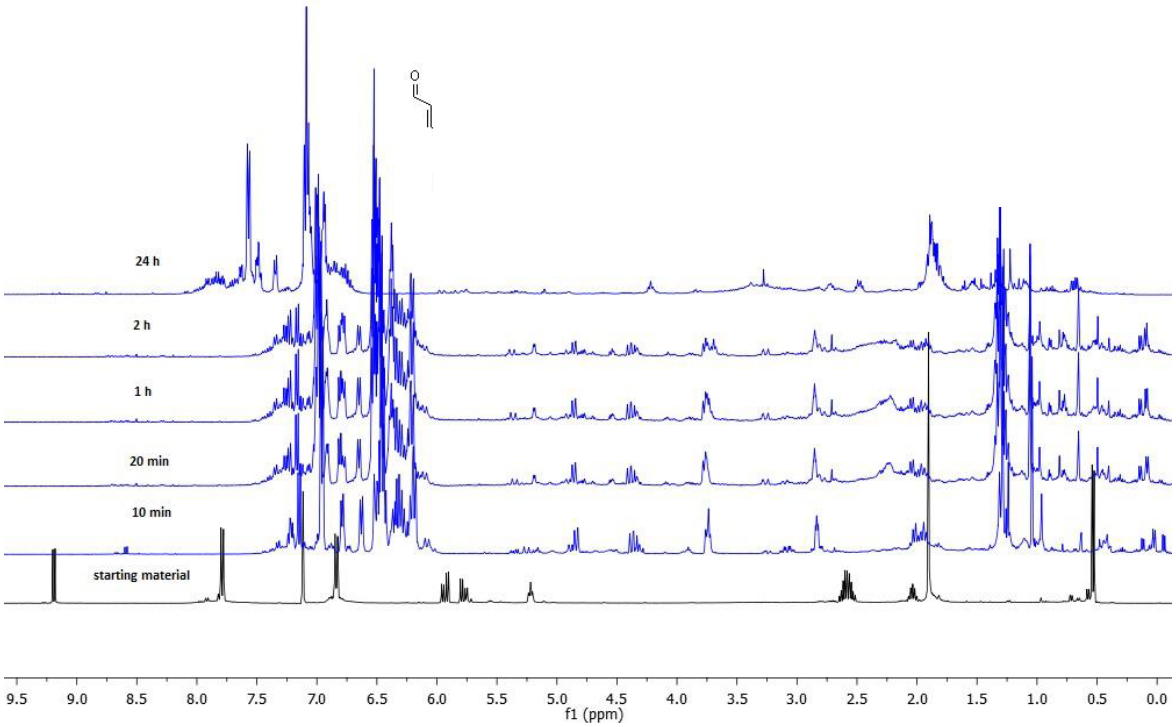
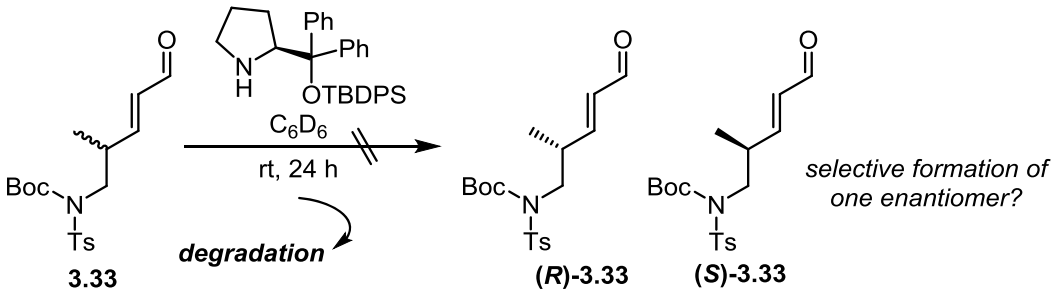


Figure 3.8 Degradation of **3.32** as observed by 1H NMR Spectroscopy.

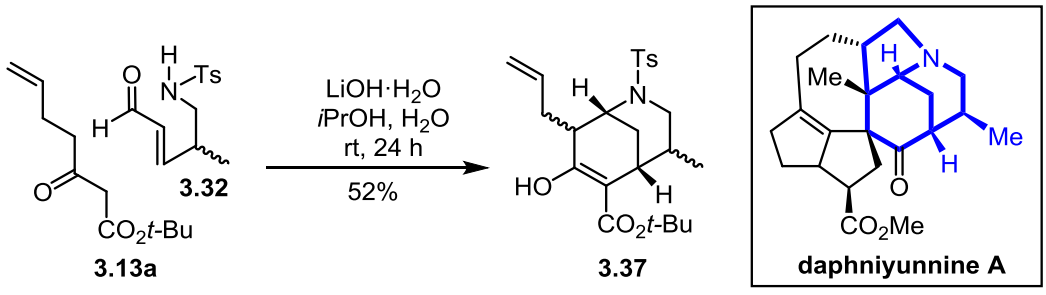
We propose that the increased formation of the dienamine intermediate brought about by presence of the methyl substituent leads to an even more rapid formation of

the *cis* enal which cyclises to various aromatic products (see section 3.8). To avoid this we evaluated the behaviour of **3.33**. Potentially the catalyst could induce the desired chirality to give **3.33** in enantiopure form which could then be used to form the desired morphans using $LiOH \cdot H_2O$. However by NMR under the same conditions as before we found that this compound also underwent a rapid conversion to a new none identifiable compound (albeit over a longer time frame).



Scheme 3.13 NMR analysis of organocatalyst and enal **3.33** in benzene

Given the problems with the organocatalyzed version of the reaction we tried coupling **3.32** under racemic conditions ($LiOH \cdot H_2O$, *i*PrOH, H_2O) which gave the compound **3.37** as an equal mixture of C-4 epimers which could not be readily separated to accurately determine the stereochemistry of the newly formed stereocenters. It seems promising though that the through deployment of the correct enantiomer of **3.32** it should be possible to obtain **3.37** as a unique diastereoisomer. This general structure could be an advanced intermediate to the daphynphyllum alkaloids such as daphynunine A.



Scheme 3.14 NMR analysis of organocatalyst and enal **3.32** in benzene

3.9.3 Synthesis of indolomorphans

The indolomorphan motif is encountered as a key structural element in many morphan alkaloids (figure 3.9).

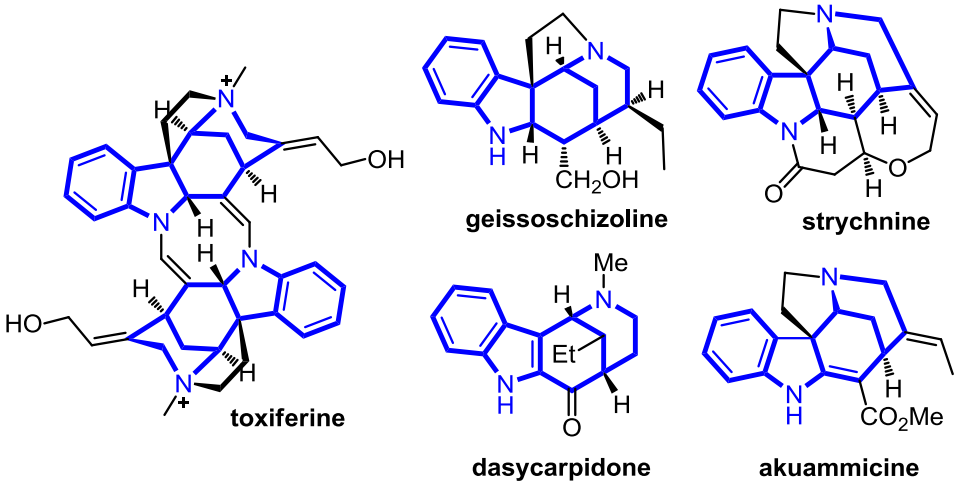
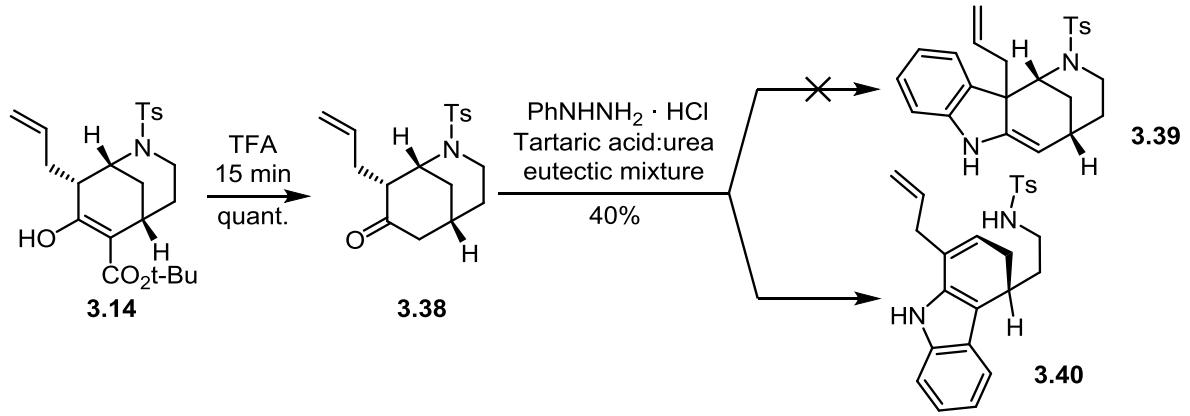


Figure 3.9. Natural products containing the indolomorphan nucleus.

Using methodology developed for the synthesis of the morphan nucleus we proposed that formation of the indole moiety could be added to the initial tandem reaction to generate these types of structures rapidly in a one-pot manner. We considered two approaches (i) introduction of the aromatic moiety via a Fischer indole reaction[105] or (ii) incorporation of the aromatic unit into the β-keto ester starting material followed by an appropriate indole ring forming reaction using the *ortho* substituent on the aromatic ring.

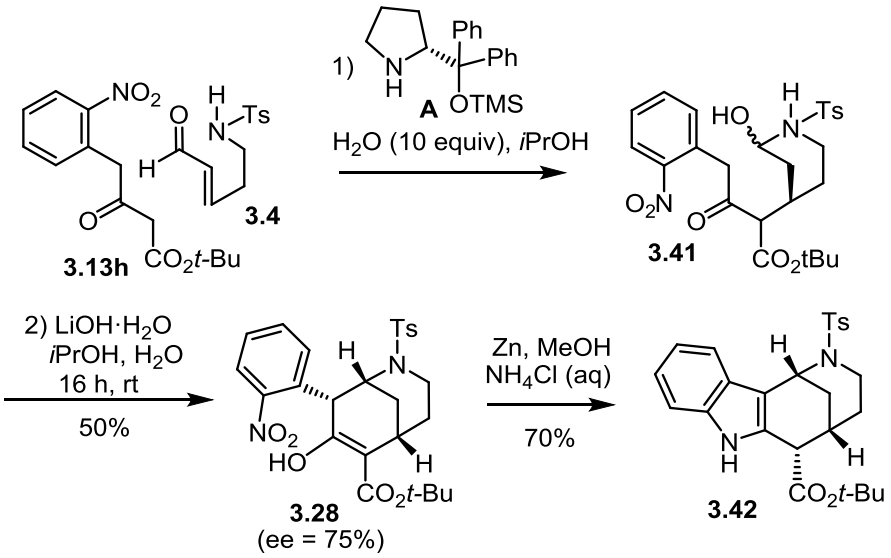
To test the first approach we took the allyl substituted compound **3.14** and removed the *t*-butyl ester group with TFA to give **3.38**. This product was added to the eutectic urea:tartaric acid mixture followed by addition of the phenylhydrazine. However, the indolemorphan formed on the less substituted side of the ring opened product (scheme 3.14).

[105] Gore, S.; Baskaran, S.; König, B.; *Org. Lett.* **2012**, *14*, 4568-4571. In the several examples presented the indole ring forms on the more substituted side forming a quaternary centre.



Scheme 3.14 Attempted Fischer Indole synthesis of allyl morphan nucleus

The 2-nitrophenyl β-keto ester **3.13h** was coupled with enal **3.4** under modified conditions[106] to give **3.41** which was then cyclised with $LiOH{\cdot}H_2O$ to morphan **3.28** possessing a latent indole moiety (Scheme 3.15). Treatment with Zn, NH_4Cl(aq)[107] gave indole **3.42**, which contains the core structure of curan-type alkaloids,[108] showing the potential of this methodology to rapidly access complex molecular scaffolds in a simple, straightforward manner.



Scheme 3.15. Synthesis of indolomorphan **3.42** via nitrophenyl condensation**.**

[106] Due to the highly crystalline nature of **3.13h** and the coupled product, mixing of the reagents proved difficult and the conditions of the initial organocatalytic step had to be modified. Heating was used to melt the substrates and the catalyst was switched to the Hayashi catalyst, which, unlike catalyst **2.16**, exists as an oil.

[107] Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *Org. Biomol. Chem.* **2008**, *6*, 772–778.

[108] Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am Chem. Soc*, **1997**, *119*, 7230-7240.

3.9.4 A one-pot assembly of indolomorphans via 'uninterrupted' sequence.

Given the success of this previous procedure we proposed it might be possible to unite three catalytic cycles and the indole forming step in a one-pot operation showing it possible to generate complex molecular architectures from a simple alkene such as **3.7**[109] (scheme 3.16a).

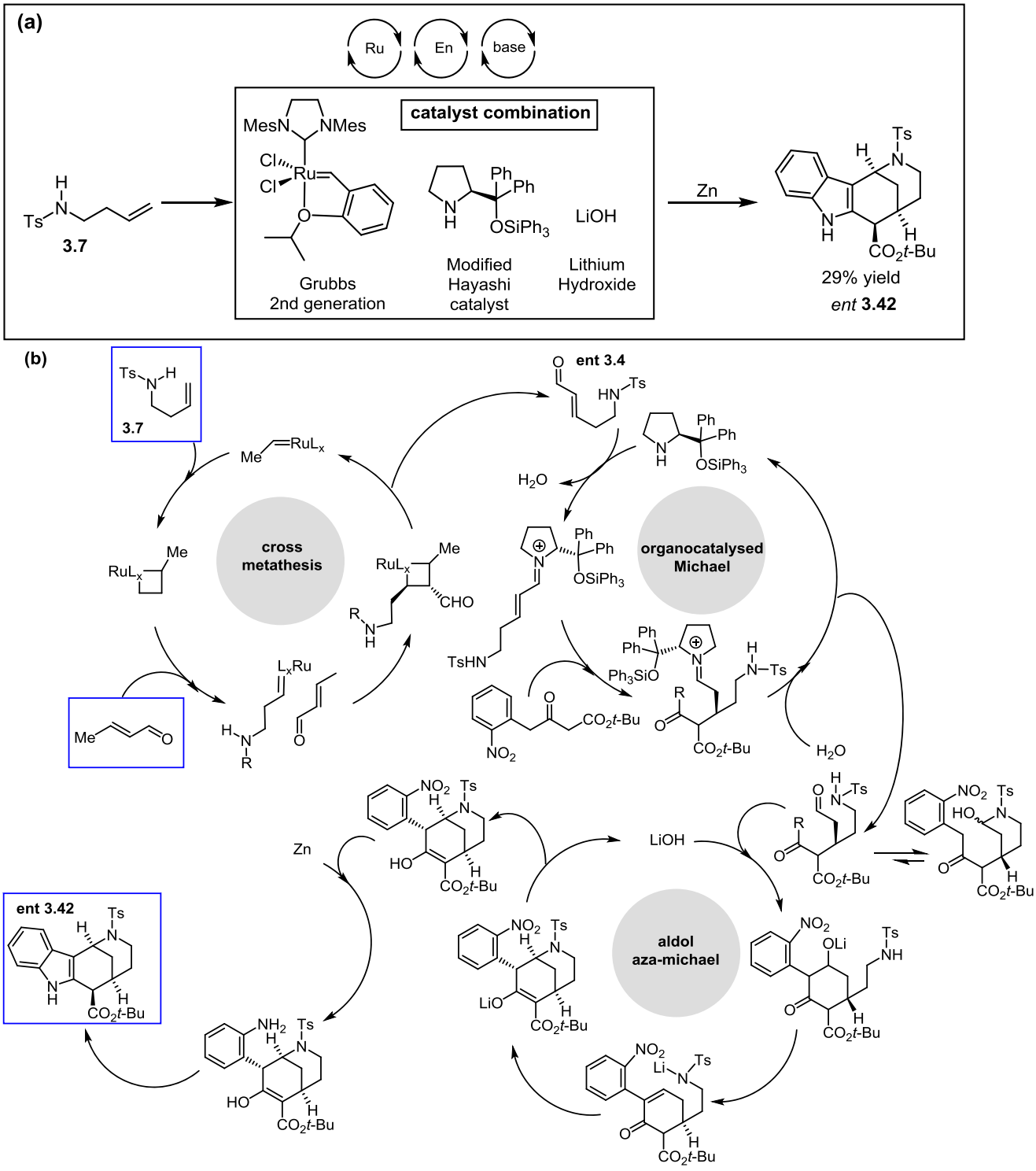
The 3 catalytic cycles are: (i) Formation of the enal via metathesis (ii) organocatalysed Michael reaction (iii) Lithium hydroxide tandem cyclisation sequence to give morphan nucleus. Finally reduction of nitro group to the amine followed by spontaneous ring closure would form the indole ring system (scheme 3.16b).

Starting from alkene **3.7**, a cross metathesis reaction gave the enal **3.4** which after removal of the solvent (along with excess crotonaldehyde) was treated with the organocatalyst **2.16** and the nitrophenyl substituted β-keto ester. After 24 h the mixture was dissolved in *i*-PrOH and treated with LiOH. After a further 24 h, Zn and ammonium chloride was added and the reaction stirred for an additional 5 h. Filtration, work-up and purification by column chromatography gave ent-**3.42** in 29% yield.

3.10. Summary and Conclusions

A general organocatalysed method for the synthesis of morphans was achieved based on an analogous Robinson-Aza-Michael reaction type sequence developed for the decahydroquinolines and octahydroindole ring systems. The reaction was explored to advanced building blocks in the synthesis of numerous morphan containing natural product systems.

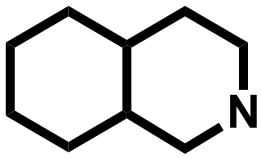
[109] For a similar sequence based on a cross metathesis reaction and an organocatalytic reaction see: Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353.



Scheme 3.16. Synthesis of indolomorphan core via a tandem one-pot via 'uninterrupted' sequence (a) overview of the reaction unifying 3 catalytic cycles (b) mechanism of the reaction.

CHAPTER 4:

SYNTHESIS OF ENANTIOPURE HYDROISOQUINOLINES VIA ORGANOCATALYSIS



4.1 The Hydroisoquinolines Nucleus: Objectives

So far we have studied the successful adaption of the initially developed tandem reaction developed for the synthesis of the decahydroquinoline nucleus to the octahydroindole nucleus and the morphan nucleus. To expand the potential of the developed methodology we decided to focus on developing ways to construct the hydroisoquinoline nucleus. This structural motif is present in a large number of natural products and for which at the start of this work no organocatalytic method had been described.[110] To achieve this we expected to draw heavily on ideas and structures developed in the previous chapters. The core approaches we investigated are presented below and can be divided into 3 different strategies (figure 4.1).

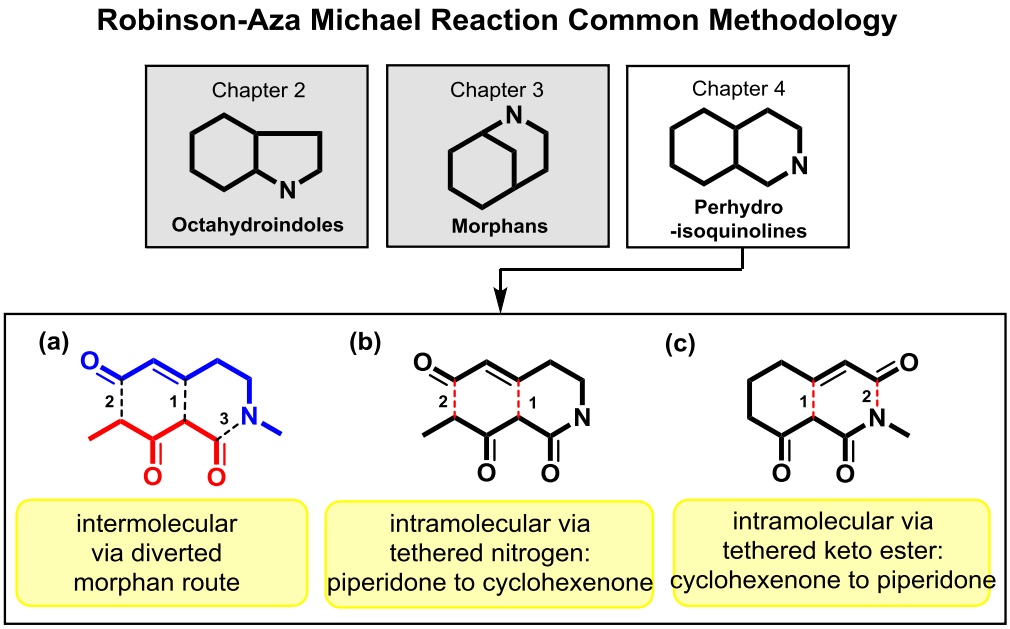


Figure 4.1 Adaptation of IMAMR methodology to perhydroisoquinoline nucleus

As before an overview of the hydroisoquinoline nucleus is presented including a survey of natural products that feature this motif and methods that have been developed to construct it.

[110] During the course of this thesis the group of Jorgensen published an organocatalytic method to hydroisoquinolines based on a dienamine Diels-Alder reaction see: Gómez, C. V.; Cruz, D. C.; Mose, R.; Jørgensen, K. A. *Chem. Commun.* **2014**, *50*, 6035–6038.

4.2 Hydroisoquinoline natural products and pharmaceuticals

Many important natural products have the hydroisoquinoline motif embedded in their structures (Figure 4.2) Functionalized hydroisoquinolines[111] are a key architectural feature in a wide array of biologically active natural products such as morphine,[64] yohimbine-reserpine type,[112] madangamine alkaloids,[71] manzamine alkaloids[113] which have received special attention due to their biological activities; particularly to their cytotoxicity and/or antitumor activities. The manadomanzamines[114] A and B (formed from an unprecedented rearrangement of the manzamine skeleton) exhibit significant activities against mycobacterium tuberculosis and human immunodeficiency virus (HIV-1) and moderate activity against several AIDS opportunistic infections.

This structure is also found in a number of pharmaceuticals including several HIV protease inhibitors as nelfinavir[115] and saquinavir.[116] The NVP-ACQ090[117] (potent and selective antagonist at the somatostatin sst3 receptor). Binaltorphimine[118] (opioid antagonist), TAN67[119] (selective δ-opioid agonist analgesic properties, induces dopamine release and protects both heart and brain tissue from hypoxic tissue damage), ciprefadol[120] (an opioid analgesic which is a mixed agonist–antagonist at μ-opioid receptors and can partly block the effects of morphine at low doses, though at higher doses it acts more like a full agonist).

[111] For previous work in this field by our group see: Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 4661–4664.
[112] (a) Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. *J. Org. Chem*. **2003**, *68*, 5274–5285, and references cited therein. (b).Chen, F-E.; Huang, J. *Chem. Rev.* **2005**, *105,* 4671–4706.
[113] Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201-6258.
[114] Peng, J.; Hu, J.F.; Kazi, A.B.; Li, Z.; Avery, M.; Peraud, O.; Hill, R.T.; Franzblau, S.G.; Zhang, F.; Schinazi, R.F.; Wirtz, S.S.; Tharnish, P.; Kelly, M.; Wahyuono, S.; Hamann, M.T. *J. Am. Chem. Soc.* **2003**, *125*, 13382–13386.
[115] Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979–3985.
[116] Wiltshire, H. R.; Prior, K. J.; Dhesi, J.; Trach, F.; Schalageter, M.; Schönenberger, H. *J. Labelled Cpd Radiopharm. XLI,* **1998**, 1103-1126.
[117] Bänziger, M.; Cercus, J.; Hirt, H.; Laumen, K.; Malan, C.; Spindler, F.; Strubera, F.; Troxlerb, T.; *Tetrahedron: Asymmetry* **2003**, *14*, 3469–3477.
[118] Kishiokaa, S.; Kiguchi, N.; Kobayashi, Y.; Yamamotoa, C.; Saikaa, F.; Wakidaa, N.; Ko, M-C.; Woods, J. H. *Neuroscience Letters* **2013**, 552, 98–102.
[119] Nagase, H.; Yajima, Y.; Fujii, H.; Kawamura, K.; Narita, M.; Kamei, J.; Suzuki, T.; *Life Sci.* **2001**, *68*, 2227-2231.
[120] Judd, D. B.; Brown, D. S.; Lloyd, J. E.; McElroy, A. B.; Scopes, D. I. C.; Birch, P. J.; Hayes, A. G.; Sheehan, M. J. *J. Med. Chem.* **1992**, *35*, 48-56.

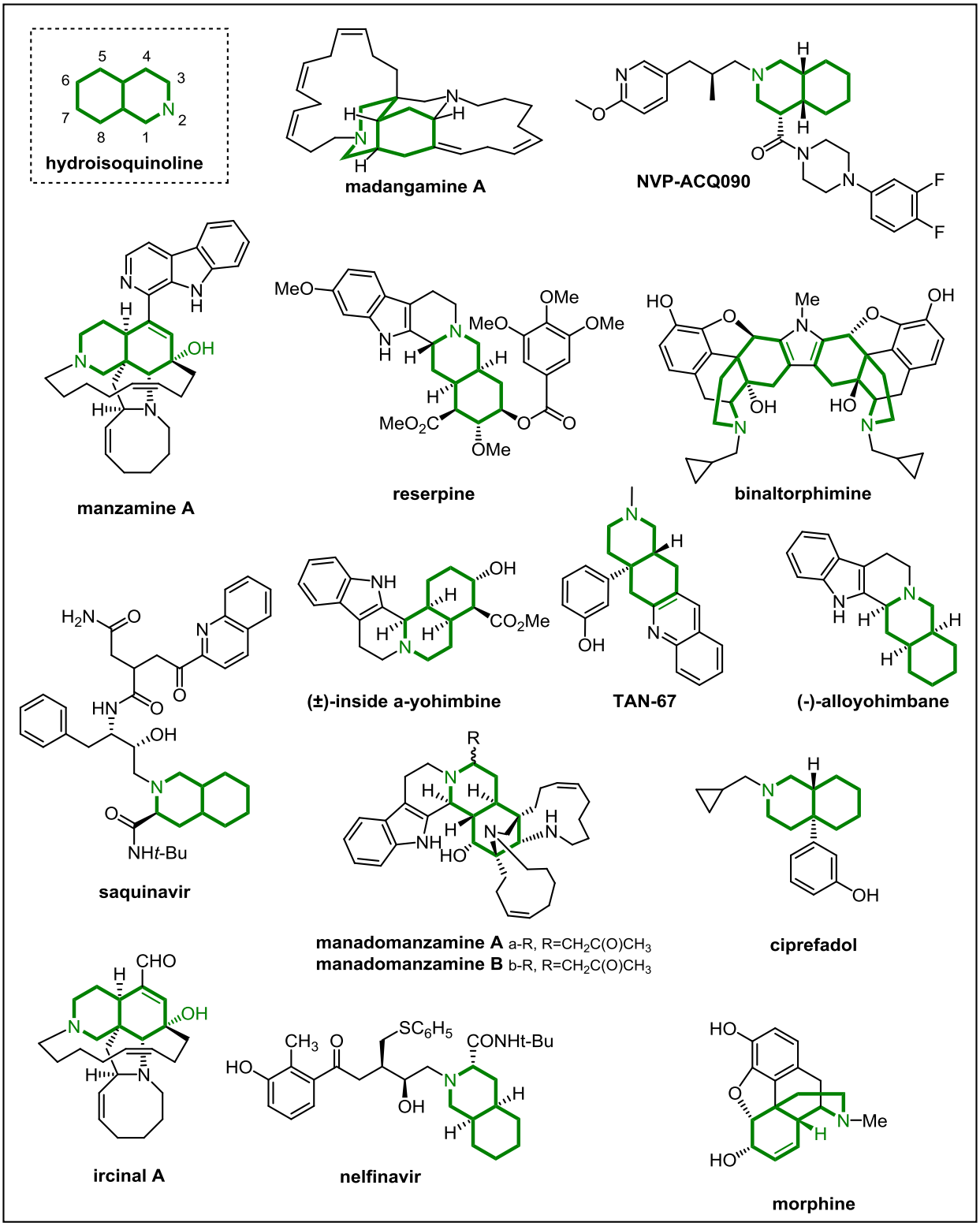


Figure 4.2 Natural products and pharmaceuticals that contain the hydroisoquinoline nucleus.

4.3 Synthesis of enantiopure hydroisoquinolines

So far the methods to access this ring system in enantiopure form have relied principally on chiral pool or chiral auxiliary strategies. As stated in the introduction no organocatalytic methods have been developed except for the recent work of Jørgensen[110] work which was published during the course of this thesis. The methods are briefly discussed below ordered by key reaction type (scheme 4.1).

(a) Diels Alder: Trova developed a strategy for the asymmetric synthesis of optically active hydroisoquinolines employing an aza-Diels-Alder reaction as the key step involving a diene and an imine bearing a chiral inductor (scheme 4.1ai).[121] Pedrosa showed that the chiral hydrobenzoxazines could also be used in an intramolecular Diels-Alder reactions. After assembly of the bicyclic structure, stereoselective ring opening of the cyclic N,O-acetal gave the hydroisoquinoline structure (scheme 4.1aii)[122] The only example of organocatalysis to form the hydroisoquinoline ring structure is that of Jørgensen who used an organocatalytic Diels–Alder/nucleophilic ring-closing reaction cascade sequence as the key step.[110] However it should be noted that the substitution pattern on the formed ring system is not evidently directly applicable to the target orientated synthesis of the natural products outlined in figure 4.2.

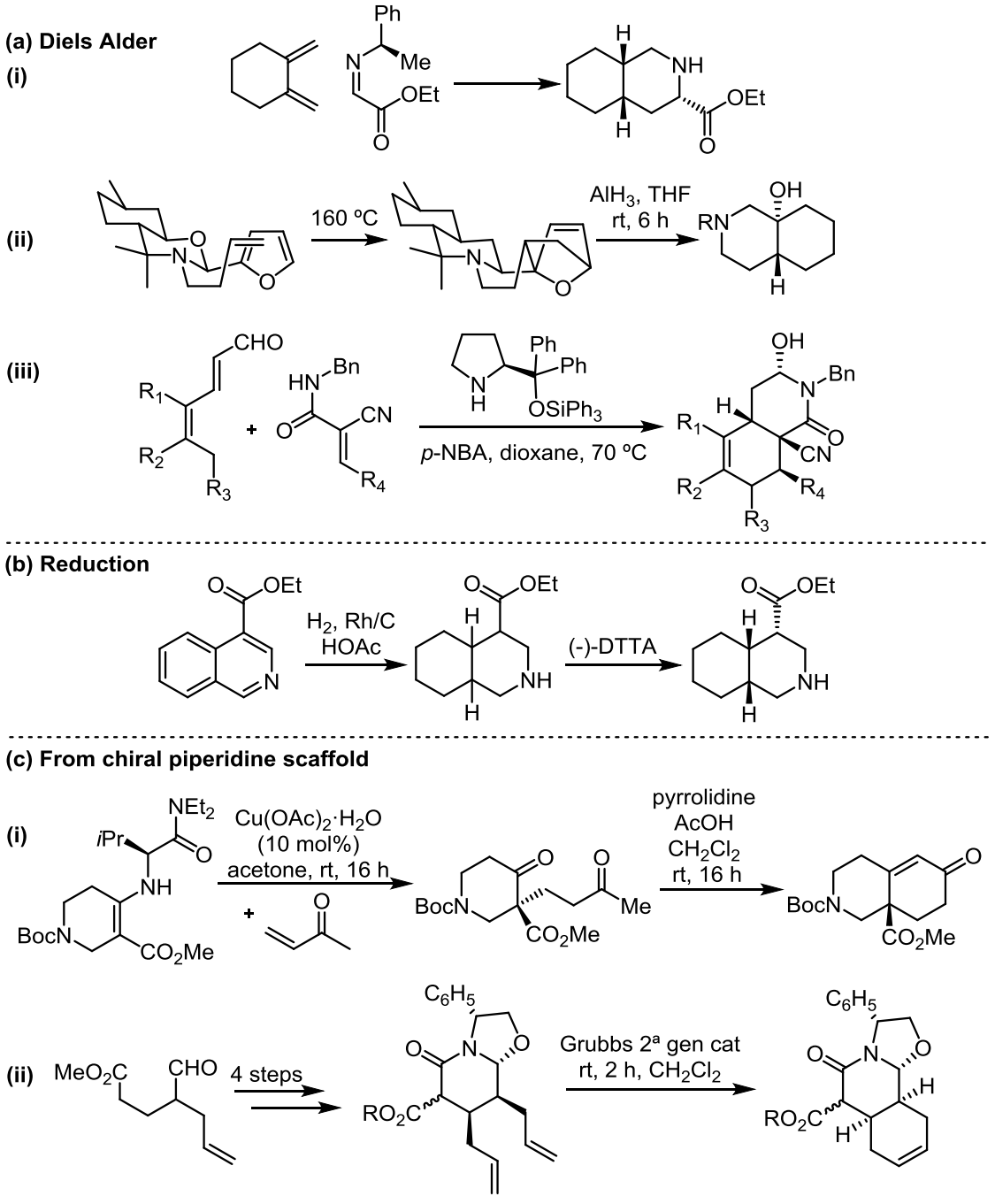
(b) Chiral Isoquinoline reduction: Bänzinger has developed a strategy for obtention of enantiopure hydroisoquinolines using a Rh-catalyzed high pressure hydrogenation as the key step. This leads to a mixture of isomers which were resolved to a single product via crystallisation.[123]

(c) Using chiral piperidine scaffold: Christoffers used a chiral enamine (embedded in a piperidine ring scaffold) in a cooper catalyzed Michael reaction with methyl vinyl ketone. Subsequent Robinson annulation provided the corresponding octahydro-6-isoquinolone derivative (scheme 4.1ci)[124]

Bosch and Amat have also employed chiral piperidines (formed from phenylglycinol) en route to cis-perhydroisoquinolines. Cuprate addition of an allyl group and closure

[121] Trova, M. P.; McGee, K. F. *Tetrahedron* **1995**, *51*, 5951–5954.
[122] Andre, C.; Nieto, J.; Pedrosa, R. **1998**, 8570–8573.
[123] Ba, M.; Cercus, J.; Hirt, H.; Laumen, K.; Malan, C.; Spindler, F.; Troxler, T. **2003**, *14*, 3469–3477.
[124] Christoffers, J.; Scharl, H.; Frey, W.; Baro, A. *Org. Lett.* **2004**, *6*, 1171–1173.

of the carbocyclic ring by a ring-closing olefin metathesis gave the hydroisoquinoline ring system[125] which was later successfully employed in the first total synthesis of Madangamine D.[71b]



Scheme 4.1 Strategies to access the hydroisoquinoline skeleton.

[125] Amat, M.; Pe, M.; Minaglia, A. T.; Bosch, J. *Org. Lett.* **2005**, 4661–4664.

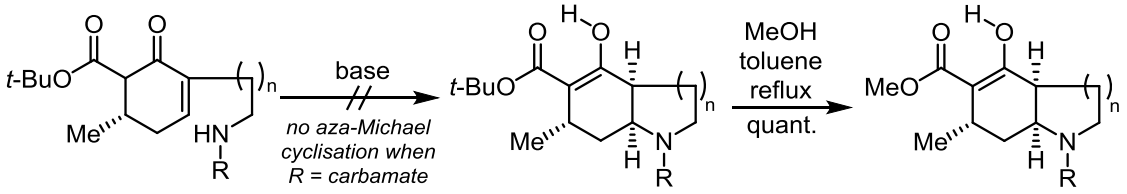
4.4 Strategy to access hydroisoquinoline ring system via diverting the morphan route

To construct the hydroisoquinoline nucleus we planned to adapt the strategy developed for the morphan ring system but divert the nitrogen ring forming step from an aza-Michael reaction to a condensation reaction on the butyl ester (Scheme 4.2).

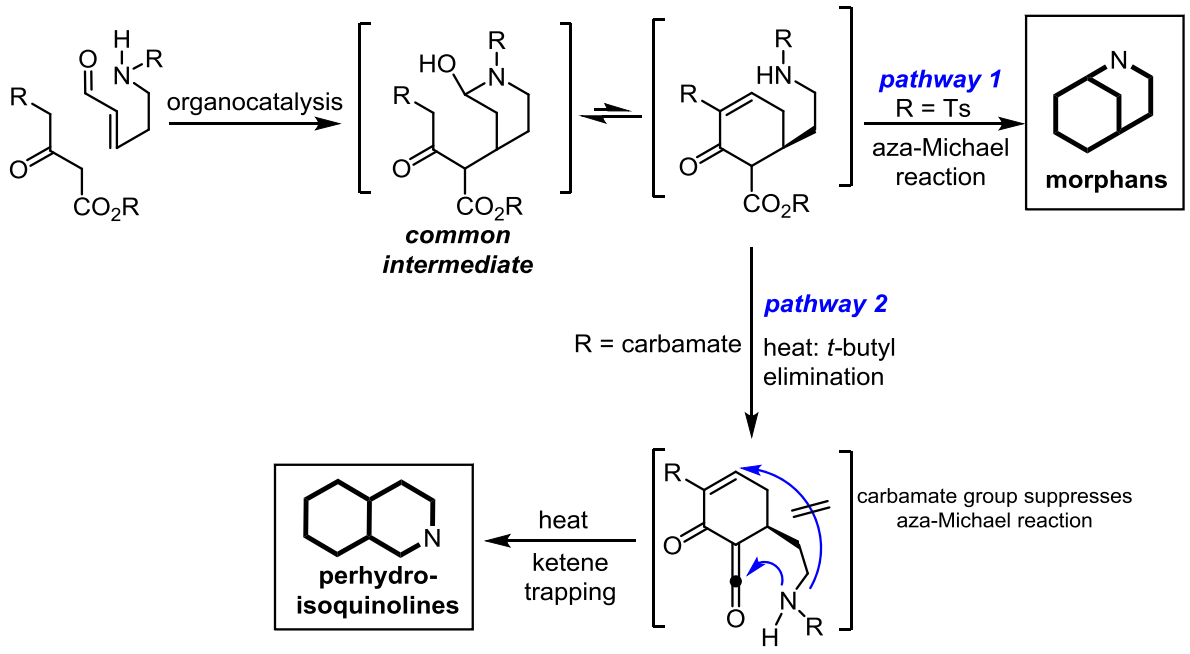
4.4.1 Overview of Strategy

Based on our experience to date of the IMAMR reaction we know that the use of the Boc on the nitrogen leads to no aza-Michael cyclisation.[17] In addition, we observed in the course of decahydroquinoline synthesis that the *t*-butyl ester group of the β-keto ester was prone to eliminate at elevated temperatures to form a ketene intermediate which can then trapped by a nucleophile - usually the solvent[18] (scheme 4.2a). Our strategy to access the hydroisoquinoline nucleus was to take these 2 observations into account and apply them to our successfully developed morphan synthesis methodology (scheme 4.2b). Essentially this was based on the idea that the morphan bearing the ester group and the hydroisoquinoline system are essentially constitutional isomers. In other words if the cyclohexenone intermediate formed via the morphan route is diverted away from undergoing an aza-Michael addition by using a carbamate protecting group which so far had been shown not to undergo the aza-Michael reaction and instead is condensed onto the ester via a reactive ketene intermediate (pathway 2). The advantage of this diverted approach is that the initial organocatalytic step to form the hemiaminal type intermediate would be the essentially the same as for the morphan route which had been extensively optimised previously and which we knew we could obtain excellent enantioselectivities.

(a) Precedents for strategy taken from decahydroquinoline and octahydroindole syntheses



(b) Overview of plan to access hydroisoquinoline ring system via diverted morphan strategy



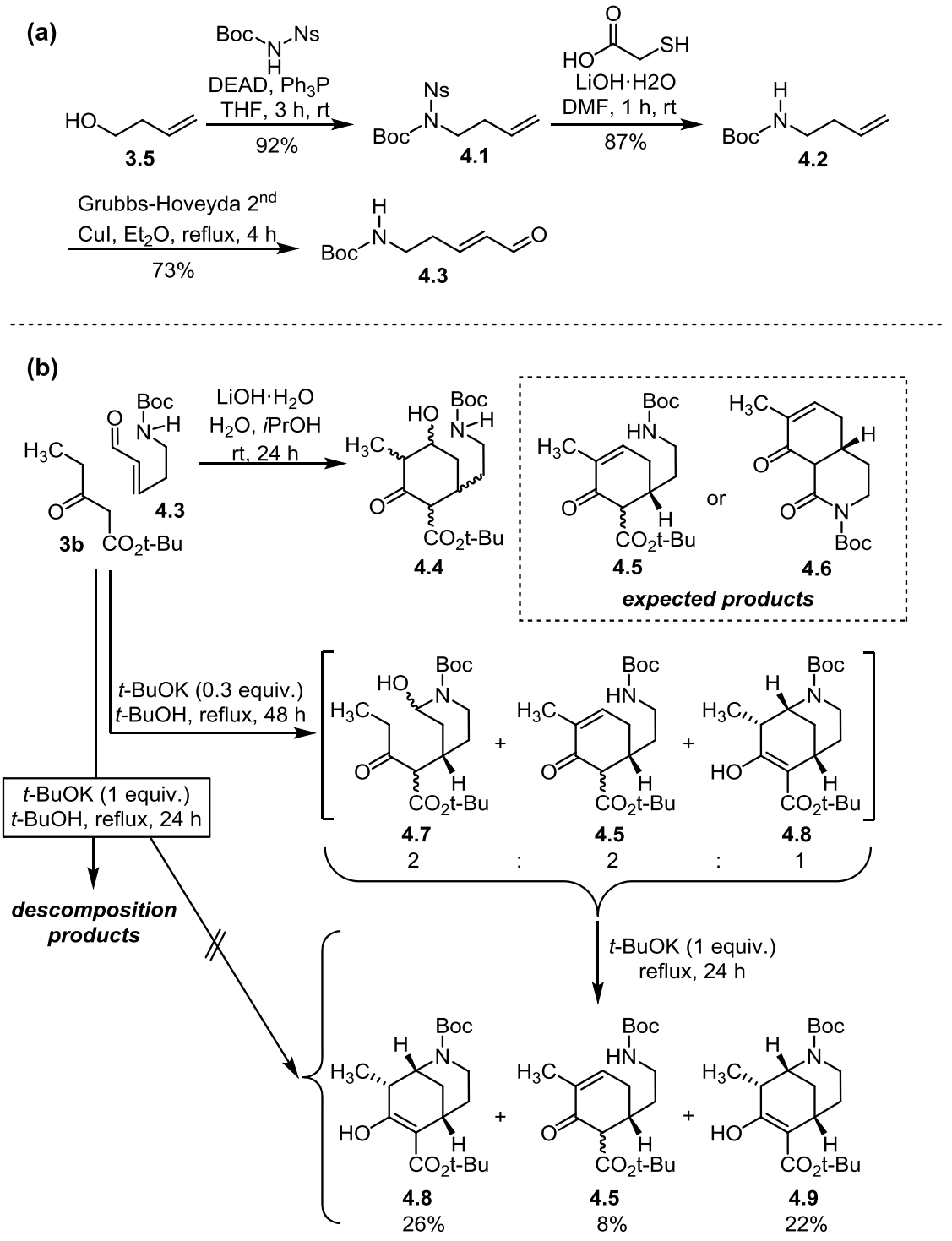
Scheme 4.2 Proposed access to the enenatiopure hydroisoquinoine nucleus via diverting the organocatalysed morphan route (a) precedents based on octahydroindole and decahydroquinoline series (b) overview of strategy.

4.4.2 Cyclisation using Boc protected enal

The enal **4.3** required to test our strategy was prepared by Mitsonobu reaction 3-butenyl alcohol with Boc protected nosylamide to give **4.1** followed by deprotection of the nosyl group to the Boc amine **4.2** and then cross metathesis reaction (Scheme 4.3a).[126] Compound **4.3** was then reacted with the methyl substituted β-keto ester **3b** under various conditions. Perhaps not surprisingly using the standard conditions of LiOH/*i*PrOH the reaction only gave essentially the non-dehydrated Robinson product **4.4** due to the aza-Michael reaction not being able to drive the reaction to completion. Switching to 0.3 equivalents of *t*-BuOK in *t*-BuOH, gave a mixture of compounds which however instead of the expected cyclohexenone **4.5** or possibly the desired hydroisoquinoline ring system **4.6**, we observed the corresponding morphan products. However, the reaction did not go to completion so we re-exposed this material to 1 equivalent of *t*-BuOK in refluxing *t*-BuOH which gave cyclohexenone **4.5** along with the morphan ring structure **4.8** and **4.9** with the substituent at the C-8 position in equatorial corresponding to the thermodynamic isomer. When the reaction was repeated by carrying out the reaction directly from **3b** and **4.3** with 1 equivalent *t*-BuOK we were surprised to find that very little of the desired product **4.9** was formed. Instead a complex mixture of products were observed that could not be discerned was formed (Scheme 4.3b).

Given the ready propensity of carbamates to cyclise in the morphan series we were forced to revaluate our synthetic plan.

[126] It should be noted that 3-butenylamine is commercially available but that it is prohibitively expensive.



Scheme 4.3 Attempted synthesis for hydroisoquinolines nucleus by diverting morphan ring forming route. (a) Synthesis of starting material enal (b) Unexpected aza-Michael cyclisation to the thermodynamic morphan ring structure.

4.4.3 Modified strategy removing Michael acceptor "in-situ"

As a result of the unexpected way in which the Boc protected nitrogen could readily undergo the aza-Michael reaction we revaluated the reaction this time employing the bisprotected enal **4.12** which was prepared from bromobutene as shown in scheme 4.4a. The idea was to form enone **4.13** and then expose it to hydrogenation conditions which would remove the double bond to prevent the undesired aza-Michael reaction pathway whilst at the same time removing the Cbz group. This would give a free benzylamine to cyclise on to the ester to give the hydroisoquinoline compound **4.15**. In theory this whole sequence could be carried out in the same flask.

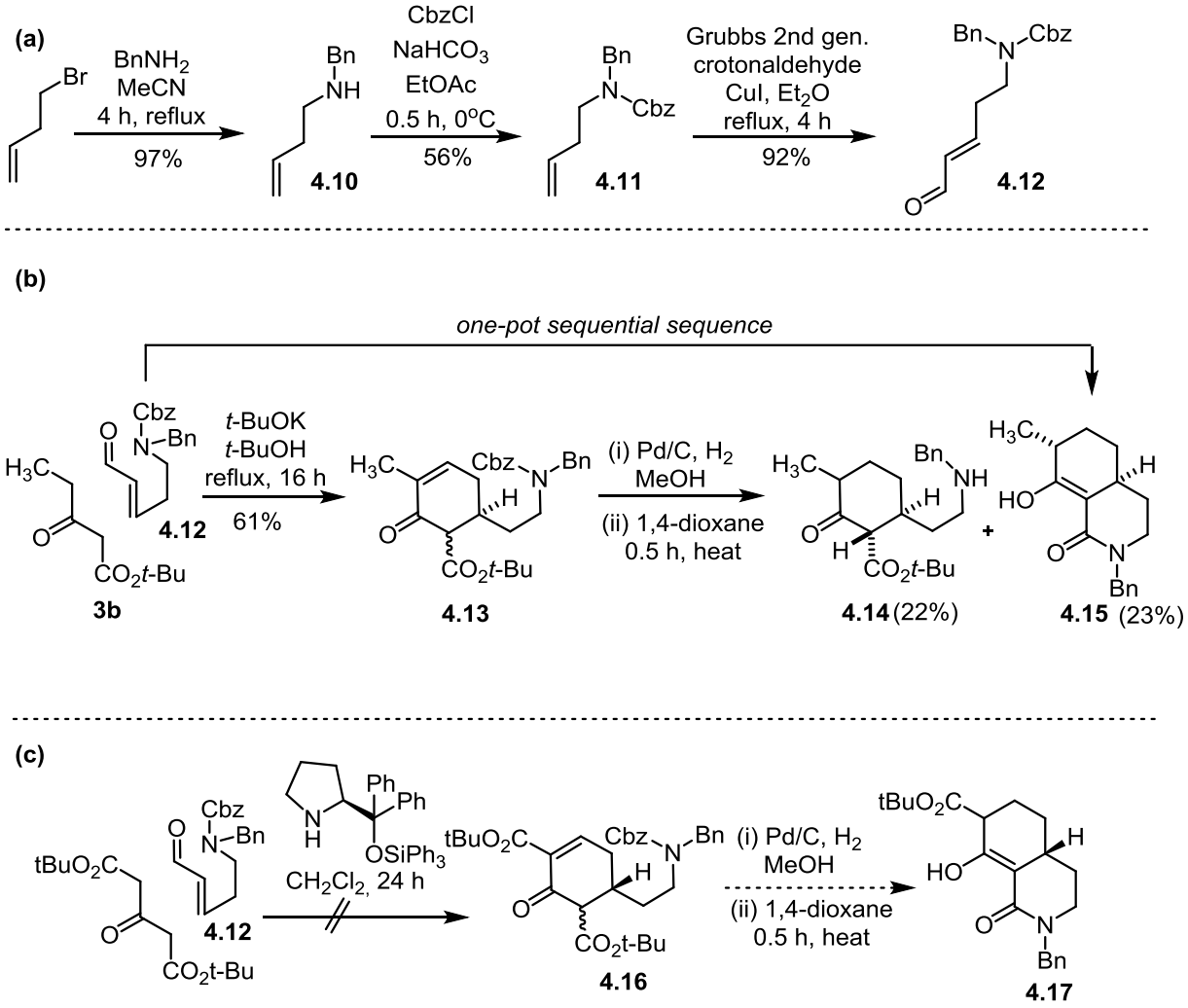
Treatment of **3.13b** and **4.12** in the presence of *t*-BuOK gave the cyclohexenone **4.13** which underwent smooth hydrogenation to remove the double bond and the benzyl group. Heating this compound in dioxane gave a mixture of 2 compounds which were identified as the desired hydroisoquinoline **4.15** (along with a small amount of the C-7 epimeric methyl product ~4:1 ratio) and the non-cyclised product **4.14** with the ester in *trans*. Given this result it is likely that the cyclisation therefore goes through a direct substitution reaction rather than the ketene type intermediate postulated (which would destroy the chirality of the β-keto ester group).

4.4.4 Using a bisketo ester as the nucleophilic component

One of the problems of driving the cyclohexenone forming step to completion can be overcome by employing a bisketo ester as the Michael donor. Indeed these products will cyclise directly in only the presence of the organocatalyst alone[127] with often the problem being overreaction via a second equivalent of the bisketo ester. We initially tried the reaction with the tosyl protected enal **3.4** used as the common test product, however the reaction progressed only as far as the heminal form and no cyclohexenone or morphan products were observed. We therefore tried the bis

[127] For examples see (a) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45-48. (b) Bertelsen, R. L. Johanssen and K. A. Jørgensen, *Chem.Commun.*, **2008**, 3016-3018. (c) E.; Sayalero, S.; Cambeiro, X. C.; Martín-Rapún, R.; Miranda, P. O.; Pericàs, M. A. *Synlett* **2011**, 464-468. For an initial example in racemic form see: Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4148–4151.

protected enal **4.12** to avoid the heminal however no product corresponding to the desired compound **4.16** was observed.



Scheme 4.4 (a) Synthesis of starting material (b) Synthesis of hydroisoquinoline nucleus via hydrogenation/condensation strategy (c) Attempted synthesis of hydroisoquinoline using organocatalysis with a bisketo ester

4.5 Intramolecular strategy via tethering of amine component to β-keto ester component

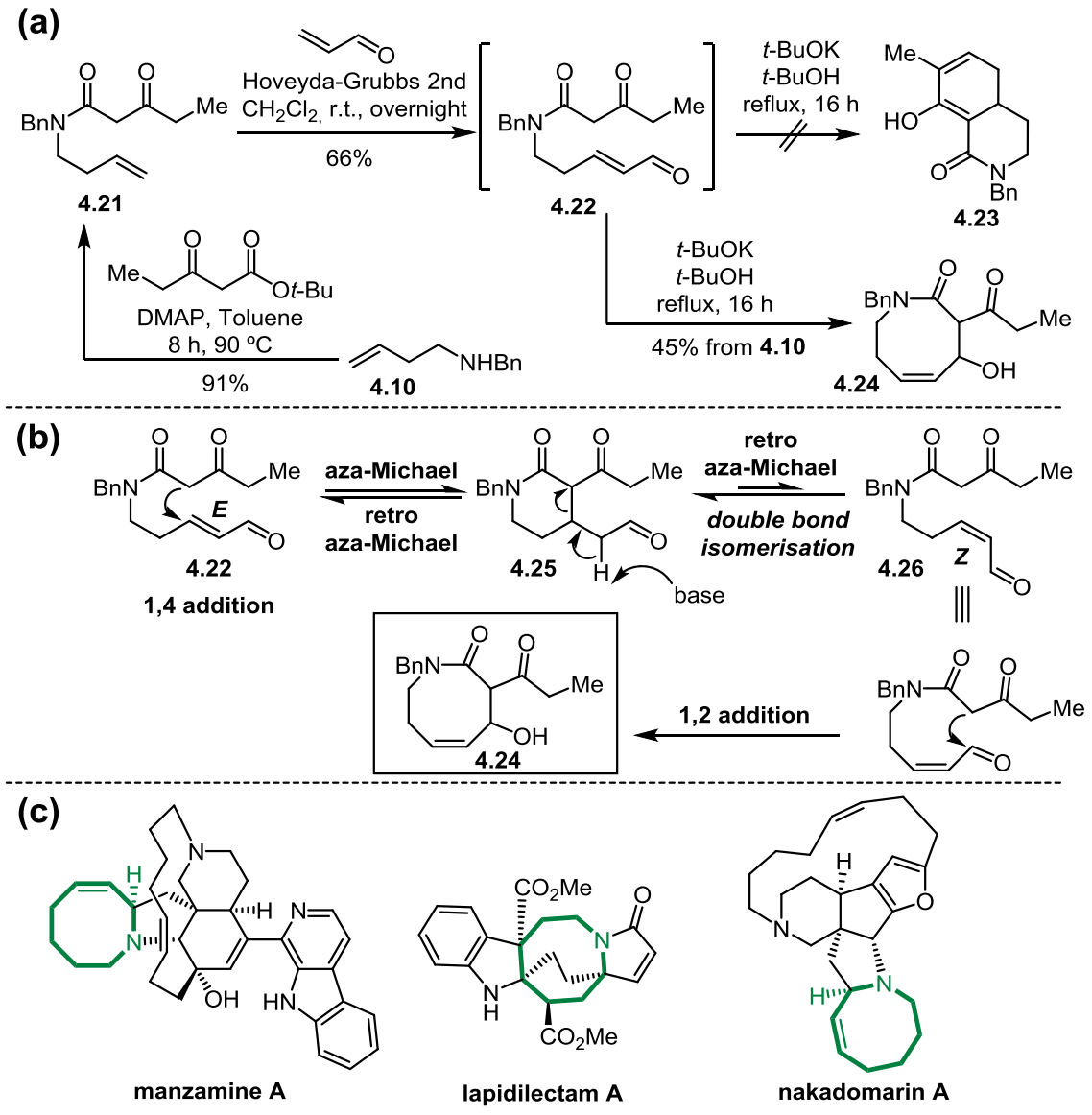
Due to problems encountered in the competing cyclizations of the first strategy, we considered a second alternative for the formation of hydroisoquinoline nucleus. We envisioned that if the nitrogen of the enal was joined to the β-keto ester at nitrogen allowing the reaction to be carried out in an intramolecular manner it should be possible to arrive at the desired ring product system. Thus, if the order of the sequence above was reversed and the amine is coupled first this would lead to the formation of the piperidine nucleus followed by formation ring cyclohexenone ring. We therefore could avoid the problems encountered with the previous approach whilst taking advantage of the improved reactivity by carrying out the reaction in an intramolecular fashion.

4.5.1 Racemic version: Methyl analog

Condensation of the β-keto ester **3.13b** with amine **4.10** in the presence of DMAP gave the amide **4.21** as a mixture of rotamers (scheme 4.6a). The resulting product was subjected to a cross metathesis reaction with acrolein catalysed by Hoveyda-Grubbs catalyst second generation to give the coupled product **4.22** along with by-products which turned out to be the Michael addition product **4.25**. Attempted purification by column chromatography resulted additional cyclisation presumably catalysed by silica to generate an intermediary piperidone nucleus. Attempts to purify **4.22** using either alumina or florisil were no better. Whilst the ready manner that this compound could undergo the intramolecular Michael addition was surprising we realised that would have to employ the crude reaction mixture in any subsequent organocatalysed reactions. Reacting the crude metathesis product[128] under the *t*-BuOK/*t*-BuOH conditions led to none of the desired product **4.23** but instead to the azocane type ring system **4.24**. Presumably this arises via an initial Michael cyclisation, however due to the reduced reactivity of the methyl ketone to perform the aldol reaction allows the intermediate to undergo a retro aza-Michael reaction which for the most part likely regenerates the starting material **4.22**. However, in addition it may produce small amounts of the alkene isomerisation product **4.26** (*Z*

[128] The crude cross metathesis product was identified as **4.22** by ^{1}H NMR but was not purified based on the propensity of these products to cyclise during chromatography

configuration) which can react in a 1,2 fashion with aldehyde to give **4.24** (scheme 4.6b). The outcome is highly unexpected as larger rings are generally hard to form. Regardless this product is interesting from the point of view that it is present in a number of natural products such as the manzamines alkaloids,[113] the related compound nakadomarin[129] as well as the indole containing product lapidilectam.[130] Interestingly, the manzamines contain both a hydroisoquinoline ring system as well as the azocane ring system raising the possibility that both ring systems could be prepared from the same methodology by modulating the reaction conditions.



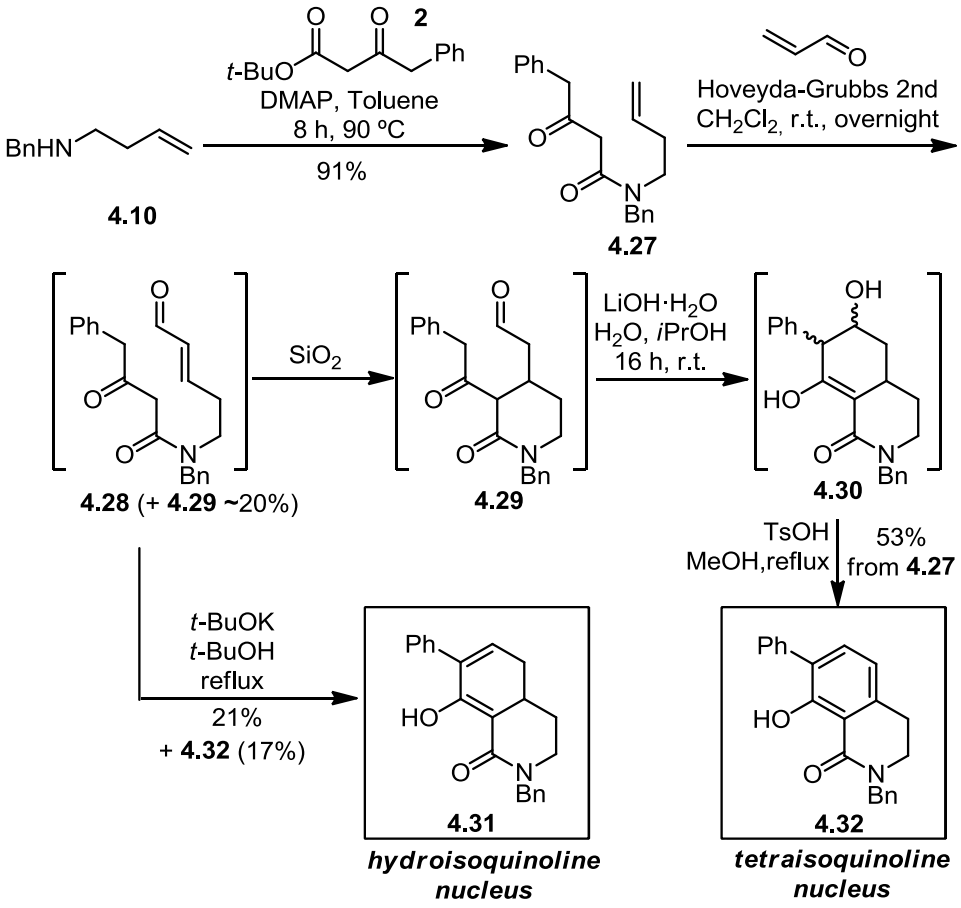
Scheme 4.6 (a) Cross-methatesis and cyclisation of methyl derivative (b) Mechanism to account for the formation of azocane byproduct **4.24** (c) Natural products that contain the azocane ring system

[129] Jakubec, P.; Cockfield,D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632-16633.
[130] Awang, K.; Sévenet, T.; Païs, M.; Hadi, A. H. A. *J. Nat. Prod.*, **1993**, *56*, 1134-1139.

4.5.2 Racemic version – phenyl analog

In an attempt to avoid the side reaction that forms an 8-membered ring we modified the aforementioned strategy to using a β-keto ester with a phenyl substituent hoping that the increased stability generated from this group would drive the aldol dehydration step.

Formation of **4.27** followed by cross metathesis gave the enal **4.28** which as before underwent partial cyclisation as well as additional cyclisation upon purification. Upon exposure of **4.28** to base ($LiOH \cdot H_2O$ in *i*PrOH/H_2O), we observed the formation of predominantly the undehydrated Robinson aldol product **4.30**. Whilst this was to be not entirely unexpected, we thought that the use of the phenyl group might favour sufficiently the formation of the elimination product. Subsequent treatment with TsOH in methanol to complete the dehydration was evidently successfully but instead of stopping at the desired hydroisoquinoline product **4.31** the product underwent an oxidation to the tetrahydroisoquinoline compound **4.32** as a result of the enol form of the β-keto ester and the conjugation with the aromatic ring forming a conjugated diene. However, upon treating the crude reaction mixture of **4.28** with *t*-BuOK in *t*-BuOH we observed the formation of the hydroisoquinoline **4.31** as the major product (along with a small amount of the tetraisoquinoline compound) **4.32** in a 5:1 ratio. However the separation of product of these products was not readily accomplished due to their close running nature by TLC.



Scheme 4.7 Synthesis of racemic hydroisoquinolines and tetrahydroisoquinolines.

So far we have investigated two approaches to the hydroisoquinoline ring system with only very moderate success. Regardless of any improvements to the overall process it seemed difficult in both cases to adapt either to an organocatalytic process. For this reason we decided to evaluate a third approach

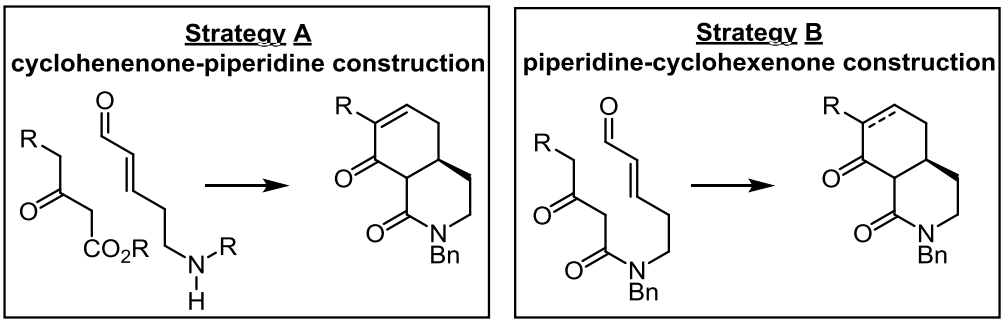


Figure 4.3 Previous inter and intramolecular strategies to hydroisoquinoline motif

4.6 A Revised Intramolecular approach to hydroisoquinolines: Synthesis of Structures Related to the Yohimbinoid Alkaloids

This third approach would also be based on an intramolecular strategy but this time the tether would be the along the C6-C7 bond of the hydroisoquinoline nucleus. Additionally a Mannich reaction would drive the formation of the nitrogen containing ring. We proposed that this strategy could be used to construct pentacyclic compounds similar to the natural products yohimbine and reserpine. The construction of the pentacyclic skeleton **4.34** of these types of molecules could be accomplished in a tandem reaction using an intramolecular strategy of a key intermediate such as **4.33** which we believed should be readily assembled from simple readily available starting materials such as tryptamine and a β-keto ester. The key strategy is outlined in figure 4.4.

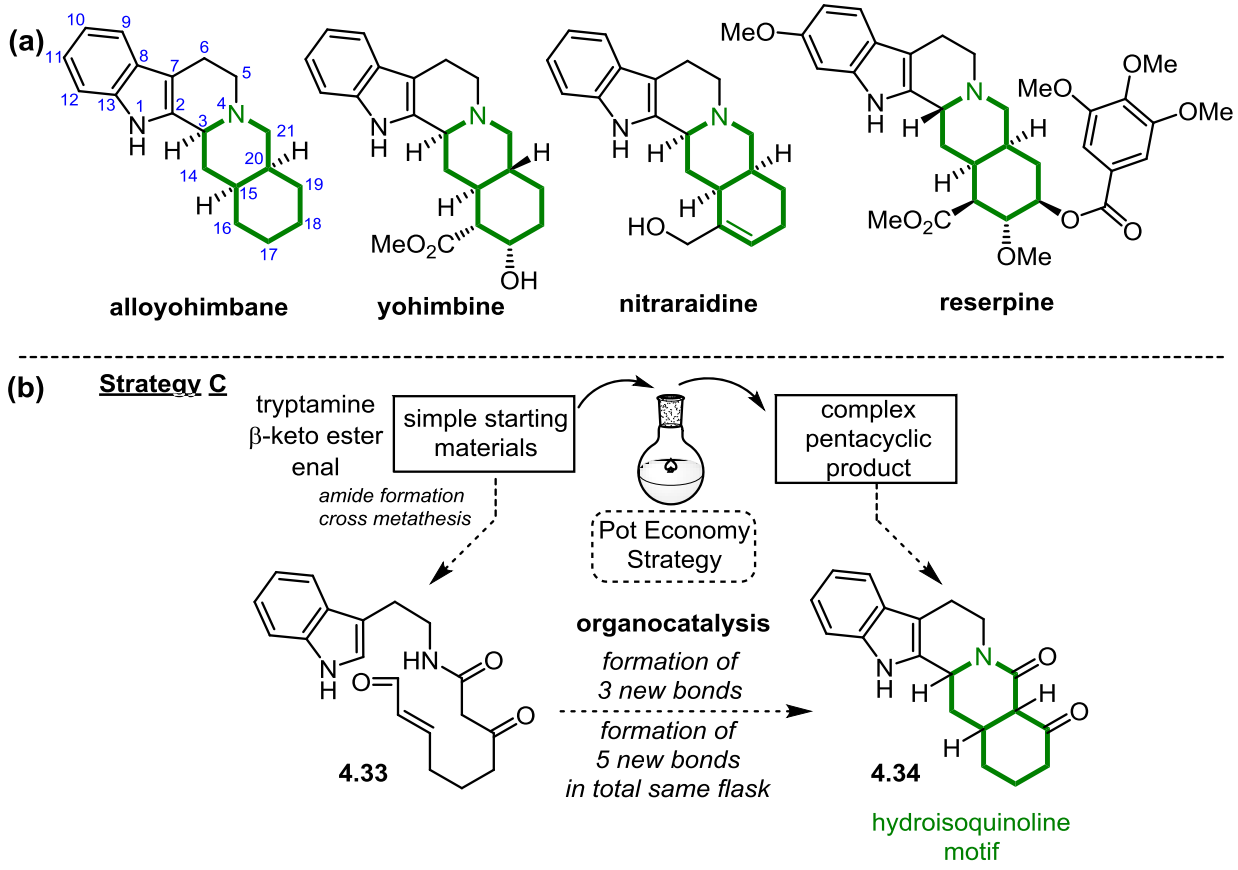
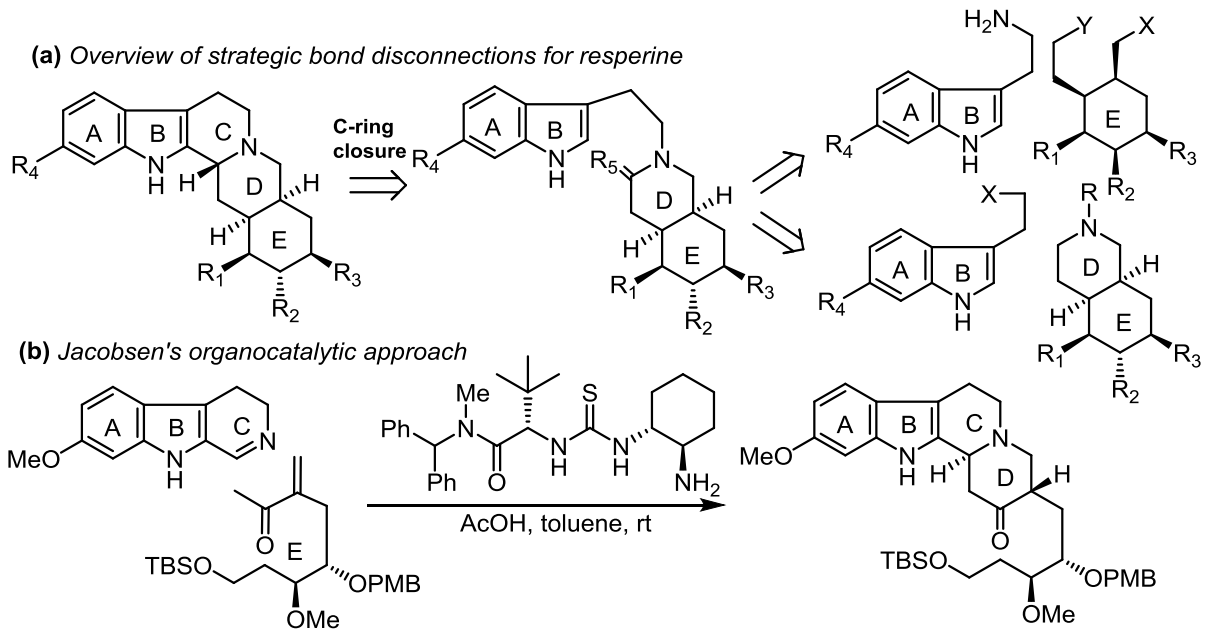


Figure 4.4 (a) Examples yohimbinoid alkaloids (b) Proposed tandem intramolecular strategy

It was hoped that when **4.33** when exposed to an organocatalyst (such as a chiral phosphoric acid) it should undergo a tandem cyclisation – Michael addition, condensation to an imine followed by a Pictet-Spengler reaction.

4.6.1 Overview of previous synthetic strategies to reserpine

Due to their biological activities[112] much effort has been devoted to the synthesis of yohimbine[131] type alkaloids in particular the archetypal member reserpine.[112] Historically, two fundamental synthetic strategies have provided successful access to this compound (Scheme 4.8a). The more widely employed strategy focuses on the synthesis of the E-ring portion of the molecule followed by elaboration of the D, C, B, and A-rings in "ascending order". The alternative strategy[132] targets the chiral *cis*-fused DE- hydroisoquinoline ring. The methods to construct these ring systems are beyond the scope of this thesis however it should be commented that none have used organocatalysis and the only method that does reported by Jacobsen employs a different retrosynthetic approach based on the use of a carboline unit (ABC rings) and a formal aza Diels-Alder reaction to construct the D ring[133] (scheme 4.8b).



Scheme 4.8 (a) Standard disconnections employed to reserpine (b) Jacobsen's organocatalytic based approach using an alternative key disconnection.

[131] For recent approaches see: Lebold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. *Nat. Chem.* **2013**, *5*, 126–131. For tandem radical process see: Kaoudi, T.; Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 3125–3127.

[132] Wender, P. A.; Schaus, J. M.; White, A. W.*J. Am. Chem. Soc.* **1980**, *102*, 6157-6159.

[133] (a) For organocatalysis in the synthesis of resperine see: D. J. Mergott, S. J. Zuend and E. N. Jacobsen, *Org. Lett.*, **2008**, *10*, 745–748 (b) for organocatalysis in the synthesis of the Corynantheine and Ipeic alkaloids see: Zhang, W.; Bah, J.; Wohlfarth, A.; Franzén, J. *Chemistry* **2011**, *17*, 13814–13824.

4.6.2 Precedents to indolquinazoline system via organocatalysis

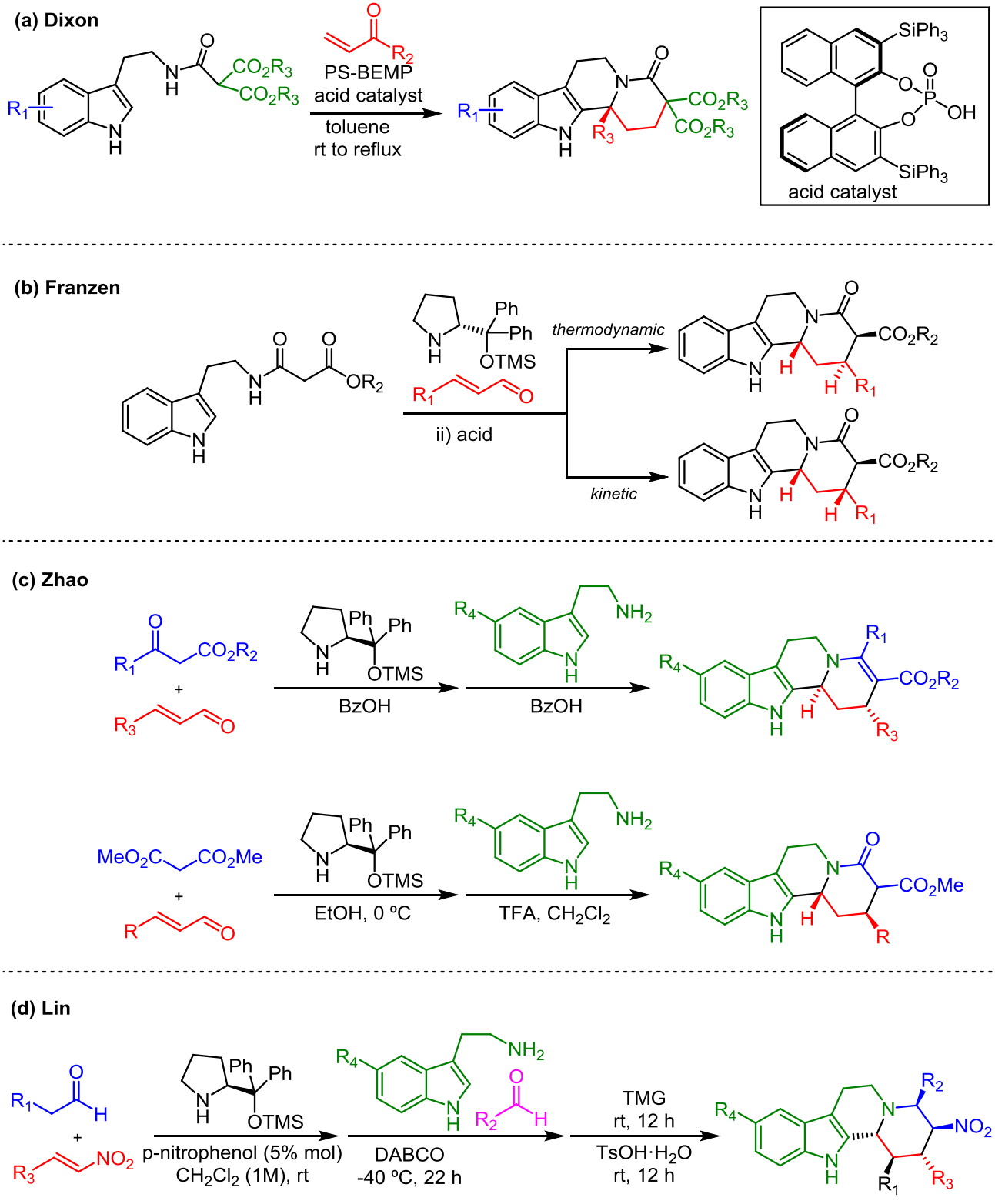
Whilst there is little work been carried out to construct the yohimbine skeleton via organocatalysis a number have groups have reported elegant strategies to the indoloquinazoline motif using Brönsted acid or Lewis base (iminium) catalysis. However it should be noted that these strategies are not readily adaptable to total synthesis due to the substituent patterns produced.

Dixon achieved a concise entry toward the indoloquinazoline structure through a novel size exclusion phenomenon between PS-BEMP and sterically bulky BINOL phosphoric acid catalysis (scheme 4.9a). This strategy was exploited in a one-pot base-catalysed Michael addition/acid-catalysed enantioselective N-acyliminium cyclisation cascade, allowing the preparation of structurally complex β-carbolines with moderate to good enantiocontrol.[134]

Zhao[135] and Franzen[136] independently reported efficient the synthesis of highly funtionalized quinazolidines by organocatalyzed enantioselective cascade reaction between α,β-unsaturated aldehydes and active methylene compounds, with good yield and high enantioselectivities (scheme 4.9b-c). Rueping also developed an identical approach but using a chiral Brönsted acid instead of the secondary amine catalyst.[137]

Finally an alternative route to access to indoloquinolizidine derivates was developed by Lin, though an organocatalytic cascade reaction which generated five contiguous stereocenters from readily available aliphatic aldehydes, nitroethylenes, and tryptamine (scheme 4.9d)[138]

[134] Muratore, M. E.; Shi, L.; Pilling, A. W.; Storer, R. I.; Dixon, D. J. *Chem. Commun.* **2012**, *48*, 6351-6353.
[135] (a) Wu, X.Y.; Dai, X.Y.; Nie, L.L.; Fang, H.H.; Chen, J.; Ren, Z. J.; Cao, W. G.; Zhao, G.; *Chem. Commun.* **2010**, *46*, 2733-2735. (b) H.H. Fang, X.Y. Wu, L.L. Nie, X.Y. Dai, J. Chen, W.G. Cao, G. Zhao *Org.Lett.*, **2010**, *12*, 5366–5369.
[136] (a) Franzén, J.; Fisher, A.; *Angew. Chem., Int. Ed.,* **2009**, *48*, 787-791. (b) Zhang, W.; Franzén, J.; *Adv. Synth. Catal*. **2010**, *352*, 499-518.
[137] Rueping, M.; Volla, C. M. R. *RSC Adv*., **2011**, *1*, 79-82.
[138] Tan, Y.; Luan, H-L.; Lin, H.; Sun, X-W.; Yang, X-D.; Dong, H-Q.; Lin, G-Q *Chem. Commun.,* **2014,** *50*, 10027-10030.

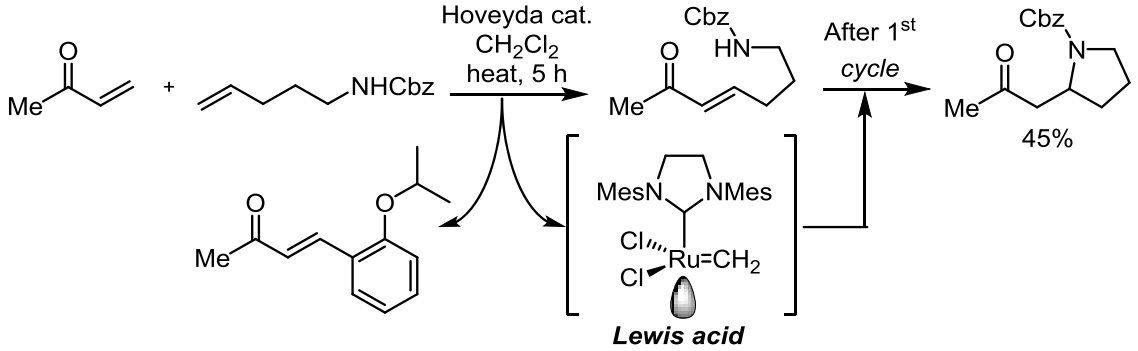


Scheme 4.9 Examples of indoloquinazoline syntheses via organocatalysis

4.6.3 Synthesis of starting material

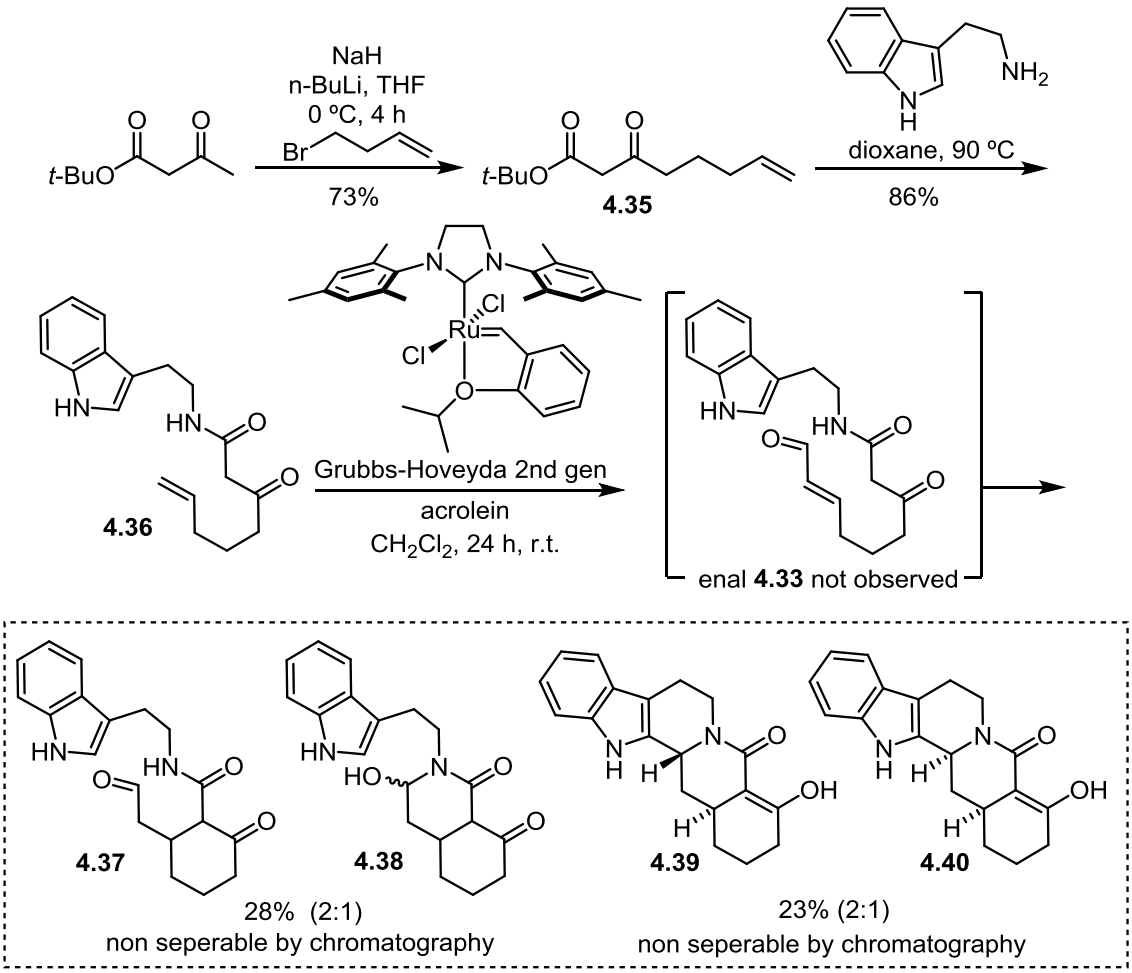
The synthesis of the required starting material was carried out based on protocols we had previously developed (scheme 4.9). Thus *tert*-butyl keto ester was alkylated with bromobutene to give the β-keto ester **4.35** which was then coupled with tryptamine by heating in dioxane to give the keto amide **4.36** in good yield. To install the key enal moiety essential for the organocatalytic cyclisation reaction, **4.36** was subjected to a cross metathesis reaction with acrolein in the presence of the Grubbs-Hoveyda II catalyst. However, somewhat surprisingly instead of isolating the expected enal **4.33 (**and perhaps in addition a small amount of the Michael addition product **4.37** based on the previous observations in section 4.5) we obtained a mixture of cyclized compounds which included **4.37** and **4.38** along with the desired penatacyclic yohimbine skeleton product **4.39** and its epimer **4.40**. The unexpected cyclisation to the yohimbine skeleton under metathesis conditions is presumed to be due to the formation of a Lewis acidic species from the Grubbs-Hoveyda 2nd generation catalyst which during the turnover in the metathesis reaction generates a Lewis acidic species when the styrene moiety leaves the metal coordination sphere, leaving the ruthenium to act as a Lewis acid through its empty d orbital.[139] This then goes on to catalyze both the Michael addition, imine condensation and indole cyclisation reactions. Whilst increasing the temperature and time of the reaction were attempted it was difficult to drive the reaction to completion under these conditions.[140] However, as a proof of concept it indicated the ease of the proposed tandem reaction when carried out in an intramolecular sense.

[139] Fustero, S.; Jiménez, D.; Pozo, C.; Sánchez-Roselló, M.; *J. Am. Chem. Soc.*, **2007**, *129*, 6700–6701. Notably Fustero found that the reaction had to be driven to completion by the addition of BF_3OEt_2/an additional Lewis acid.



[140] For example increasing the time to 48 h or carrying out the reaction at reflux only led to slightly improved ratio of the pentacyclic products.

The ease with which **4.33** would undergo cyclisation was further illustrated by the ease the reaction would take place on silica. Attempts to use basic alumina or florisil also produced varying degrees of cyclisation thus eliminating the possibility to obtain compound **4.33** by purification.

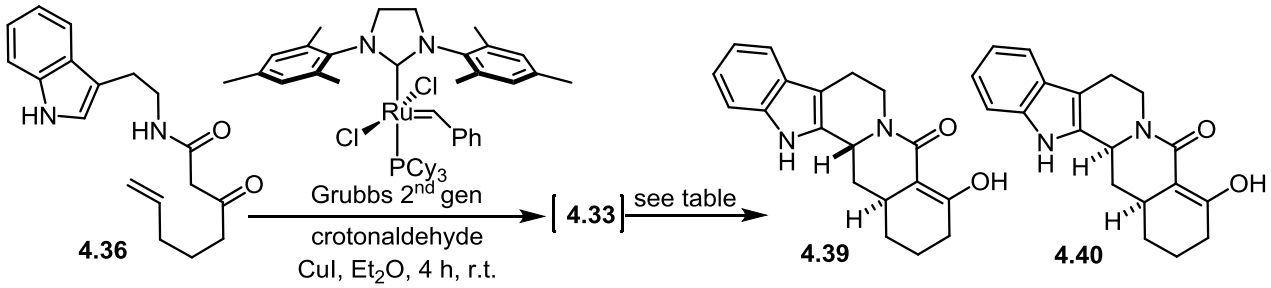


Scheme 4.9 Attempted preparation of starting material for the cyclisation and unexpected tandem cyclisation reaction to yohimbine skeleton catalyzed by Grubbs-Hoveyda catalyst.

4.6.4 Optimization of the reaction – racemic version

After switching to the Grubbs 2nd catalyst we found we could effect the formation of **4.33** with negligible Michael addition side-product formation although the reaction was not complete (also some homodimerisation observed). The use of small ammounts of CuI[85] greatly improved the reaction but led to minor amounts of cyclized products although it was sufficiently clean to evaluate the conditions for the tandem cyclisation sequence. To illustrate the ease with which it would cyclise the addition of silica caused the formation of the cyclisation products in a 1:1 ratio (entry 1). We then evaluated a number of cyclisation conditions to obtain both a complete reaction and control the formation of either **4.39** or **4.40** in a selective manner. Following the precedents laid down by Franzen[133] in his synthesis of the related corynantheine alkaloids, screening of various acids revealed that BzCl gave predominantly the *trans* **4.39** (entry 2), whilst AcCl (entry 3) gave almost exclusively the *cis* **4.40** whilst TFA gave an 1:1 mixture (entry 4).

Table 4.1. Optmisation of tandem cyclisation reaction



Entry[a]	*Reagent*	*Equiv.*	*Solvent*	*temp*	*d:r of 4.39/4.40*[(b)]
1	Silica	1	CH_2Cl_2	rt	1:1
2	BzCl	1	CH_2Cl_2	-78°C to rt	2:1
3	AcCl	1	CH_2Cl_2	reflux	1:10
4	TFA	1	CH_2Cl_2	reflux	1:1
5	CuI	1	CH_2Cl_2	rt	1:1

[a] All reactions were carried out for 24 h. **[b]** Determined by 1H NMR analysis of the crude reaction mixture.

Of note the use of copper iodide itself could induce the cyclisation as well (entry 5) which undoubtedly accounts for the small amount of the Michael addition product that forms when it is used as a minor additive in the metathesis reaction. Notably as well addition of AcCl to mixtures of the two epimers would convert **4.39** to **4.40**. Whilst Franzen screened an extensive range of conditions he found AcCl and BzCl were the best and given the similar pattern of reactivity of our compounds we did not pursue additional screenings.

Given the similarities of the outcomes of this cyclisation reaction to that of Franzen we assumed the course of the reaction follows the same principals of control. Thus, the bridgehead stereocenter is formed through an N-acyliminium ion cyclization a reaction that is known to be under kinetic control.[141] Addition of the indole moiety to the *Si*-face of the iminium ion would give the thermodynamically more stable β-epimer owing to the all-equatorial orientation of the substituents on the piperidine ring. However, under kinetic reactions conditions the α-epimer is obtained as the major product with addition of the indole moiety from the *Re*-face of the iminium ion (Figure 4.5). This due to there being less steric hindrance from the equatorial α-proton of the iminium ion in the transition state leading to the α-epimer, as compared to the higher steric interactions between the indole moiety and the axial α-proton in the transition state leading to the β-epimer.

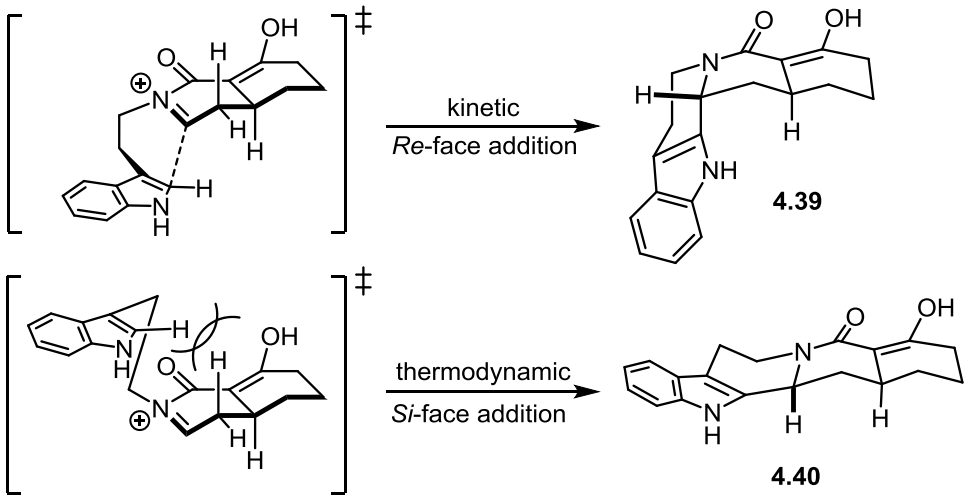


Figure 4.5. Proposed transition states in the formation of thermodynamically and kinetically favoured ring-junction epimers in the *N*-acyliminium ion cyclization.

[141] (a) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062-5074; (b) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc*. **1987**, *109*, 7901-7903; (c) Lounasmaa, M.; Berner, M.; Tolvanen, A. *Heterocycles* **1998**, *48*, 1275-1290.

4.6.5 Determination of stereochemistry

This screening allowed us to obtain pure material to determine to be the relative structural configurations of **4.39** and **4.40** by NMR analysis (Figure 4.6).

The assignment of the relative configurations of pentacyclic yohimbane-type compounds was accomplished on the basis of the NMR data, taking into account the available data in the yohimbane series, as well in related compounds. Thus in the 1H-NMR of **4.40**, the H-3 signal appears at δ 4.82 as a dd (*J* = 11.6, 2.8 Hz) indicating this axial disposition. Moreover, the H-14ax appears isolated at δ 1.50 as a quadruplet (*J* = 12.0 Hz) that implies its axial disposition having an anti relationship both H-3ax and H-14ax) and hence the cis 1,3-relationship between the H-15 at H-3, as is reflected in the stereostructure of **4.40**.

The major compound formed under kinetic control reactions showed a 1H NMR pattern similar for H-3ax and H-5eq, but the ^{13}C NMR data showed a noteworthy difference for the chemical shift at C5 (δ 43.1) with respect that the observed (δ 39.5) in the above kinetically favored compound **4.39**. For this reason the stereostructure assigned corresponds to the epimeric compound at C-3. This change involves a conformational change, maintaining the H-3 in axial disposition, but the E ring has a different special arrangement that avoids the compression upon C-5.

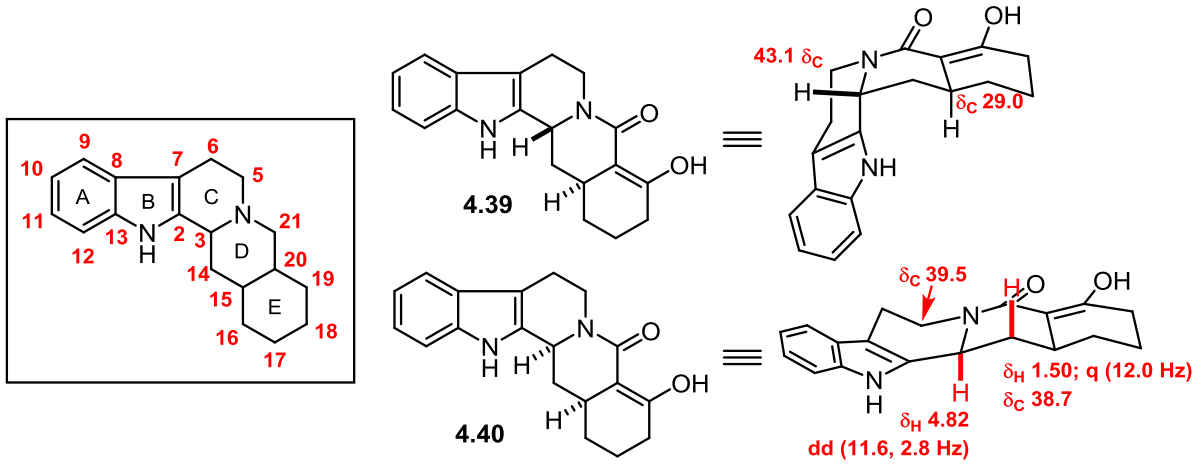


Figure 4.6. Determination of stereochemistry of **4.39** and **4.40**

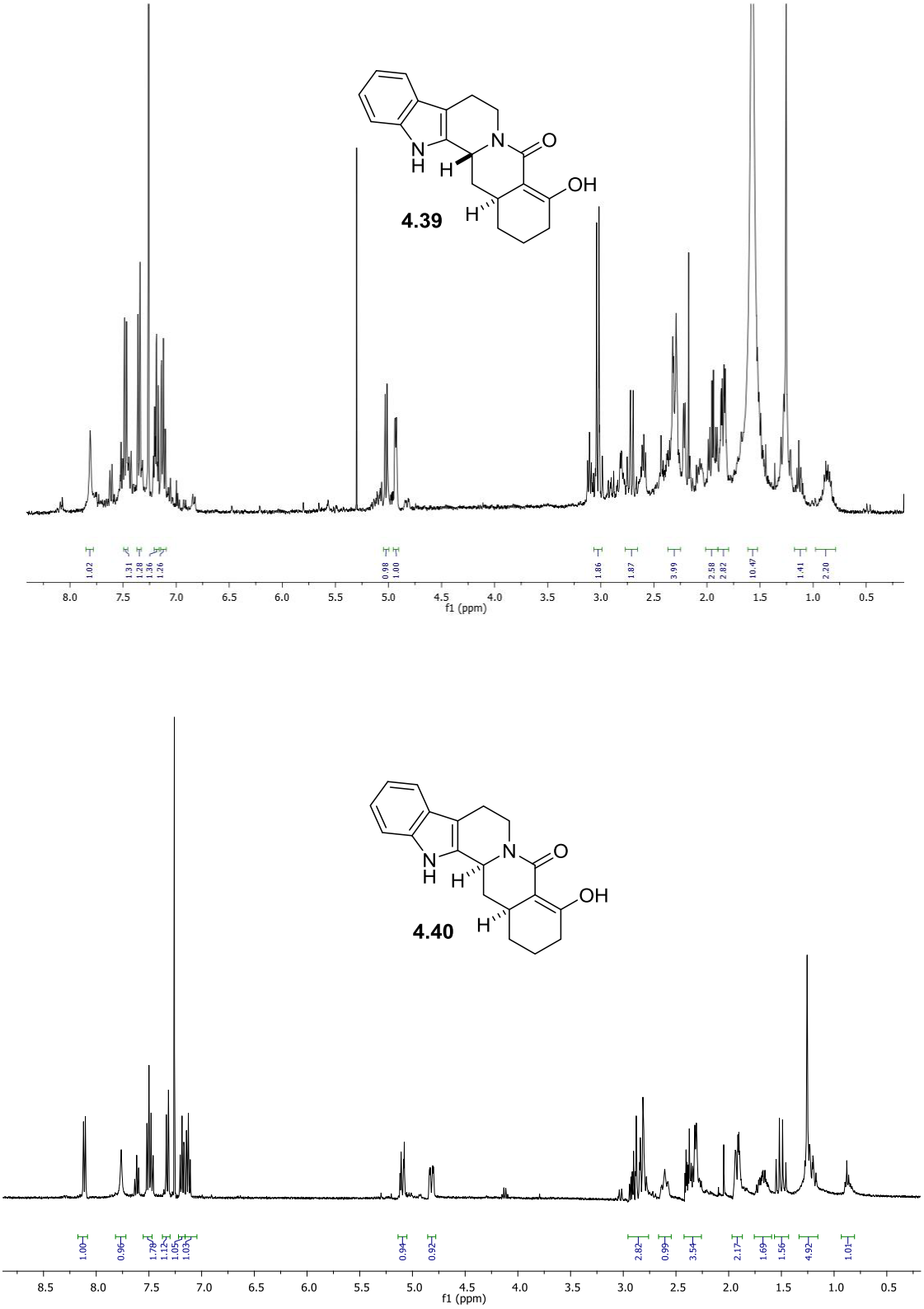
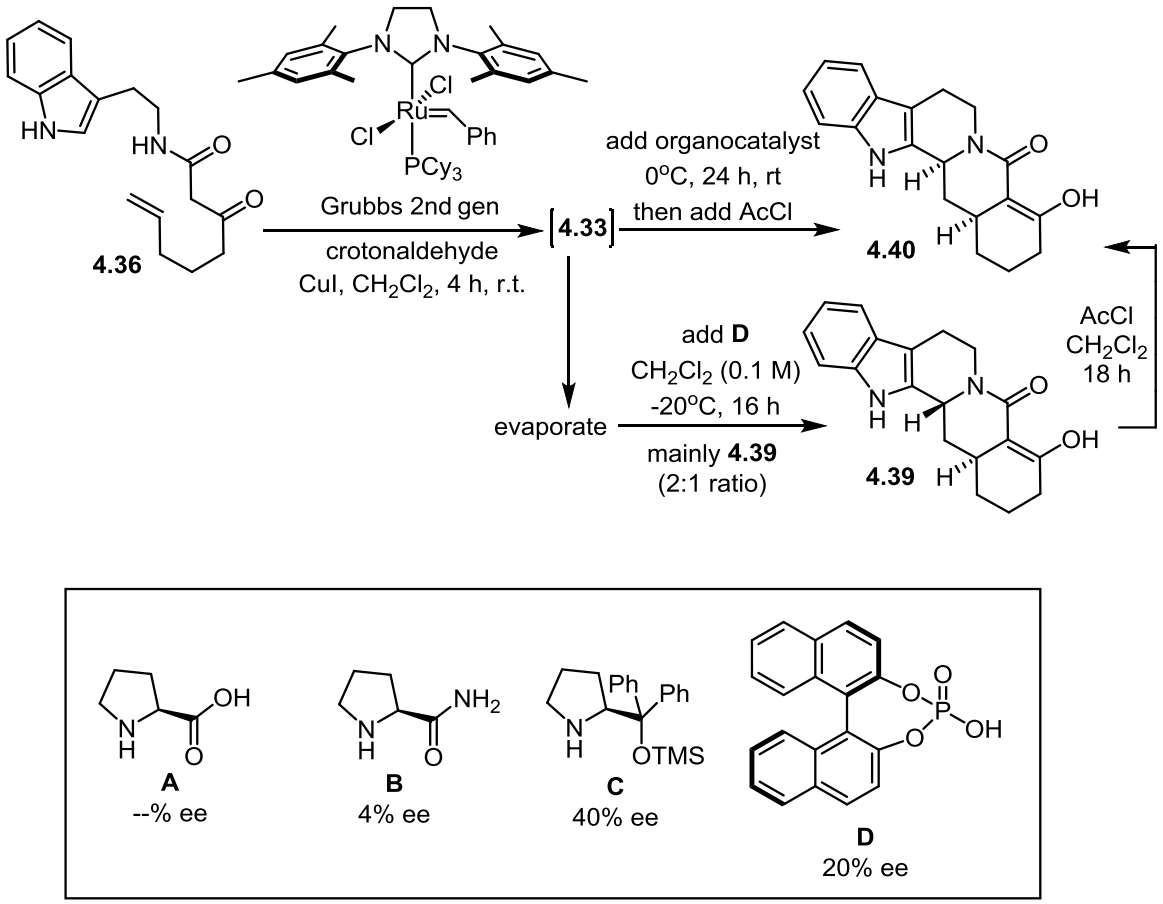


Figure 4.7. NMR spectra of yohimbine pentacycle C-3 epimers

4.6.6 Evaluation of an Enantioselective version of the cyclisation

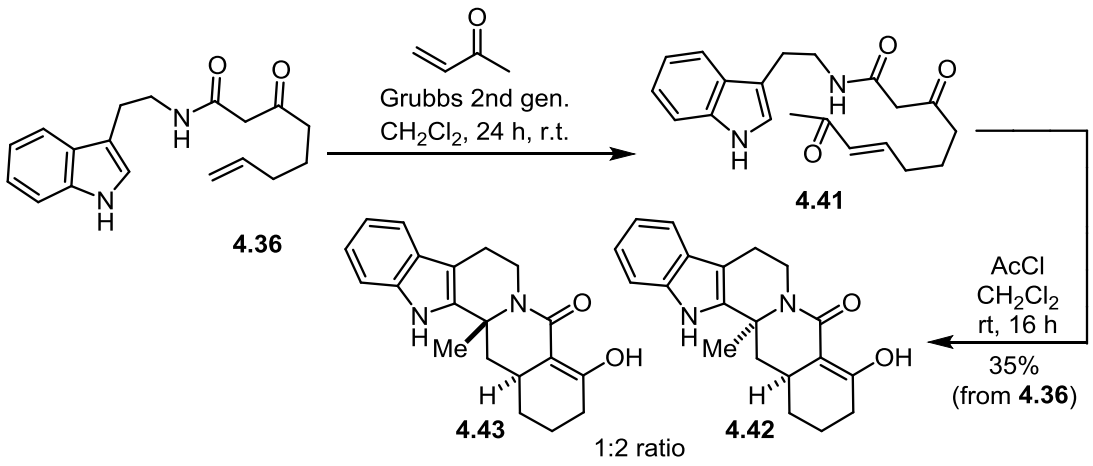
Despite initial problems in obtaining **4.33** absolutely free of cyclised products we decided to attempt the asymmetric organocatalyzed version of the reaction to evaluate the potential of preparing **4.40** in enantiopure form. After preparation of the crude enal it was treated to a range of organocatalysts followed by addition of AcCl to complete the formation of the pentacyclic compound **4.40** (scheme 4.11). Proline (catalyst **A**) gave no reaction due to problems of solubility. On the other hand the prolinamide catalyst **B** did give a complete Michael reaction but gave no appreciable enantioselectivity. The use of the Hayashi catalyst was more favourable giving a more promising 40% ee. The use of the chiral phosphoric acid **D** gave cyclisation directly to the yohimbine skeleton as a mixture of epimers favouring **4.39** (2:1) Subsequent exposure to AcCl converted all of this material to **4.40** but with a moderately low ee of 20%.



Scheme 4.11 Preliminary screening of organocatalyzed version of the tandem sequence to **4.38**.

To obtain **4.40** in good enantioselectivity would require the modification of the metathesis reaction so that no coupled product formed, a more extensive screening of catalysts and additives to see if it was possible to improve on the Hayashi catalyst and finally a thorough solvent screen. Rather than carry this out immediately[142] we surveyed a few structural modifications to the substrates which we hoped might both increase the enantioselectivity as well as avoid the problem of the cross metathesis reaction generating small amount of racemic cyclisation products.

We next prepared the enone analog of **4.33** to see what effect this would have on the outcome of the reaction.[143] Cross metathesis of **4.36** with methyl vinyl ketone in the presence of Grubbs 2nd generation catalyst gave enone **4.41** which unfortunately was also found to readily cyclise on purification. Treatment with AcCl gave the analogous methyl substituted yohimbine type structure as a 2:1 mixture of C-3 epimers **4.42** and **4.43** which could not be readily separated by chromatography. We therefore did not pursue this approach further. From an NMR perspective these products are similar to **4.39** and **4.40** and the same general rules for their interpretation apply. Of note the methyl group in axial disposition causes the corresponding deshielding effect by compression about the axial C-H bonds at carbons C-5 (δ 39.3 to 36.0) and C-15 (δ 32.1 to 29.1).



Scheme 4.12 Synthesis of C-3 methyl yohimbine compounds (a) racemic form (b) attempted organocatalysed version.

[142] This investigation was carried out at the end of the work carried out in this thesis and time constraints did not allow us to extend this study further.

[143] In the work by the Dixon group using chiral phosphoric acids in which they obtain excellent enantioselectivites the substituent at C-3 is never H. See reference 134 and references cited therein for similar examples by the same group.

4.6.7 Towards more elaborated resperine–yohimbine type structures

Given the problems with the completely spontaneous nature that the yohimbine skeleton formed making it difficult to have the enal **4.33** in pure form we proposed a modified strategy using a enyne metathesis which would have 2 possible advantages (i) it would provide an allylic alcohol product which would not be able to cyclise and (ii) it would bear the requisite methylene functionality at C-5 of the hydroisoquinoline unit required for the yohimbinoid alkaloids.

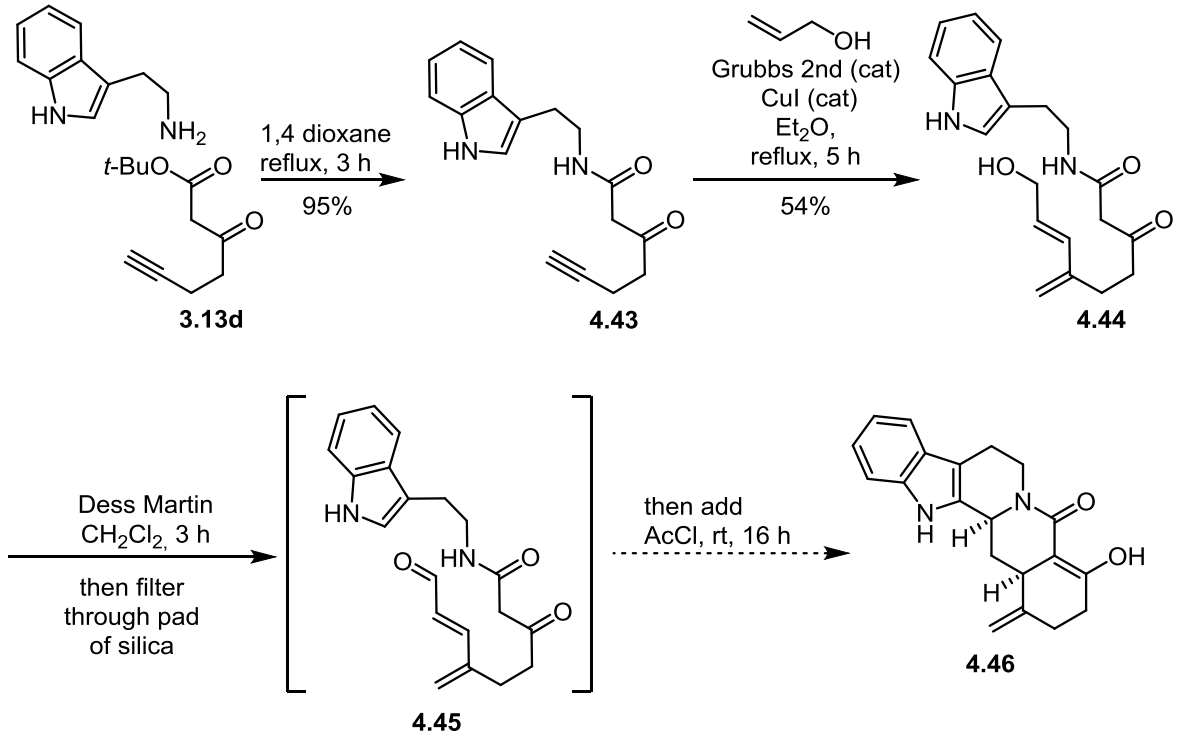
The material to evaluate the reaction was as carried out as in scheme 4.13. Condensation of alkyne **3.13d** (the same as used previously in the morphan methodology) was carried out with tryptamine. Then an enyne metathesis reaction with allyl alcohol using the same CuI protocol as before[85] then gave the key cyclisation intermediate **4.44**.

It was thought that in-situ oxidation of the allyl alcohol in the presence of an organocatalyst based on precedents developed by Rueping[144] using MnO_2 or TPAP/NMO could streamline the process to the desired compound **4.44** with the advantage that the enal **4.45** could be induced to cyclise the moment it forms instead of allowing time for it to undergo any side reactions. To test the possibility of applying the combined oxidation/organocatalysis conditions we first evaluated the oxidation step. However, oxidation with MnO_2[145] only gave low amounts of the desired aldehyde **4.45** intermediate due to poor solubility of the substrate in CH_2Cl_2. Upon prolonging the reaction time the oxidized product was observed to begin to degrade. We therefore tried Dess-Martin periodinane as an alternative which gave the desired product **4.45**. Removal of the oxidant by filtration through a pad of silica also led to some change in the product (principally Michael addition products). Exposure to AcCl in CH_2Cl_2 then did give some products possibly corresponding to **4.46** in the crude NMR spectrum but it was evident this cyclisation reaction will require further

[144] (a) Using MnO_2 with allyl alcohols see: Rueping, M.; Sundén, H.; Hubener, L.; Sugiono, E. *Chem. Commun.* **2012**, *48*, 2201-2203. (b) Using TPAP see: Rueping, M.; Sundén, H.; Sugiono, E. *Chem. - A Eur. J.* **2012**, *18*, 3649–3653.

[145] 10-fold excess of activated MnO_2 (prior to use, the commercial reagent obtained from Sigma-Aldrich was heated at 100 °C overnight; the use of unactivated commercial MnO_2 resulted in longer reaction times and poor conversion). See Nair, R. N.; Bannister, T. D. *J. Org. Chem.* **2014**, *79*, 1467-1472 for full conditions.

optimization. Unfortunately again due to time restraints we could not conduct the extensive screening required to resolve this question.



Scheme 4.13. Synthesis of cyclisation precursor using enyne-metathesis and initial evaluation of tandem cyclisation sequence.

4.7 Summary and Conclusions for Chapter 4

In conclusion, a number of varied strategies were investigated to develop an organocatalysed approach to the hydroisoquinoline motif. In total 3 routes were investigated including diverting the morphan route, a modified intramolecular based approach and finally an alternative intramolecular approach directly aimed at constructing the yohimbine skeleton. All approaches met with a moderate level of success with the intramolecular versions being somewhat complicated due to the extremely spontaneous nature of these compounds to cyclise making the evaluation via organocatalysis problematic.[146] Regardless having obtained an overview of the positives as well as the various potential difficulties of the various methods it should be possible to exploit a modified version of these strategies to enable the synthesis of the hydroisoquinoline nucleus in enantiopure form via organocatalysis.

[146] However, this outcome may be beneficial in cyclisations of densely functionalized compounds which might not readily cyclise due to steric factors in the intermolecular variant.

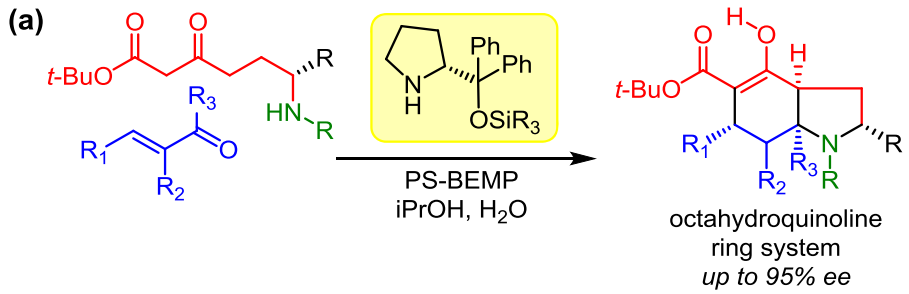
CHAPTER 5:

CONCLUSIONS

1) Octahydroindoles

(a) The reaction of a *tert*-butyl β-keto ester tethered to a monoprotected amino group with crotonaldehyde using a range of basic conditions (LiOH, *t*-BuOK or n-Bu_4NOH furnishes domino reactions (intermolecular Michael, intramolecular aldol, intramolecular aza-Michael reaction sequence). The reaction was found to work well with the solid supported basic resin PS-BEMP which greatly simplified the reaction procedure. The diastereoselectivity of this reaction followed the same course as the analogous decahydroquinoline system.

(b) The optimized organocatalytic conditions developed for the decahydroquinoline series (Michael step) also proved to be transferable to the octahydroindole series however it was found that n-Bu_4NOH or PS-BEMP give slightly better enantioselectivies than LiOH for the tandem ring closure reaction. As well as using crotonaldehyde as the Michael acceptor a range of other enals allowed the formation of different analogs in excellent enantioselectivities. The use of a β-keto ester with a chiral substituent α to the nitrogen led to complete diastereoslectivity when PS-BEMP was used as the base. Presumably this 1,6 induction effect arises via coordination between the base, the dicarbonyl and the amino side chain to generate a cyclic intermediate which blocks the approach of the one of the faces of the β-keto ester.



Scheme 5.1 Synthesis of variously substituted octahydroindole ring systems via organocatalysis or remote induction.

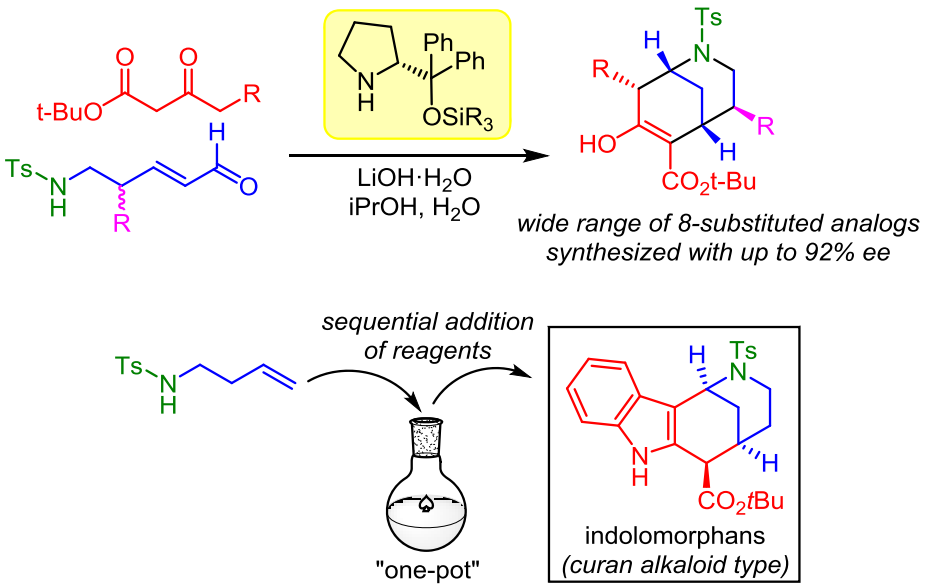
(c) Attempts to synthesize the analogous 7-membered ring compounds (perhydro[b]azepines) were unsuccessful leading only to the Robinson adduct. None of the desired biscyclized compound was observed under a wide range of cyclisation conditions. Presumably whilst in the 5 and 6 membered nitrogen ring series the generally low potential of the aza-Michael due to the deprotonation of the β-keto

ester can be overcome, the increased entropic difficulties of forming 7-membered ring completely inhibits the aza-Michael reaction from taking place.

2) Morphans

(a) The application of the core methodology could be used to give a general organocatalytic entry to morphan ring system for the first time by moving the nitrogen tethered chain from the β-keto ester component to the Michael Acceptor component. In contrast to decahydroquinoline and octahydroquinoline series the reaction worked only under solvent free conditions which were needed to overcome the competing intramolecular reaction (via organocatalysed dienamine equilibration) of the enal bearing both nucleophilic and electrophilic centres. Initial attempts harness the dienamine intermediate to give chiral substituted enals was unsuccessful due to the rapid degradation of these products.

(b) The one-pot philosophy could be used to generate indolomorphans (of the curan alkaloid type) from a simple butenyl amino tosylate allowing for the rapid assembly asymmetric assembly of this nucleus in one-pot.



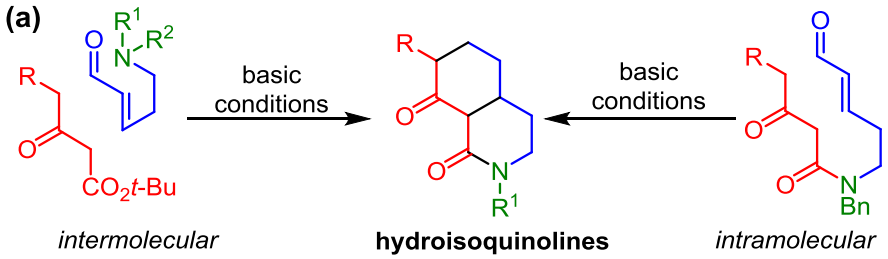
Scheme 5.2. Organocatalysed synthesis of the morphan nucleus employing a tandem cyclisation reaction.

3) Hydroisoquinolines

To extend the scope of the reaction to hydroisoquinoline nucleus 3 approaches were evaluated:

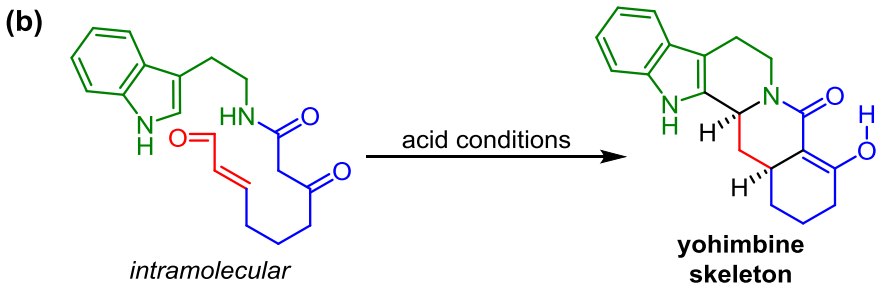
(a) An intermolecular approach based on rerouting the course of the morphan reaction by cyclising the nitrogen (protected as a carbamate) onto the β-keto ester group was investigated. However, unexpectedly in contrast to the decahydroquinoline and octahydroindole series it was found that carbamates did undergo the aza-Michael reaction in the morphan series. The use of bis-protected nitrogen compounds were then employed allowing the formation of a cyclohexenone ring which upon hydrogenation cleaved the carbamate group and reduced the enone functionality. Subsequent heating the benzyl protected amine resulted in cyclisation to form the hydroisoquinoline ring system.

(b) Inverting the ring assembly order (forming the nitrogen ring first) via an intramolecular tethered approach was also found to give the hydroisoquinoline ring system but was complicated by the highly spontaneous manner that the intramolecular Michael reaction would occur.



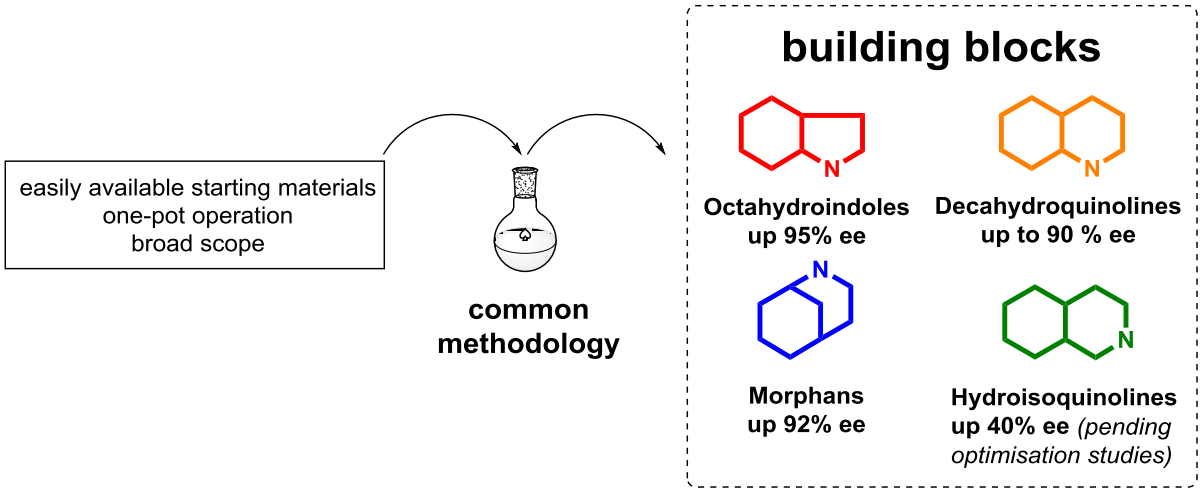
Scheme 5.3. Synthesis of hydroisoquinoline ring system via inter and intramolecular approaches.

(c) An alternative intramolecular variation was investigated that allowed the formation of the pentacyclic yohimbine skeleton in a single reaction. Instead of an aza-Michael reaction a Pictet Spengler reaction was employed. Upon formation of the enal (via metathesis) the pentacyclic structure would readily assemble in a spontaneous manner via the Lewic acidic nature of the Hoveyda-Grubbs catalyst.



Scheme 5.5 Synthesis of hydroisoquinolines as part of the yohimbinoid alkaloid skeleton

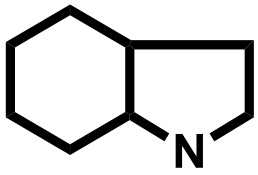
The work carried out in this thesis has expanded the potential of the initially developed tandem reaction for decahydroquinolines and shown that it is a general process that can enable the synthesis of various important nitrogen containing ring systems in an asymmetric manner.



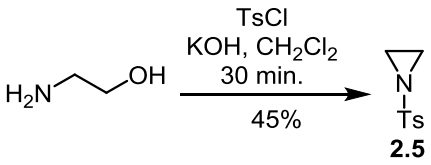
Scheme 5.6 Common methodology for the asymmetric preparation of a wide range of important nuclei found in natural products and pharmaceutical compounds.

CHAPTER 6
EXPERIMENTAL

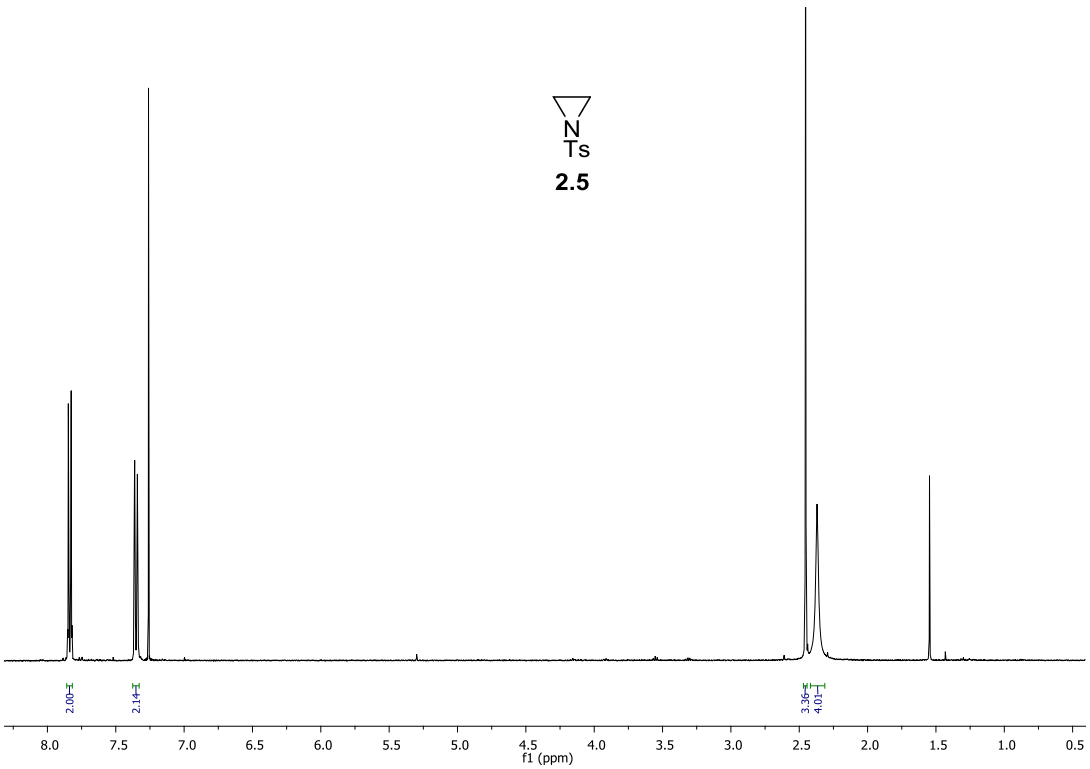
OCTAHYDROINDOLES



1-Tosylaziridine (2.5)

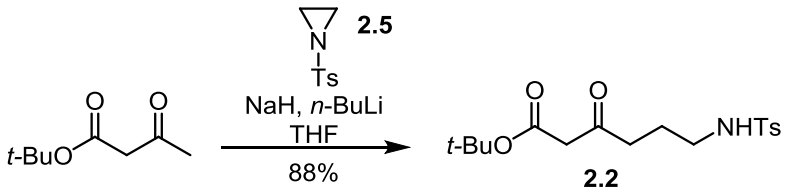


Tosyl chloride (23.4 g, 0.123 mol) was added portionwise at r.t. under vigorous stirring to a mixture of KOH (98.2 g, 1.75 mol), 2-aminoethanol (3.0 g, 0.049 mol) in dichloromethane (98 mL) and water (98 mL). After 30 min, ice and water were added, the organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography (0→10→25→50% EtOAc/hexane) gave aziridene **2.5** (4.35 g, 45%) as a white solid. Spectral data was identical to that previously reported.[147]

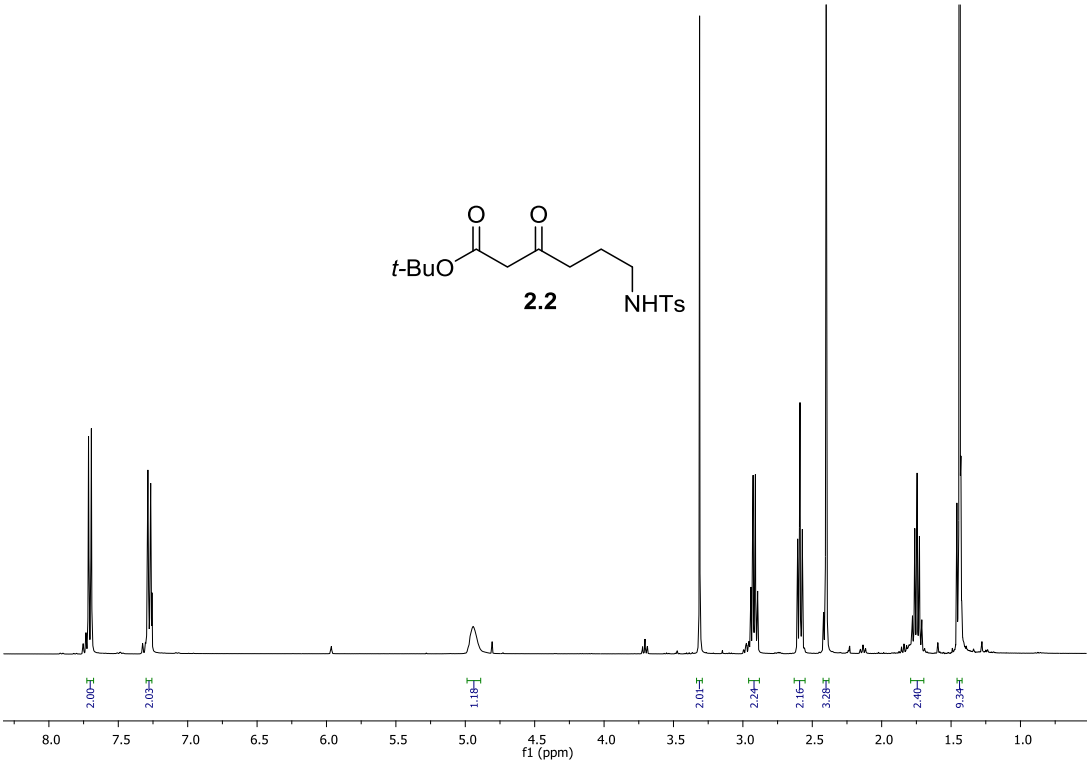


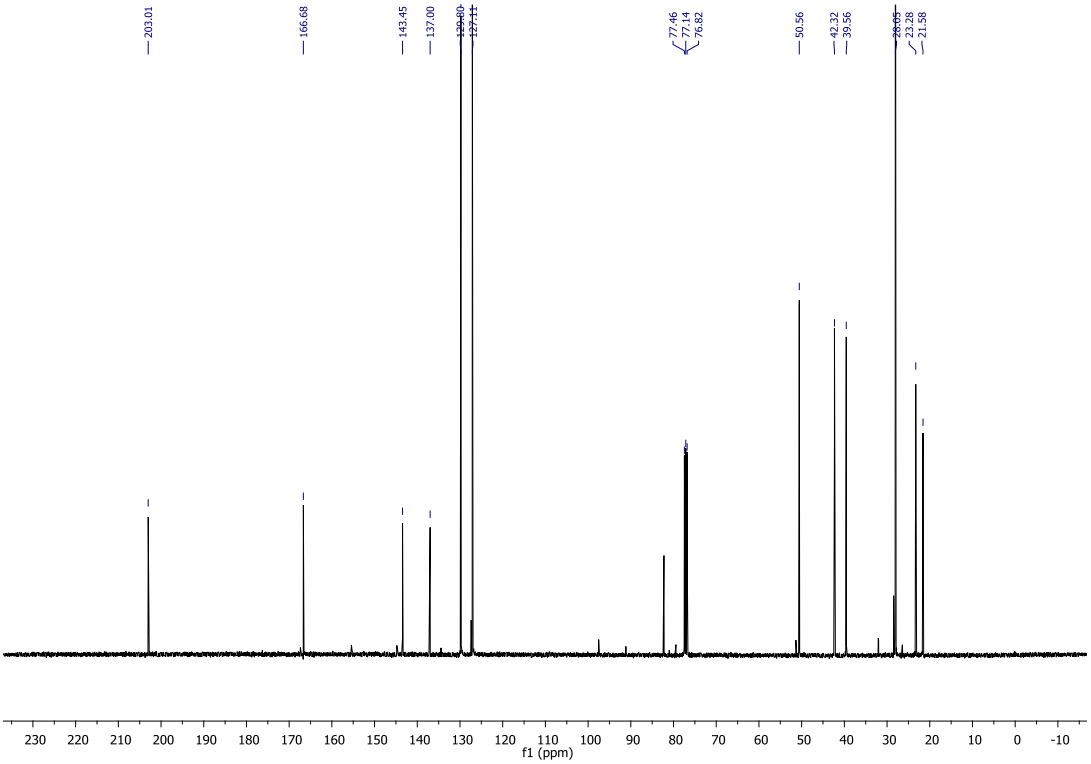
[147] Lygo, B. *Synlett* **1993**, 764-766

tert-Butyl 6-(4-Methylphenylsulfonamido)-3-oxohexanoate. (2.2)

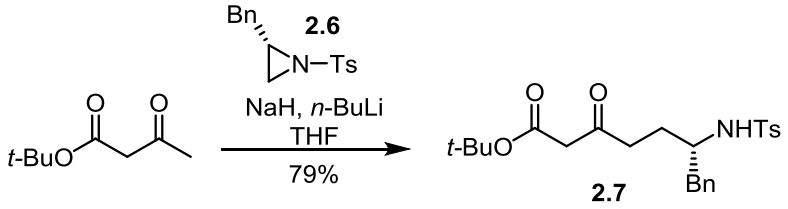


THF (40 mL) was added to NaH (60% in mineral oil) (0.33 g, 13.8 mol) and the resulting suspension was cooled 0ºC. *tert*-butyl acetoacetate (0.73 g, 4.61 mmol) was added dropwise and the colorless solution was stirred at 0 ºC for 10 min. Then *n*-butyllithium (2.2 mL of 2.6 *M* in hexanes*,* 4.84 mmol*)* was added dropwise and the resulting orange solution was stirred at 0 ºC for an additional 10 min. Aziridine **2.5** (1.00 g, 5.07 mmol) in 5 ml of dry THF was added (the color of the dianion faded immediately on addition of the aziridine) and the reaction mixture was stirred at room temperature for 15 min. The mixture was quenched with 2 mL of NH_4Cl(aq) plus 5 mL of water and diluted with 15 ml of Et_2O. The organic phase was washed with water, dried (MgSO4) and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave β-keto ester **2.2** (1.58 g, 88%) as a light coloured oil. ^{1}H NMR (400 MHz, COSY) δ 1.44 (s ,9H, CH_3), 1.75 (qd, *J* = 6.4, 0.8 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.54 (td, *J* = 6.8, 1.2 Hz, 2H, CH_2), 2.92 (qd, *J* = 6.8, 1.2 Hz, 2H, CH_2), 3.31 (s, 2H, CH_2), 4.76 (br, 1H, NH), 7.28 (d, 2H, *m*-ArH), 7.71 (d, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 21.4 ($ArCH_3$), 23.1 (C-5), 27.8 (CH_3), 39.4 (C-4), 42.2 (C-6), 50.4 (C-2), 82.1 (C), 127.1 (*o*-Ar), 129.7 (*m*-Ar), 136.9 (*p*-Ar), 143.3 (i*pso*-Ar), 166.6 (C-3), 202.9 (CO); HRMS calcd for $C17H29N_2O_5S$ $[M+NH_4]^+$ 373.1792, found 373.1798.

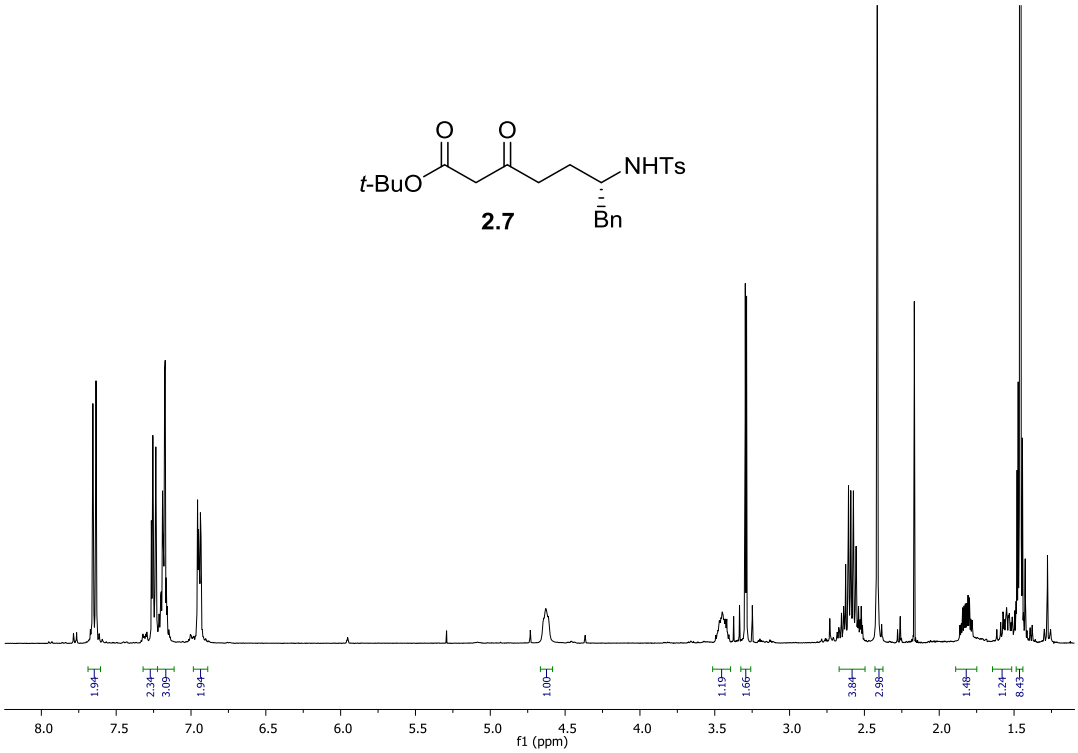

O
O
t-BuO
NHTs
2.2
2.00
2.03
1.18
2.01
2.24
2.16
3.28
2.40
9.34
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

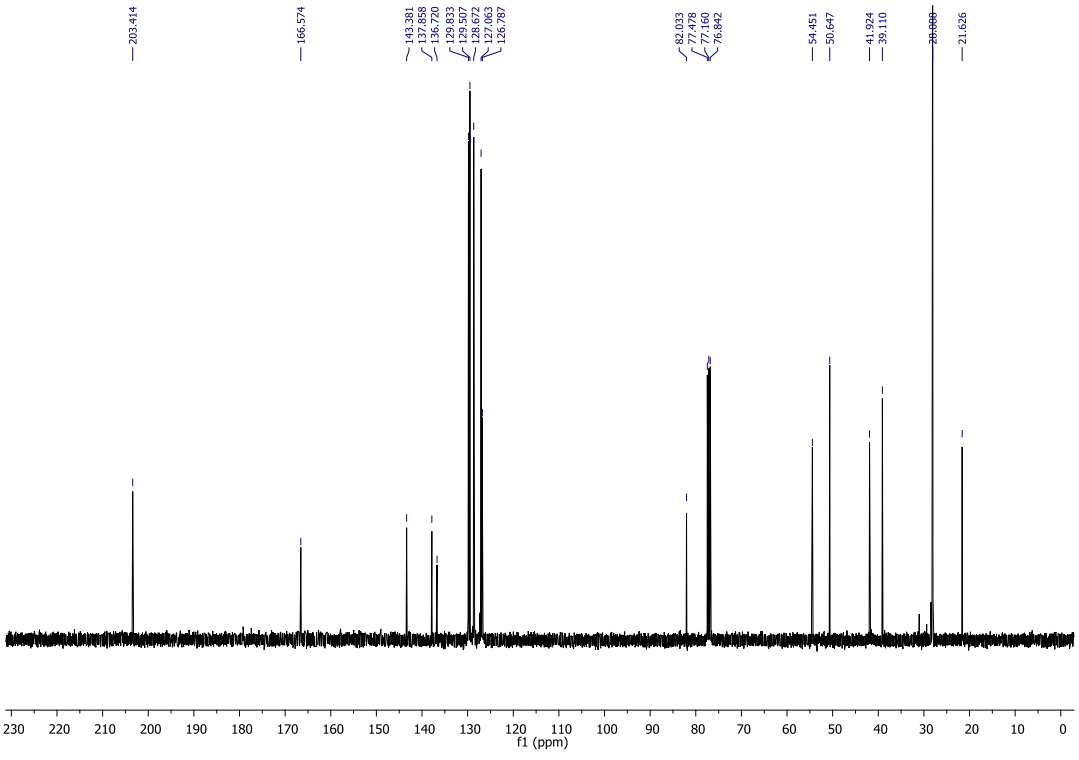

203.01
166.68
143.45
137.00
130.80
127.11
77.46
77.14
76.82
50.56
42.32
39.56
28.05
23.28
21.58
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

tert-Butyl (_S_)-6-((4-Methylphenyl)sulfonamido)-3-oxo-7-phenylheptanoate. (2.7)

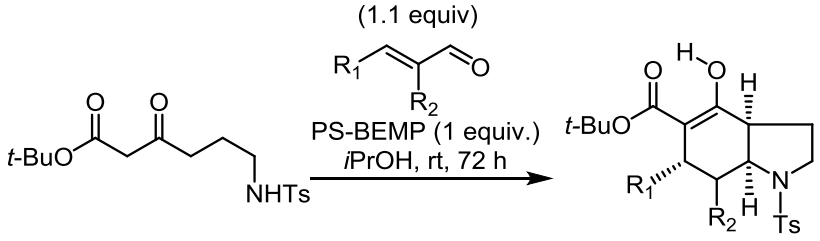


THF (10 mL) was added to of NaH (60% mineral oil) (68 mg, 2.84 mmol) and the resulting suspension was cooled 0ºC. *tert*-butyl acetoacetate (0.949 mmol, 144 mg) was added dropwise and the colorless solution was stirred at 0 ºC for 10 min. Then *n*-butyllithium (0.5 mL of 2.6 *M* in hexanes, 0.996 mmol) was added dropwise and the orange solution was stirred at 0 ºC for an additional 10 min. Aziridine **2.6** (1.04 mmol, 300 mg) in THF (1 mL) was added (the color of the dianion faded immediately on addition of the aziridine) and the reaction mixture was stirred at room temperature for 15 min. The mixture was quenched with 1 mL of NH_4Cl(aq) plus 3 mL of water and diluted with 7 ml of Et_2O. The organic phase was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave β-keto ester **2.7** (320 mg, 79%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.46 (s ,9H, CH_3), 1.51-1.61 (m, 1H, H-5), 1.78-1.86 (m, 1H, H-5), 2.41 (s, 3H, CH_3), 2.52-2.65 (m, 4H, $2CH_2$), 3.29 (dd, *J* = 3.2 Hz, 2H, CH_2), 3.40-3.49 (m, 1H, H-6), 4.63 (br, 1H, NH), 6.94 (dd, *J* = 7.6, 2.8 Hz, 2H, Ph), 7.17-7.20 (m, 3H, Ph), 7.24 (d, *J* = 8.4 Hz, 2H, *m*-ArH), 7.64 (d, *J* = 8.4 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 21.5 ($ArCH_3$), 27.9 (C-5), 28.0 (CH_3), 38.9 (C-4), 41.8 (CH_2), 50.5 (C-2), 54.3 (C-6), 81.9 (C), 126.7 (*p*-Ph), 126.9 (*o*-Ph), 128.5 (*o*-Ar), 129.3 (*m*-Ph), 129.7 (*m*-Ar), 136.6 (*p*-Ar), 137.7(*p*-Ph), 143.3 (i*pso*-Ar), 166.6 (C-3), 203.3 (CO); HRMS calcd for $C_{24}H_{35}N_2O_5S$ $[M+NH_4]^+$ 463.2261, found 463.2254.


O
O
t-BuO
NHTs
Bn
2.7
1.94
2.34
3.09
1.94
1.00
1.19
1.66
3.84
2.98
1.48
1.24
8.43
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

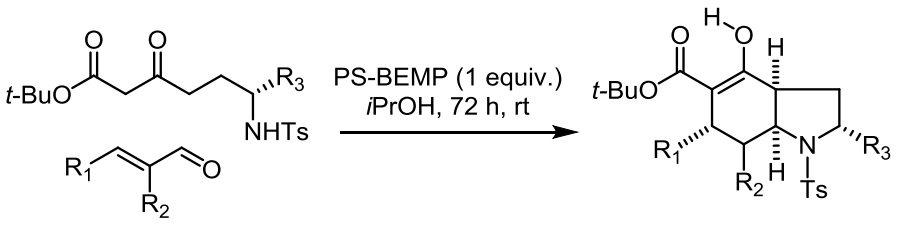

203.414
166.574
143.381
137.858
136.720
129.833
129.507
128.672
127.063
126.787
82.033
77.478
77.160
76.842
54.451
50.647
41.924
39.110
28.088
21.626
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

General Procedure for the synthesis of octahydroindoles – racemic version



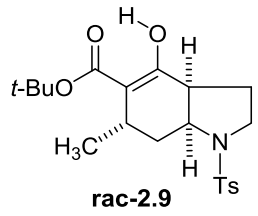
General method A: PS-BEMP (1.0 equiv) was added to a solution of the β-keto ester (1.0 equiv) and Michael acceptor (1.1 equiv) in *i*-PrOH (4 mL/mmol) and the resulting mixture was stirred at room temperature for 72 h. Filtration, evaporation of the solvent *in vacuo* and purification by column chromatography (silica gel, EtOAc/hexane gradient) gave the corresponding octahydroindole product.

Table 1: Synthesis of C-2, 6, 7 substituted octahydroindoles using general method A



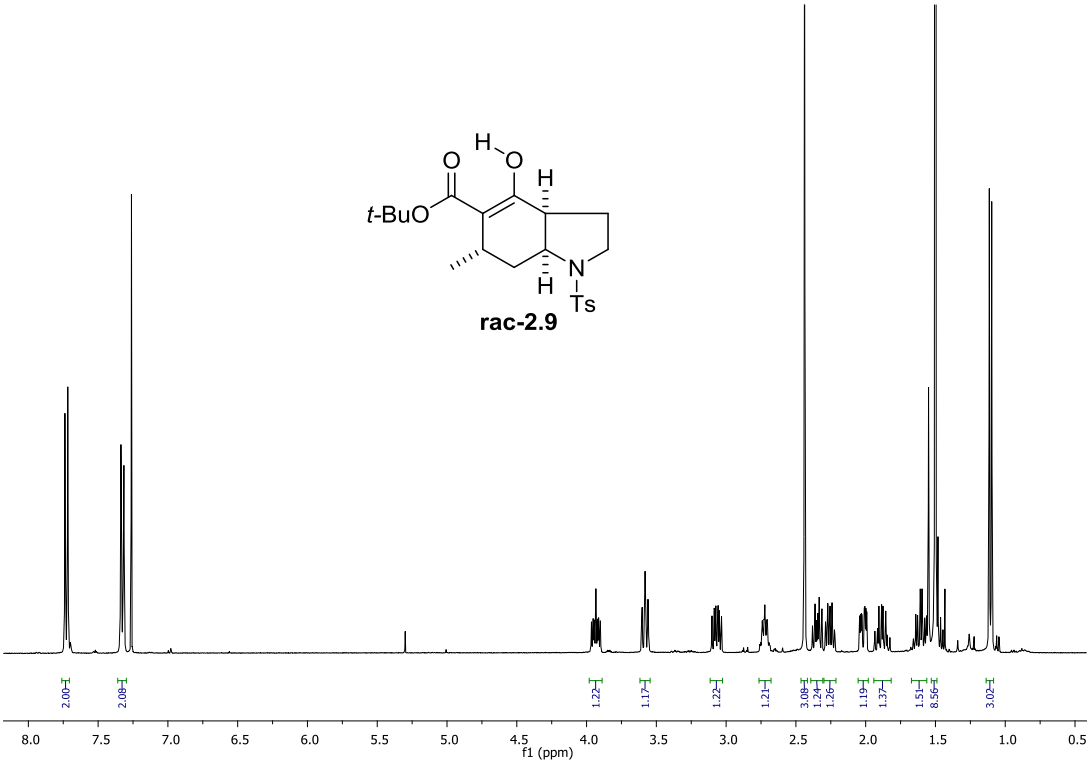
Entry	-R_1	-R_2	-R_3	Yield
1	Me	H	H	68
2	Et	H	H	59
3	$(CH_2)_5CH_3$	H	H	51
4	CH_2CH_2OH	H	H	61
5	Ph	H	H	54
6	*o*-ClPh	H	H	54
7	*o*-OMePh	H	H	52
8	$(CH_2)_2NHTs$	H	H	42
9	Me	Me	H	35
10	Me	H	Bn	44

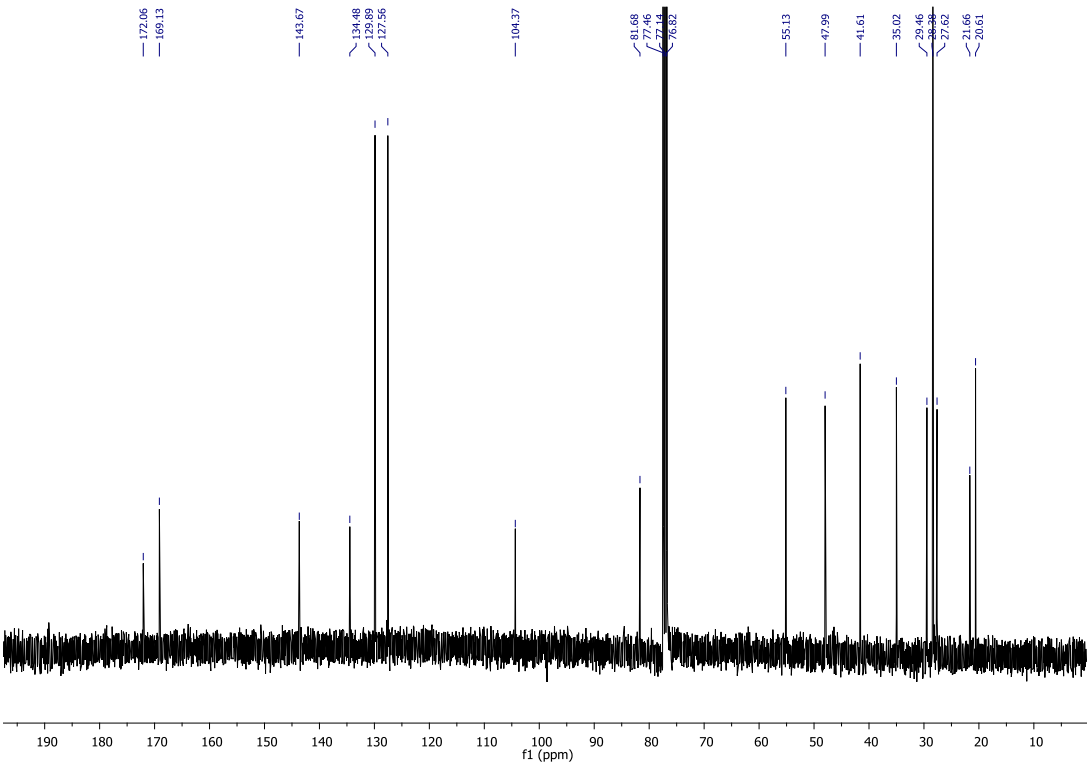
rac-(3a*R*,6*R*,7a*R*)-*tert*-Butyl 4-Hydroxy-6-methyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (rac-2.9)



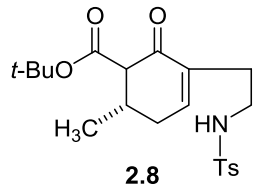
rac-2.9

This compound was prepared according to the above general procedure **A** using crotonaldehyde (15 mg, 0.213 mmol), β-keto ester **2.2** (69 mg, 0.194 mmol), PS-BEMP (88 mg, 0.194mmol) and *i*PrOH (1 mL). Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave octahydroindole ***rac*-2.9** (54 mg, 68%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.10 (s, 3H, CH_3), 1.50 (s, 9H, CH_3), 1.60 (td, *J* = 12.8, 5.2 Hz, 1H, H-7ax), 1.90 (qd, *J* = 12.0, 8.0 Hz, 1H, H-3β), 2.02 (ddd, *J* = 13.0, 5.0, 2.4 Hz, 1H, H-7eq), 2.26 (dt, *J* = 12.0, 6.0 Hz, 1H, H-3α), 2.35 (ddd, *J* = 12.0, 8.0, 7.2 Hz, 1H, H-3a), 2.44 (s, 3H,), 2.72 (qdd, *J* = 7.2, 2.8, 2.0 Hz, 1H, H-6eq), 3.06 (ddd, *J* = 12.0, 8.0, 6.0 Hz, 1H, H-2α), 3.58 (t, *J* = 8.0 Hz, 1H, H-2β), 3.93 (ddd, *J* = 12.8, 8.0, 4.8 Hz, 1H, H-7a), 7.35 (d, 2H, *m*-ArH), 7.75 (d, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 20.5 (CH_3), 21.5 ($ArCH_3$). 27.5 (C-6), 28.2 (CH_3), 29.3 (C-3), 34.9 (C-7), 41.5 (C-3a), 47.9 (C-2), 55.0 (C-7a) 81.5 (C), 104.2 (C-5), 127.4 (*o*-Ar), 129.8 (*m*-Ar), 134.4 (*p*-Ar), 143.5 (i*pso*-Ar), 169.0 (C-4), 171.9 (CO); HRMS calcd for $C_{21}H_{30}NO_5S$ $[M+H]^+$ 408.1839, found 408.1848.


H
O
O
H
t-BuO
H
N
Ts
rac-2.9
2.00
2.08
1.22
1.17
1.22
1.21
3.08
1.24
1.26
1.19
1.37
1.51
8.56
3.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

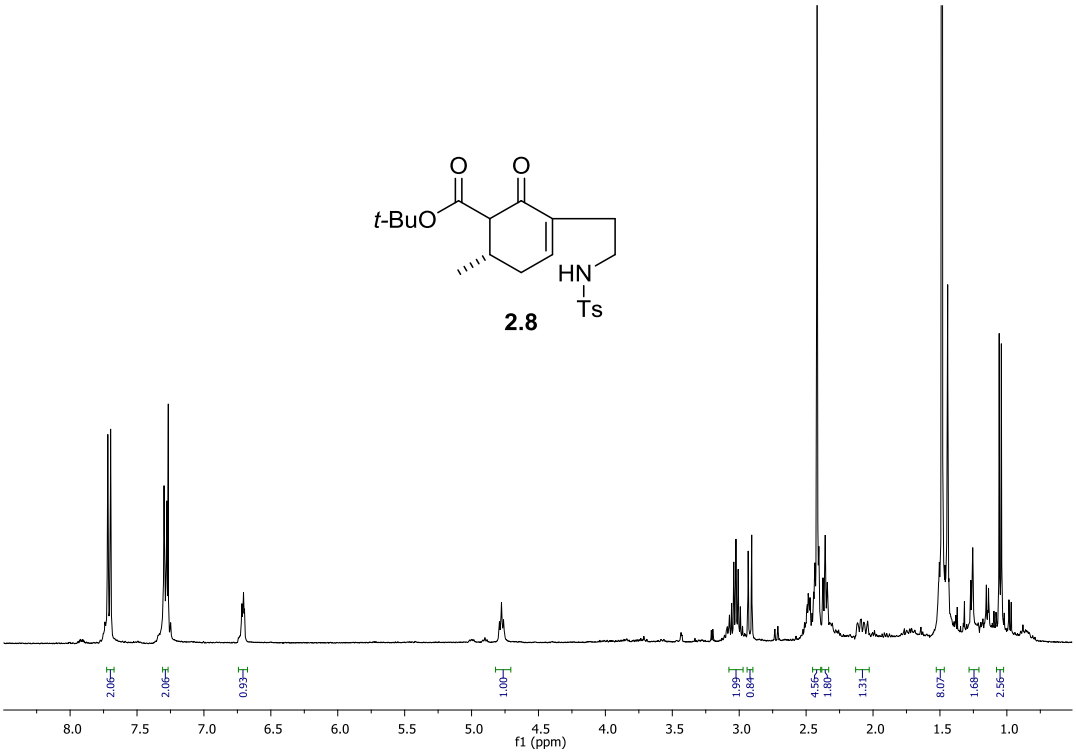

172.06
169.13
143.67
134.48
129.89
127.56
104.37
81.68
77.46
77.14
76.82
55.13
47.99
41.61
35.02
29.46
28.38
27.62
21.66
20.61
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

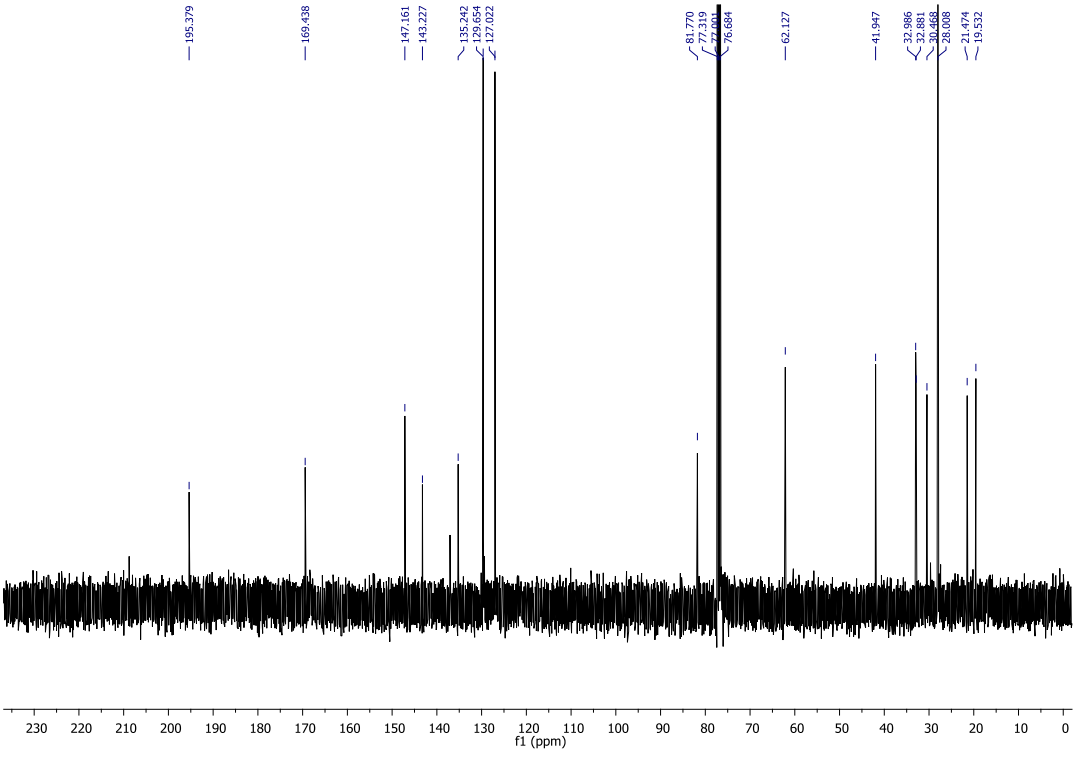
tert-Butyl 6-Methyl-3-(2-((4-methylphenyl)sulfonamido)ethyl)-2-oxocyclohex-3-ene-1-carboxylate (2.8)



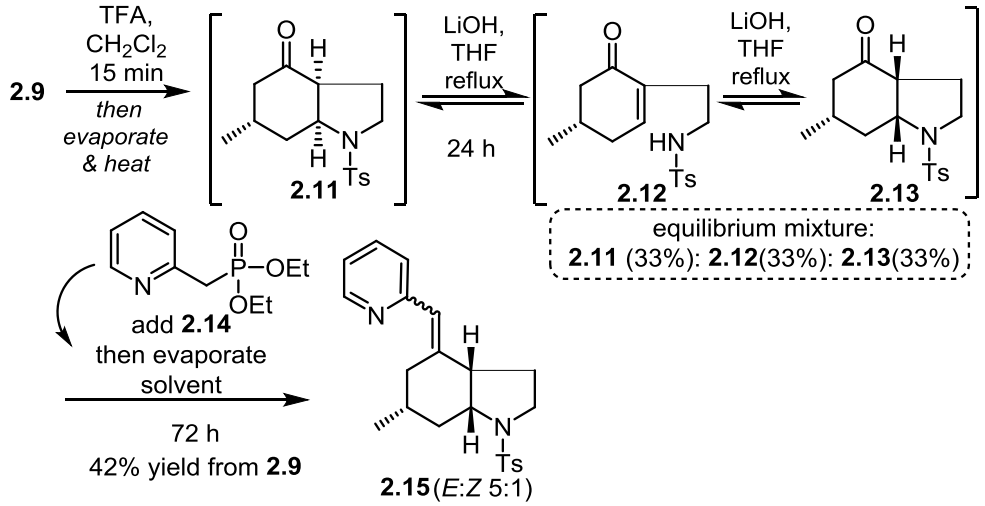
2.8

Data for 2.8: ^{1}H NMR (400 MHz, COSY) δ 1.05 (d, *J* = 6.4 Hz, 3H, CH_3), 1.49 (s, 9H, CH_3), 2.08 (ddq, *J* = 11.8, 8.9, 2.1 Hz, 1H, H-6ax), 2.36 (t, *J* = 6.5 Hz, 2H, H-1´), 2.42-2.54 (masked, 2H, H-5), 2.43 (s, 3H, CH_3Ar), 2.92 (d, *J* = 10.7 Hz, 1H, H-1ax), 3.02 (m, 2H, H-2'), 4.78 (t, *J* = 6.2 Hz, 1H, NH), 6.71 (br, 1H, H-4), 7.29 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.71 (d, *J* = 8.4 Hz, 2H, *o*-Ts). ^{13}C NMR (400 MHz, HSQC) δ 19.5 (CH_3), 21.5 (ArCH_3), 28.0 (CH_3), 30.5 (C-2´), 32.9 (C-5), 33.0 (C-6), 41.9 (C-1´), 62.1 (C-1), 81.8 (C), 127.0 (*o*-Ts), 129.7 (*m*-Ts), 135.2 (*p*-Ts), 143.2 (*ipso*-Ts), 147.2 (C-4), 169.4 (CO), 195.4 (C-2). HRMS calcd for $C_{21}H_{33}N_2O_5S$ (M+NH_4^+) 425.2105, found 425.2121.


O
O
t-BuO
HN
Ts
2.8
2.06
2.06
0.93
1.00
1.99
0.84
4.56
1.80
1.31
8.07
1.68
2.56
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


195.379
169.438
147.161
143.227
135.242
129.654
127.022
81.770
77.319
77.001
76.684
62.127
41.947
32.986
32.881
30.468
28.008
21.474
19.532
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

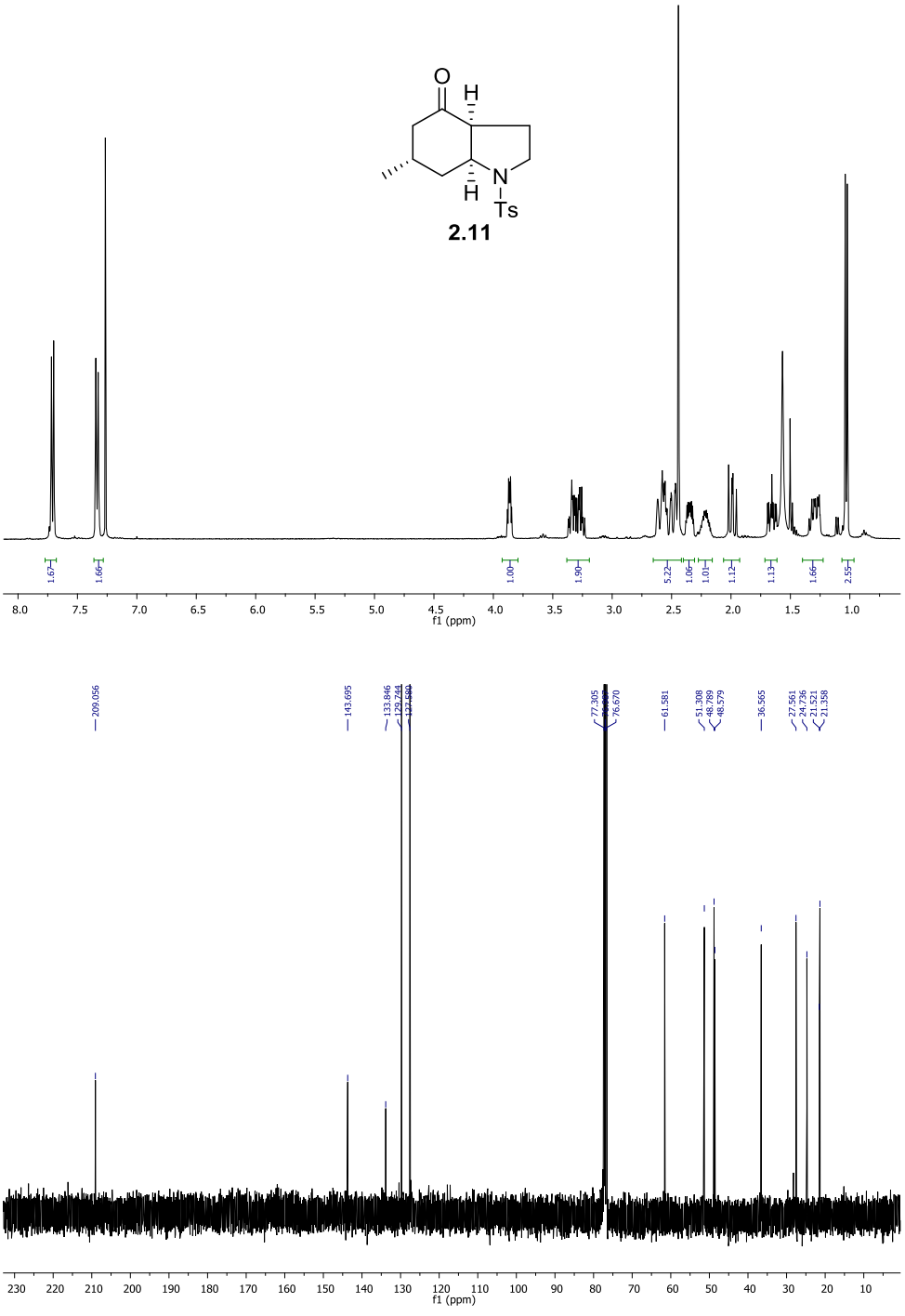
(3aS,6*R*,7a*R,E*)-6-Methyl-4-(pyridin-2-ylmethylene)-1-tosyloctahydro-1*H*-indol. (2.15)



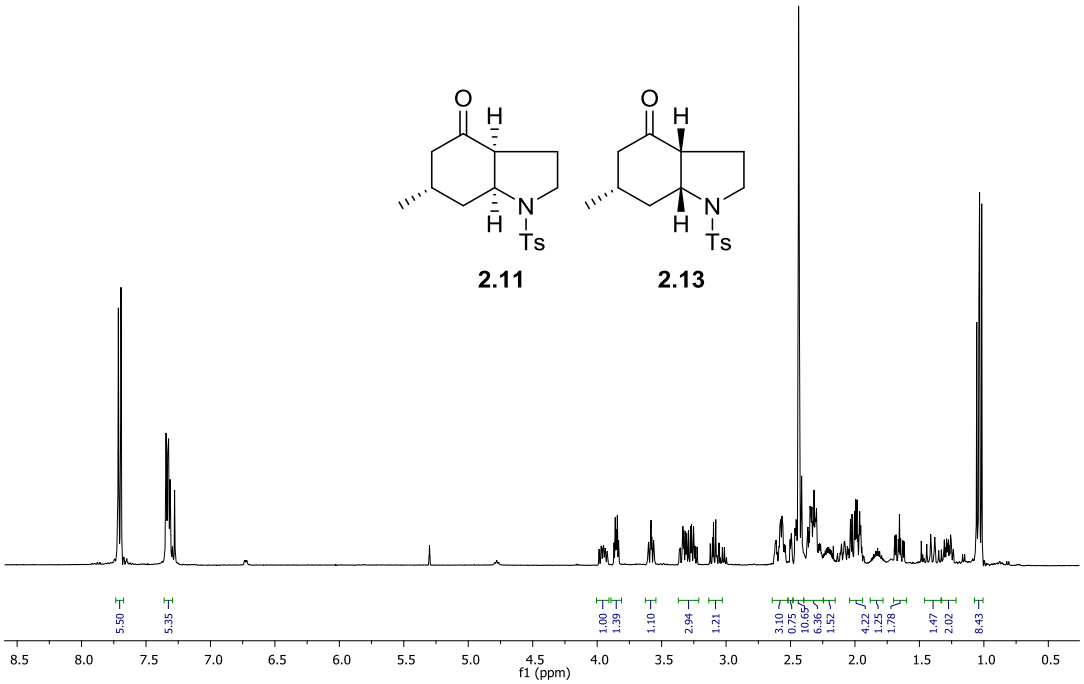
The keto ester **2.9** (191mg, 0.471 mmol) was dissolved in TFA (1 mL) and stirred for 15 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 x 2 mL). The crude mixture was treated with acetic acid (4 mL) and the reaction flask was maintained on the rotator evaporator under vacuum at 90 ºC for 3 h to give the compound **2.11** as brown oil. The crude octahydroindole **2.11** was dissolved in THF (9 mL), LiOH (113 mg, 4.71 mmol) was added and the resulting mixture was refluxed for 24 h. After cooling to room temperature, phosphonate **2.14** (323 mg, 1.41 mmol) was added in one portion followed by further portions of finely ground LiOH (56 mg, 2.36 mmol) and the solvent was evaporated. The mixture was stirred without solvent at room temperature for 3 days. The crude mixture was filtered and concentrated *in vacuo*. Purification by column chromatography (25→50→100% EtOAc/hexane) gave the coupled product **2.15** (75 mg, 42%) as a brown solid and as a 5:1 mixture of *E*/*Z* isomers.[148] **Data for 2.11:** ^{1}H NMR (400 MHz, COSY) δ 1.03 (d, *J* = 6.6 Hz, 3H, CH_3), 1.25-1.34 (m, 1H, H-3β), 1.65 (ddd, *J* = 14.4, 10.8, 3.6 Hz, 1H, H-7ax), 1.99 (dd, *J* = 14.5, 11.7 Hz, 1H, H-5ax), 2.17-2.27 (m, 1H, H-6ax), 2.32-2.38 (m, 1H, H-3α), 2.44 (s, 3H, $ArCH_3$), 2.49 (dt, *J* = 3.6, 2.0 Hz, 1H, H-5eq), 2.54-2.56 (m, 1H, H-7a), 2.58-2.62 (m, 1H, H-7eq), 3.23-3.37 (m, 2H, H-2), 3.86 (dt, *J* = 7.2, 3.6 Hz, 1H, H-3a), 7.34 (d, *J* = 7.9 Hz, 2H, *m*-Ar), 7.71 (d, *J* = 7.5 Hz, 2H, *o*-Ar), ^{13}C NMR (400 MHz, HSQC) δ 21.3 ($ArCH_3$), 21.5 (CH_3), 24.7 (C-3), 27.6 (C-6), 36.6 (C-7), 48.6 (C-

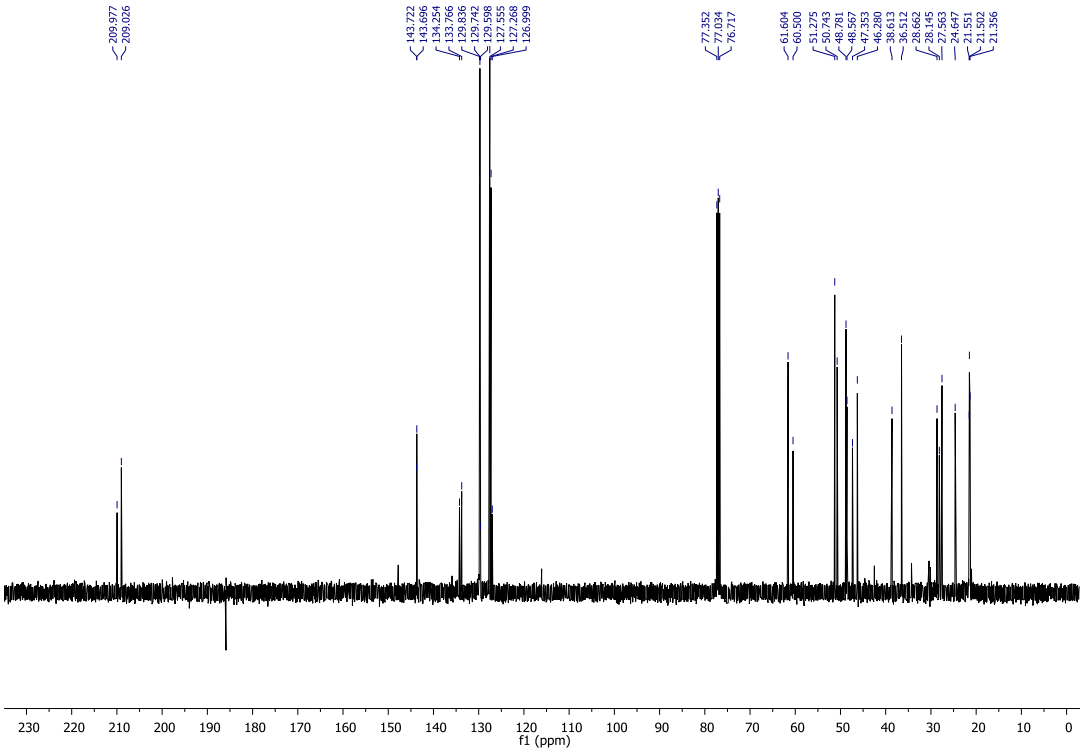
[148] Pure samples of **2.15-*E*** and **2.15-*Z*** could be obtained by careful column chromatography (25→50→100% EtOAc/hexane). Firstly eluted the minor *Z* isomer, followed by the major *E* isomer.

5), 48.8 (C-2), 51.3 (C-7a), 61.6 (C-3a), 127.6 (*o*-Ar), 129.7 (*m*-Ar), 133.8 (*p*-Ar), 143.7 (i*pso*-Ar), 209.1 (C-4); HRMS calcd for $C_{21}H_{30}NO_5S$ $[M+H]^+$ 408.1839, found 408.1848.

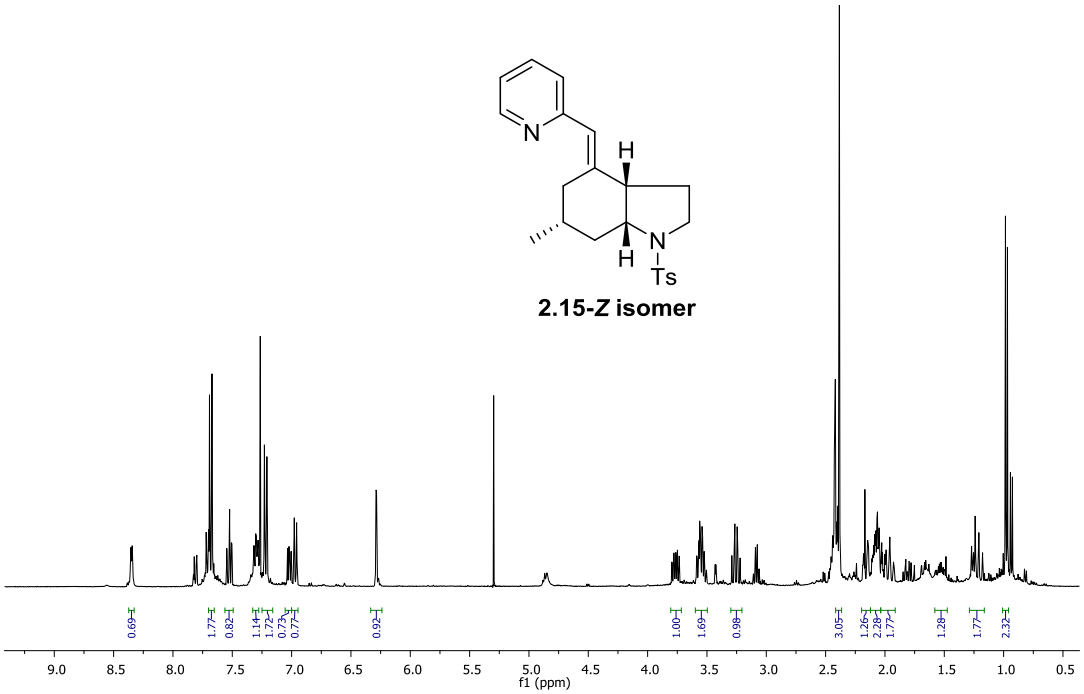


Data for 2.13: ^{1}H NMR (400 MHz, COSY) δ 1.05 (d, *J* = 6.4 Hz, 3H, CH_3), 1.33-1.39 (m, 1H, H-7ax), 1.78-1.83 (m, 1H, H-6), 1.99 (ddd, *J* = 16.4, 12.8, 4.8 Hz, 2H, H-3), 1.94-2.02 (m, 1H, H-5ax), 2.24-2.30 (m, 1H, H-7eq), 2.28-2.33 (m, 1H, H-5eq), 2.28-2.36 (m, 1H, H-7a), 2.44 (s, 3H,), 3.09 (td, *J* = 10.0, 6.8 Hz, 1H, H-2α) 3.58 (ddd, *J* = 10.0, 8.0, 2.4 Hz, 1H, H-2β), 3.95 (ddd, *J* = 11.2, 8.0, 6.0 Hz, 1H, H-3a), 7.32 (d, *J* = 8.0 Hz, 2H, *m*-Ar), 7.70 (d, *J* = 8.0 Hz, 2H, *o*-Ar), ^{13}C NMR (400 MHz, HSQC) δ 21.5 ($ArCH_3$), 21.5 (CH_3), 28.1 (C-3), 28.7 (C-6), 38.6 (C-7), 46.3 (C-5), 47.4 (C-2), 50.7 (C-7a), 60.5 (C-3a), 127.3 (*o*-Ar), 129.8 (*m*-Ar), 134.3 (*p*-Ar), 143.7 (i*pso*-Ar), 210.0 (C-4); HRMS calcd for $C_{21}H_{30}NO_5S$ $[M+H]^+$ 408.1839, found 408.1848.

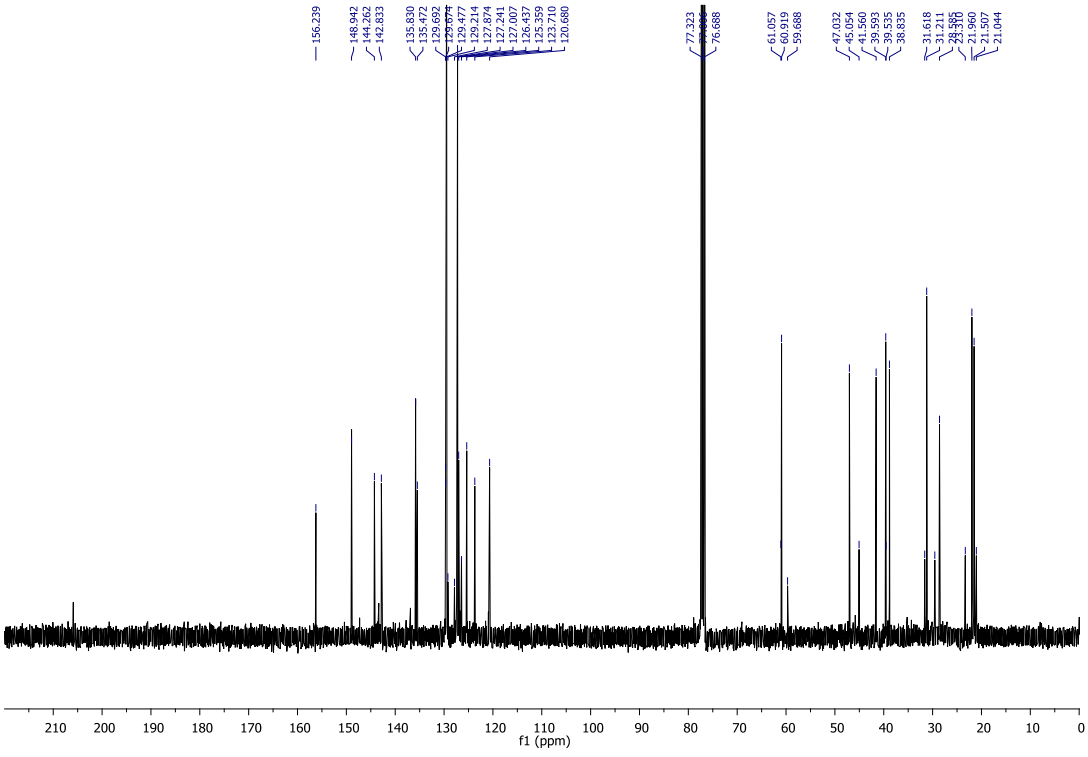

O
H
N
Ts
H
2.11
2.13
5.50
5.35
1.00
1.39
1.10
2.94
1.21
3.10
0.75
10.65
6.36
1.52
4.22
1.25
1.78
1.47
2.02
8.43
f1 (ppm)


209.977
209.026
143.722
143.696
134.254
133.766
129.856
129.742
126.598
127.555
127.268
126.999
77.352
77.034
76.717
61.604
60.500
51.275
50.743
48.781
48.567
47.353
46.280
38.613
36.512
28.662
28.145
27.563
24.647
21.551
21.502
21.356
f1 (ppm)

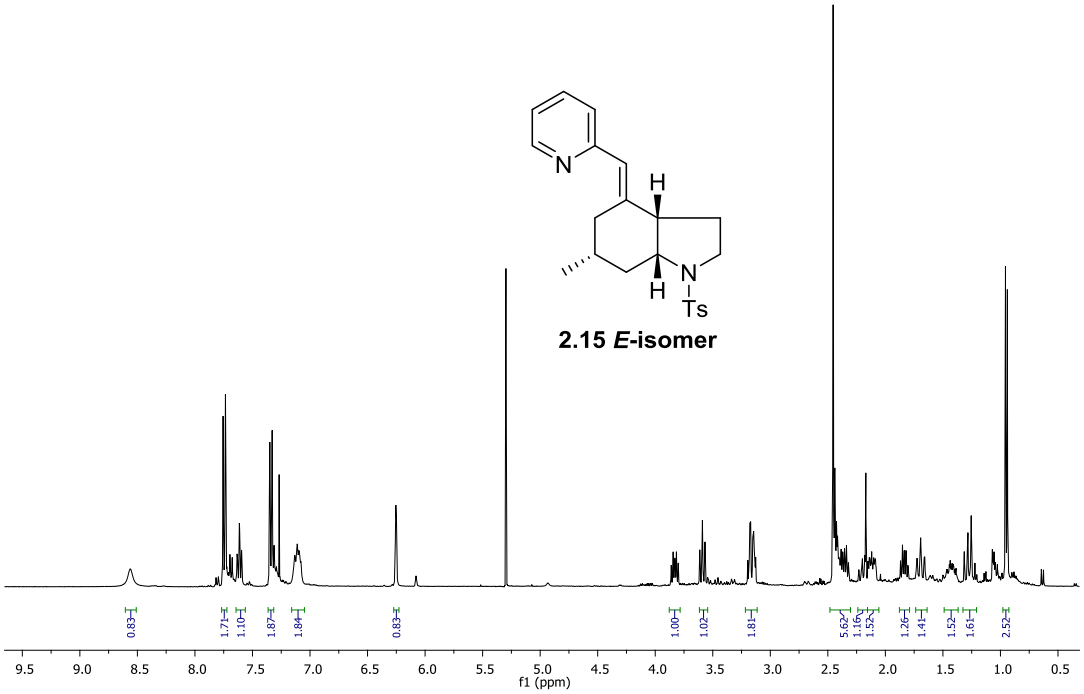
2.15-*Z* isomer: ^{1}H NMR (400 MHz, COSY) δ 0.98 (d, *J* = 6.8 Hz, CH_3), 1.22 (q, 12.0, 6.4 Hz, H-7ax), 1.49-1.58 (m, 1H, H-6), 1.96 (td, *J* = 14.4, 2.0 Hz, 1H, H-5ax), 2.03-2.11 (m, 2H, H-3 H-7eq), 2.16 (dt, *J* = 14.4, 4.8, 2.4 Hz, 1H, H-5eq), 2.38 (s, 3H, $ArCH_3$), 3.26 (td, *J* = 17.6, 10.0, 7.6 Hz, 1H, H-2ax), 3.51-3.59 (m, 2H, H-3a, H-2eq), 3.76 (ddd, *J* = 13.2, 11.6, 7.2, 6.0 Hz, 1H, H-7a), 6.29 (d, *J* = 1.6 Hz, 1H, =CH), 6.97 (d, *J* = 8.0 Hz, 1H, H-3 Py), 7.02 (ddd, *J* = 7.6, 6.0, 4.8, 0.8 Hz, 1H, H-5 Py), 7.22 and 7.68 (2d, *J* = 8.0 and 8.4 Hz, 2H each, Ts), 7.52 (td, *J* = 9.2, 7.6, 1.6 Hz, 1H, H-4 Py), 8.35 (d, *J* = 4.4 Hz, H-6 Py); ^{13}C NMR (100 MHz, HSQC) δ 21.5 (CH_3Ar), 22.0 (CH_3), 28.6 (C-3), 31.2 (C-6), 38.8 (C-7), 39.6 (C-3a), 41.6 (C-5), 47.0 (C-2), 60.9 (C-7a), 120.7 (C-5 Py), 123.7 (C-3 Py), 125.4 (=CH), 126.4 (*o*-Ts), 129.7 (*m*-Ts), 135.5 (C-4 Py), 135.8 (*p*-Ts), 142.8 (*ipso*-Ts), 144.3 (C-5), 148.9 (C-6 Py), 156.2 (C-2 Py). HRMS calcd for $C_{22}H_{27}N_2O_2S$ $(M+H)^+$ 383.1787, found 383.1788.


N
H
H
N
Ts
0.69
1.77
0.82
1.14
1.72
0.73
0.77
0.92
1.00
1.69
0.98
3.05
1.26
2.28
1.77
1.28
1.77
2.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

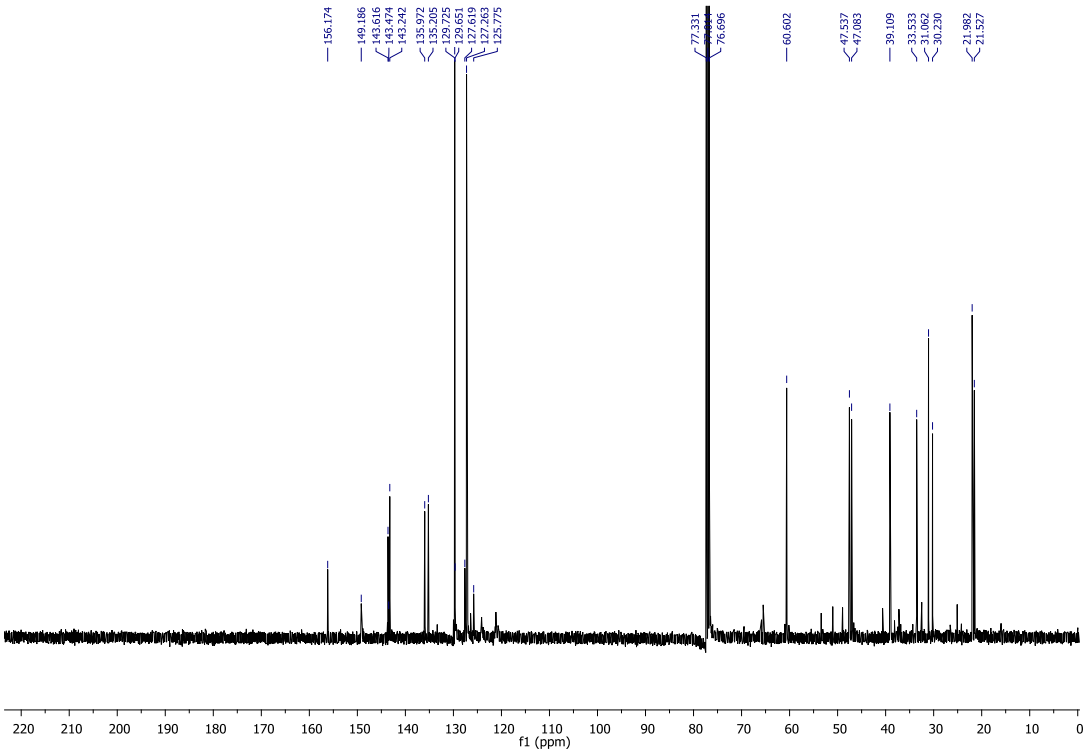
2.15-*Z* isomer


156.239
148.942
144.262
142.833
135.830
135.472
129.692
129.677
129.214
127.874
127.241
127.007
126.437
125.359
123.710
120.680
77.323
76.688
61.057
60.919
59.688
47.032
45.054
41.560
39.593
39.535
38.835
31.618
31.211
21.960
21.507
21.044
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

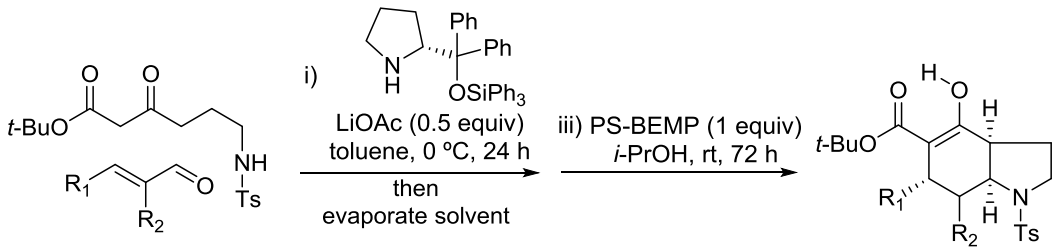
2.15-*E* isomer: ^{1}H NMR (400 MHz, COSY) δ 0.95 (d, *J* = 6.4 Hz, CH_3), 1.27 (q, 11.2 Hz, H-7ax), 1.40-1.47 (m, H-6), 1.69 (td, *J* = 14.0, 1.6 Hz, 1H, H-5), 1.84 (dt, *J* = 12.8, 6.8 Hz, H-3ax), 2.09-2.15 (m, 1H, H-7eq), 2.17-2.23 (m, 1H, H-3eq), 2.28-2.40 (m, 1H, H-3a), 2.45 (s, $ArCH_3$), 3.16 (dt, *J* = 10.8, 9.6, 7.2 Hz, 2H, H-5, H-2ax), 3.59 (ddd, *J* = 9.6, 8.4, 0.8 Hz,1H, H-2eq), 3.83 (dt, *J* = 11.6, 6.8 Hz, 1H, H-7a), 6.25 (d, *J* = 1.6 Hz, =CH), 7.08-7.14 (m, 2H, H-3 Py, H-5 Py), 7.34 and 7.75 (2d, *J* = 8 Hz, 2 H each, Ts), 7.61 (td, *J* = 8.0, 2.0 Hz, 1H, H-4 Py), 8.56 (br, 1H, H-6 Py); ^{13}C NMR (100 MHz, HSQC) δ 21.5 (CH_3Ar), 22.0 (CH_3), 30.2 (C-3), 31.1 (C-6), 33.5 (C-5), 39.1 (C-7), 47.1 (C-2), 47.5 (C-3a), 60.6 (C-7a), 120.7 (C-5 Py), 123.7 (C-3 Py), 125.4 (=CH), 126.3 (*o*-Ts), 129.7 (*m*-Ts), 135.2 (C-4 Py), 136.0 (*p*-Ts), 143.2 (*ipso*-Ts), 143.6 (C-5), 149.2 (C-6 Py), 156.2 (C-2 Py). HRMS calcd for $C_{22}H_{27}N_2O_2S$ $(M+H)^+$ 383.1787, found 383.1788.


N
H
H
N
Ts
0.83
1.71
1.10
1.87
1.84
0.83
1.00
1.02
1.81
5.62
1.16
1.52
1.26
1.41
1.52
1.61
2.52
f1 (ppm)

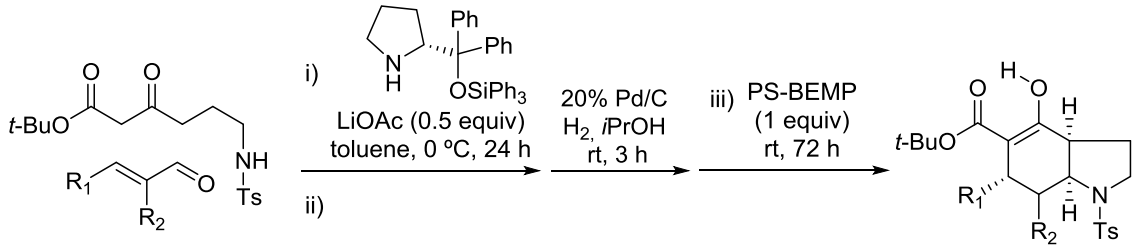
2.15 *E*-isomer


156.174
149.186
143.616
143.474
143.242
135.972
135.205
129.725
129.651
127.619
127.263
125.775
77.331
76.696
60.602
47.537
47.083
39.109
33.533
31.062
30.230
21.982
21.527
f1 (ppm)

<u>Asymmetric procedure:</u> Synthesis of octahydroindoles - enantioselective version



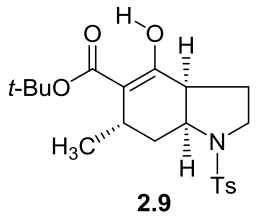
General Method B: To β-keto ester (1.0 equiv) and Michael acceptor (1.1 equiv) in toluene at 0 ºC was added LiOAc (0.5 equiv) followed by bis-phenyl-$OSiPh_3$-pyrrolidine **2.16** (0.1 equiv) and the resulting mixture was stirred at 0 ºC for 24 h. The solvent was removed *in vacuo* and the residue dissolved in *i*-PrOH (4 mL/mmol). PS-BEMP (1.0 equiv) was added and the resulting mixture was stirred at room temperature for 72 h. Filtration, concentration *in vacuo* and purification by column chromatography (silica gel, EtOAc/hexane gradient) gave the corresponding enantioenriched octahydroindole product.



General Method C: To β-keto ester (1.0 equiv) and Michael acceptor (1.1 equiv) in toluene at 0 ºC was added LiOAc (0.5 equiv) followed by bis-phenyl-$OSiPh_3$-pyrrolidine **2.16** (0.1 equiv) and the resulting mixture was stirred at 0 ºC for 24 h. The solvent was removed *in vacuo* and the residue dissolved in *i*-PrOH (4 mL/mmol). Pd/C (20% w/w) was added and the flask was fitted with a hydrogen balloon and hydrogenated until no enal was observed by TLC (~3 h). PS-BEMP (1.0 equiv) was then added and the resulting mixture was stirred at room temperature for 72 h. Filtration through celite, evaporation of the solvent *in vacuo* and purification by column chromatography (silica gel, EtOAc/hexane gradient) gave the corresponding enantioenriched octahydroindole product.

Note: In the subsequent experimental procedures if the reaction did not work using organocatalysis the racemic method (general method A) is described instead.

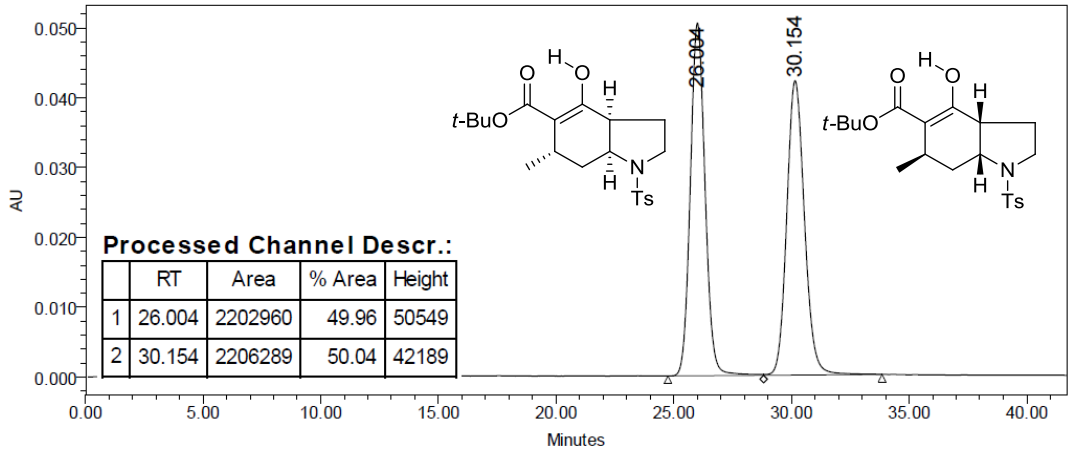
(3a*R*,6*R*,7a*R*)-*tert*-Butyl-4-Hydroxy-6-methyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.9)



2.9

This compound was prepared according to the above general method **B** using β-keto ester **2.2** (100 mg, 0.281 mmol), crotonaldehyde (22 mg, 0.309 mmol), bis-phenyl-OSiPh$_3$-pyrrolidine organocatalyst **2.16** (14 mg, 0.028 mmol), LiOAc (9 mg, 0.141 mmol) and toluene (1.0 mL) at 0 ºC for 24 h followed by cyclisation with PS-BEMP (128 mg, 0.281mmol) and *i*PrOH (1 mL). Purification by chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.9** (57 mg, 50%) as a yellow oil. For NMR data see **rac-2.9** above.

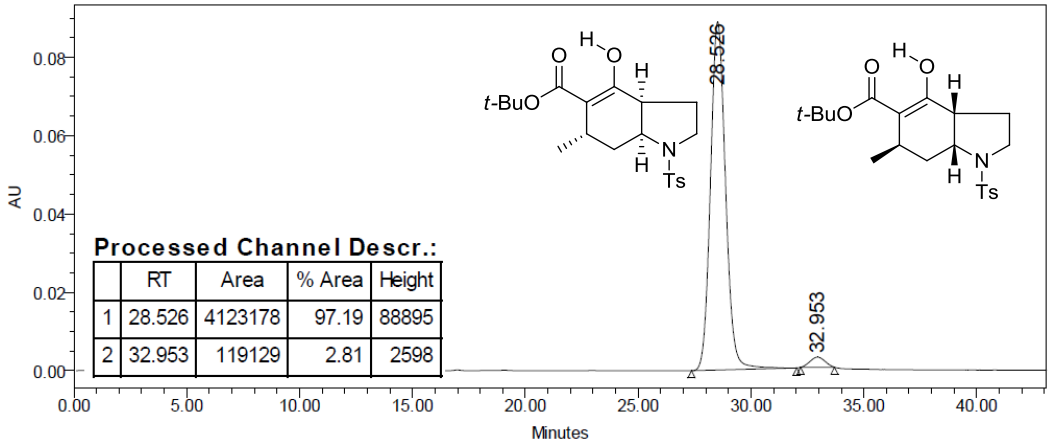
HPLC of Racemic reaction mixture (2.9)



Processed Channel Descr.:

	RT	Area	% Area	Height
1	26.004	2202960	49.96	50549
2	30.154	2206289	50.04	42189

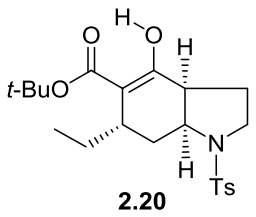
HPLC of organocatalysed reaction mixture (2.9)



Processed Channel Descr.:

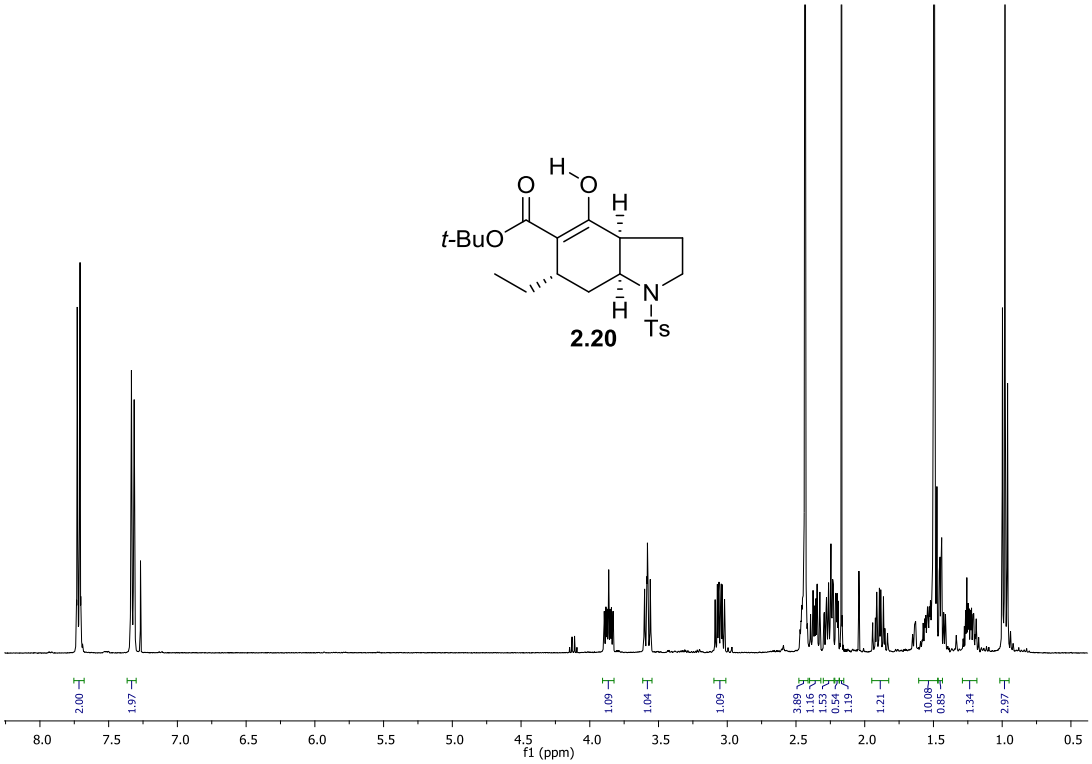
	RT	Area	% Area	Height
1	28.526	4123178	97.19	88895
2	32.953	119129	2.81	2598

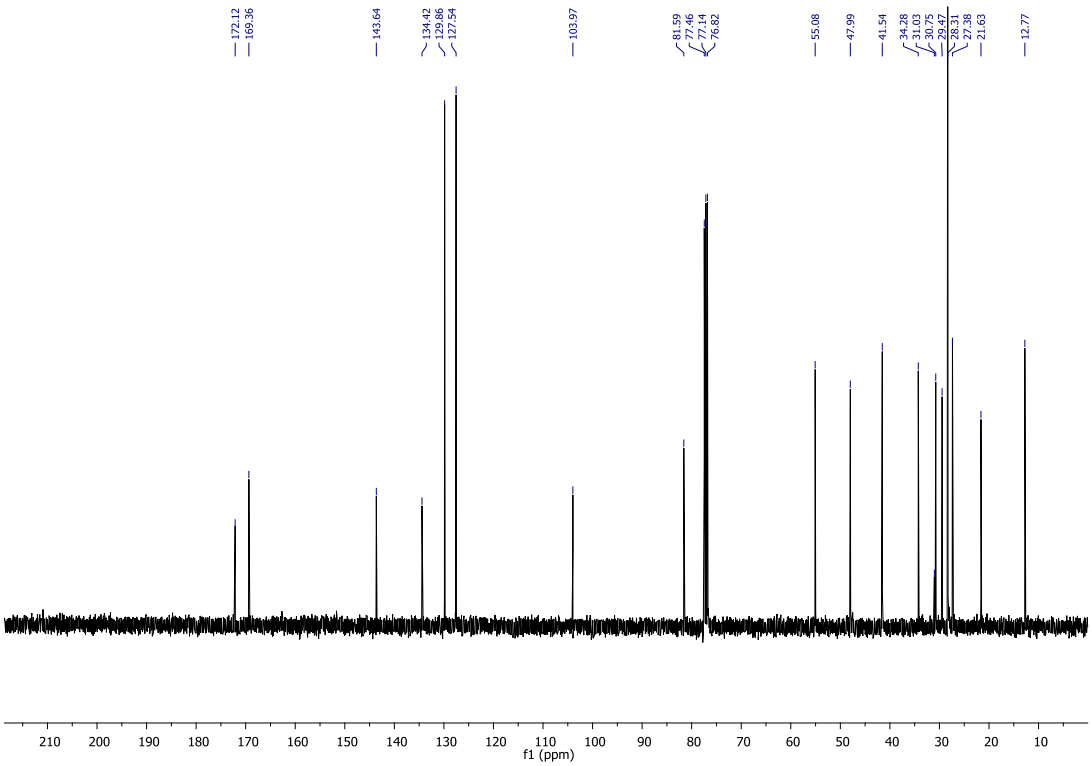
(3a*R*,6*R*,7a*R*)-*tert*-Butyl-4-Hydroxy-6-ethyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.20)



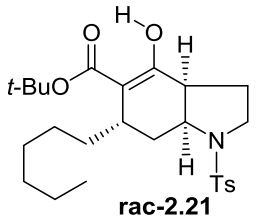
2.20

This compound was prepared according to general method **B** using *trans*-pentanal (34 mg, 0.402 mmol), β-keto ester **2.2** (130 mg, 0.366 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (19 mg, 0.037 mmol), LiOAc (12 mg, 0.183 mmol) in toluene (1.4 mL) at 0 ºC for 24 h followed by cyclisation with PS-BEMP (166 mg, 0.366 mmol) and *i*PrOH (1 mL) was stirred at room temperature. Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave octahydroindole **2.20** (78 mg, 51%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 0.98 (t, *J* = 7.4 Hz, 3H, CH_3), 1.19-1.28(m, 1H, H6-CH_2),1.38-1.44 (m, 1H, H-7), 1.49 (s, 9H, CH_3), 1.50-1.57(m, 1H, H6-CH_2) 1.89 (ddd, *J* = 19.6, 11.6, 7.6 Hz, 1H, H-3β), 2.20 (ddd, *J* = 4.7, 2.4 Hz, 1H, H-7eq), 2.21-2.29 (m, 1H, H-3α), 2.32-2.40 (m, 1H, H-6), 2.43 (s, 3H, $ArCH_3$), 2.41-2.48 (m, 1H, H-3a), 3.05 (ddd, *J* = 11.6, 9.6, 6.4 Hz, 1H, H-2α), 3.58 (ddd, *J* = 9.1, 7.8, 1.0 Hz, 1H, H-2β), 3.86 (ddd, *J* = 12.8, 8.2, 4.8 Hz, 1H, H-7a), 7.32 (d, *J* = 7.9 Hz, 2H, *m*-ArH), 7.72 (d, *J* = 8.3 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 12.8 (CH_3), 21.6 ($ArCH_3$). 27.4 (CH_2), 28.3 (CH_3), 29.5 (C-3), 30.8 (C-7), 34.3 (C-3a), 41.5 (C-6), 48.0 (C-2), 55.1 (C-7a) 81.6 (C), 104.0 (C-5), 127.5 (*o*-Ar), 129.9 (*m*-Ar), 134.4 (*p*-Ar), 143.6 (i*pso*-Ar), 169.4 (C-4), 172.1 (CO); HRMS calcd for $C_{22}H_{32}NO_5S$ $[M+H]^+$ 422.2005 found 422.1996.


H
O
O
H
t-BuO
H
N
Ts
2.20
2.00
1.97
1.09
1.04
1.09
3.89
1.16
1.53
0.54
1.19
1.21
10.08
0.85
1.34
2.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

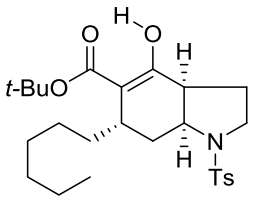

172.12
169.36
143.64
134.42
129.86
127.54
103.97
81.59
77.46
77.14
76.82
55.08
47.99
41.54
34.28
31.03
30.75
29.47
28.31
27.38
21.63
12.77
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(3a*S*,6*S*,7a*S*)-*tert*-Butyl 6-Hexyl-4-hydroxy-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate (rac-2.21)



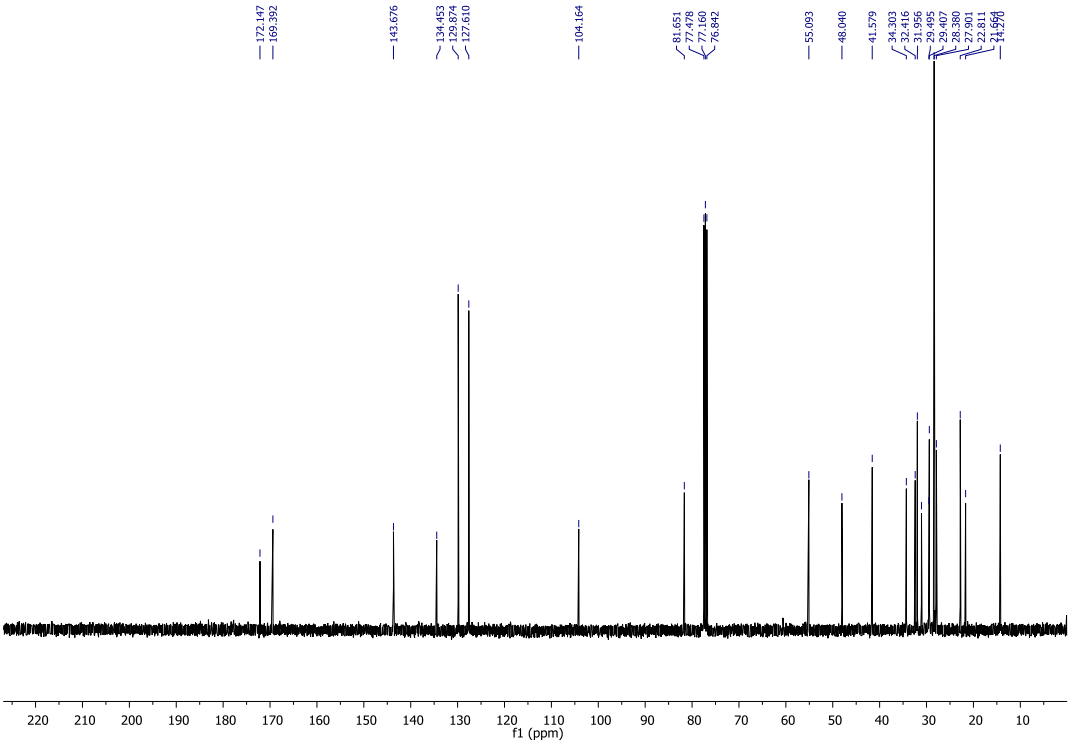
rac-2.21

This compound was prepared according to general method **A** using β-keto ester **2.2** (106 mg, 0.299 mmol), *trans*-2-nonenal (46 mg, 0.329 mmol), PS-BEMP (134 mg, 0.299 mmol) and *i*PrOH (1.2 mL). Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **rac-2.21** (73 mg, 51%) as a white solid. ^{1}H NMR (400 MHz, COSY) δ 0.92 (t, *J* = 6.8 Hz, 3H, CH_3), 1.20-1.38 (m, 8H, H-alkyl), 1.41-1.48 (m, 3H, H-alkyl, H-7), 1.50 (s, 9H, CH_3), 1.88 (ddd, *J* = 19.6, 11.6, 8.0 Hz, 1H, H-3) 2.19 (ddd, *J* = 7.2, 4.8, 2.4 Hz, 1H, H-7), 2.27 (q, *J* = 12.8, 6.4 Hz, 1H, H-3), 2.37 (dt, *J* = 11.6, 7.2 Hz, 1H, 3a), 2.44 (s, 3H, $ArCH_3$), 2.49-2.57 (m, 1H, H-6), 3.06 (ddd, *J* = 11.2, 9.6, 6.4 Hz, 1H, H-2), 3.58 (t, *J* = 8.8 Hz, 1H, H-2), 3.85 (ddd, *J* = 12.8, 8.4, 4.8 Hz, 1H, H-7a), 7.32 (d, *J* = 8.4 Hz, 2H, *m*-ArH), 7.72 (d, *J* = 8.4 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 14.3 (CH_3), 21.7 (CH_3), 22.8 (C-alkyl) 27.9 (C-alkyl), 28.4 (CH_3), 29.4 (C-alkyl), 29.5 (C-3), 31.1 (C-7), 32.0 (C-alkyl), 32.4 (C-6), 34.3 (C-1'), 41.6 (C-3a), 48.0 (C-2), 55.1 (C-7a), 81.7 (C), 104.2 (C-5), 127.6 (*o*-Ph), 129.9 (*o*-Ar), 134.5 (*p*-Ar), 143.7 (i*pso*-Ar), 169.4 (C-4), 172.1 (CO); HRMS calcd for $C_{26}H_{40}NO_5S$ $[M+H]^+$ 478.2622, found 478.2624.

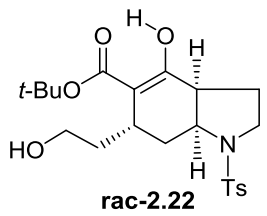

H
O
O
H
t-BuO
N
H
Ts

rac-2.21

1.84
1.78
1.00
0.96
0.99
0.99
2.63
1.08
1.05
1.04
1.17
10.90
7.99
2.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


172.147
169.392
143.676
134.453
129.874
127.610
104.164
81.651
77.478
77.160
76.842
55.093
48.040
41.579
34.303
32.416
31.956
29.495
29.407
28.380
27.901
22.811
14.270
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

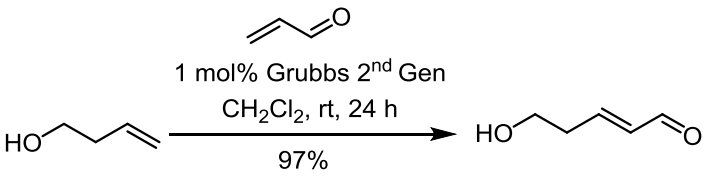
(3a*S*,6*R*,7a*S*)-*tert*-Butyl-4-Hydroxy-6-(2-hydroxyethyl)-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (rac-2.22)



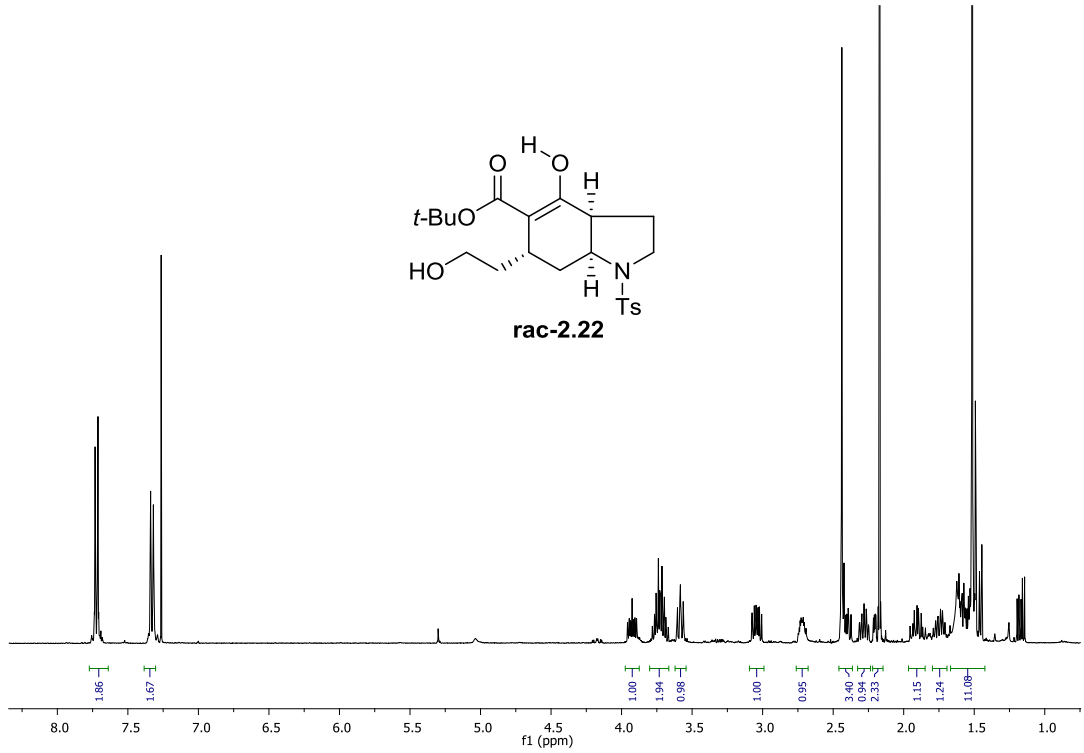
rac-2.22

This compound was prepared according to general method **A** using (*E*)-5-hydroxypent-2-enal[149] (17 mg, 0.171 mmol), β-keto ester **2.2** (55 mg, 0.155 mmol), PS-BEMP (70 mg, 0.155 mmol) and *i*PrOH (0.6 mL). Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole ***rac*-2.22** (42 mg, 61%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.52 (s, 9H, CH_3), 1.53-1.62 (m, 2H, H-7 and H-1'), 1.71-1.79 (m, 1H, H-1') 1.90 (ddd, *J* = 12.0, 4.0 Hz, 1H, H-3), 2.19 (ddd, *J* = 4.8, 2.4 Hz, 1H, H-7eq), 2.25-2.32 (m, 1H, H-3α), 2.37-2.42 (m, 1H, H-3a), 2.44 (s, 3H, $ArCH_3$), 2.69-2.75 (m, 1H, H-6), 3.04 (ddd, *J* = 11.2, 9.6, 6.4 Hz, 1H, H-2α), 3.58 (ddd, *J* = 9.2, 7.6, 0.8 Hz, 1H, H-2β), 3.67-3.78 (m, 2H, H-2'), 3.93 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1H, H-7a), 7.32 (d, *J* = 7.9 Hz, 2H, *m*-ArH), 7.72 (d, *J* = 8.3 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 21.7 ($ArCH_3$), 28.4 (CH_3), 29.4 (C-3), 29.5 (C-6), 32.2 (C-7), 37.6 (C-1'), 41.6 (C-3a), 48.0 (C-2), 55.1 (C-7a), 61.4 (C-2'), 82.3 (C), 103.3 (C-5), 127.6 (*o*-Ar), 129.9 (*m*-Ar), 134.3 (*p*-Ar), 143.8 (i*pso*-Ar), 170.1 (C-4), 171.9 (CO); HRMS calcd for $C_{22}H_{32}NO_6S$ $[M+H]^+$ 438.1949, found 438.1945.

[149] (*E*)-5-hydroxypent-2-enal was prepared according to the method of Franzen: see reference[133b]



A solution of acrolein (0.36 ml, 5.547 mmol), 3-buten-1-ol (0.11 ml, 1.386 mmol), and Grubbs catalyst 2nd generation (12 mg, 0.014 mmol) was stirred in dry CH_2Cl_2 (1 mL) at r.t. for 24 h. Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave the enal (135 mg, 97%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (br s, 1H), 2.61 (tdd, *J* = 6.5 Hz, 6.0 Hz, 1.5 Hz, 2H), 3.85 (dd, *J* = 6.5, 6.5 Hz, 2H), 6.20 (ddt, *J* = 15.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 6.90 (dt, *J* = 15.5 Hz, 7.0 Hz, 1H), 9.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, HSQC) δ 35.8 (C-4), 60.4 (C-5), 134.3 (C-2), 155.8 (C-3), 194.5 (C-1).


H
O
O
H
t-BuO
HO
N
H
Ts
rac-2.22
1.86
1.67
1.00
1.94
0.98
1.00
0.95
3.40
0.94
2.33
1.15
1.24
11.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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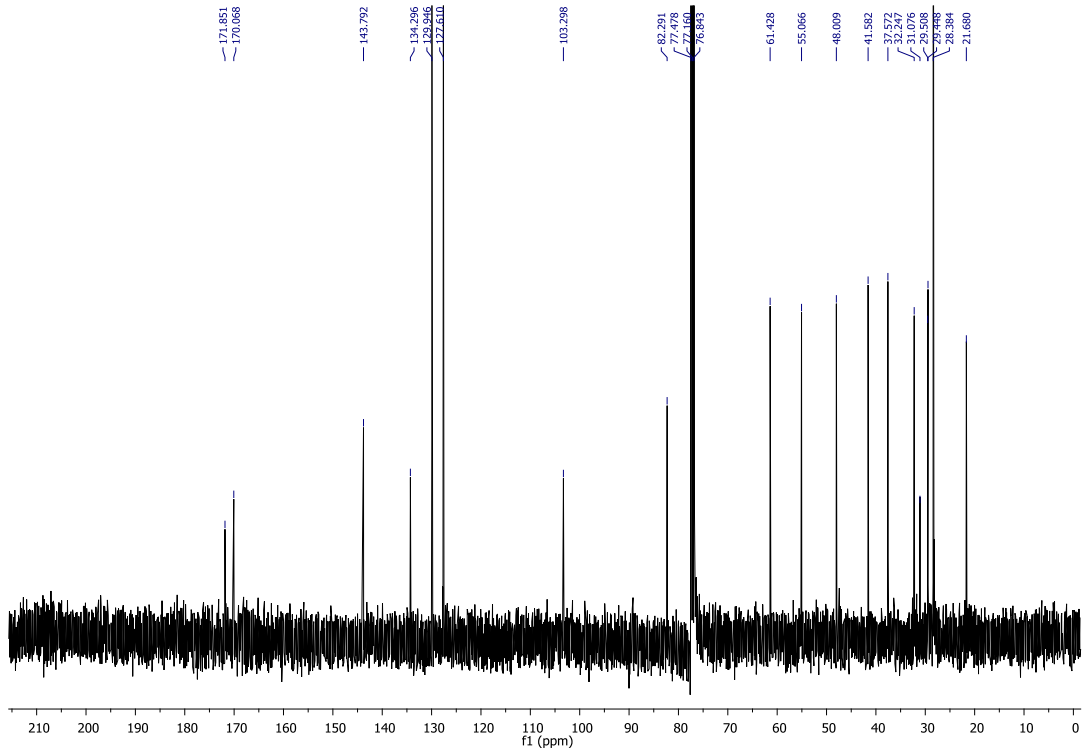
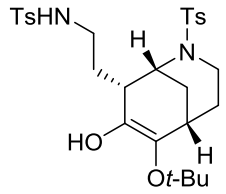
2.5
2.0
1.5
1.0
f1 (ppm)

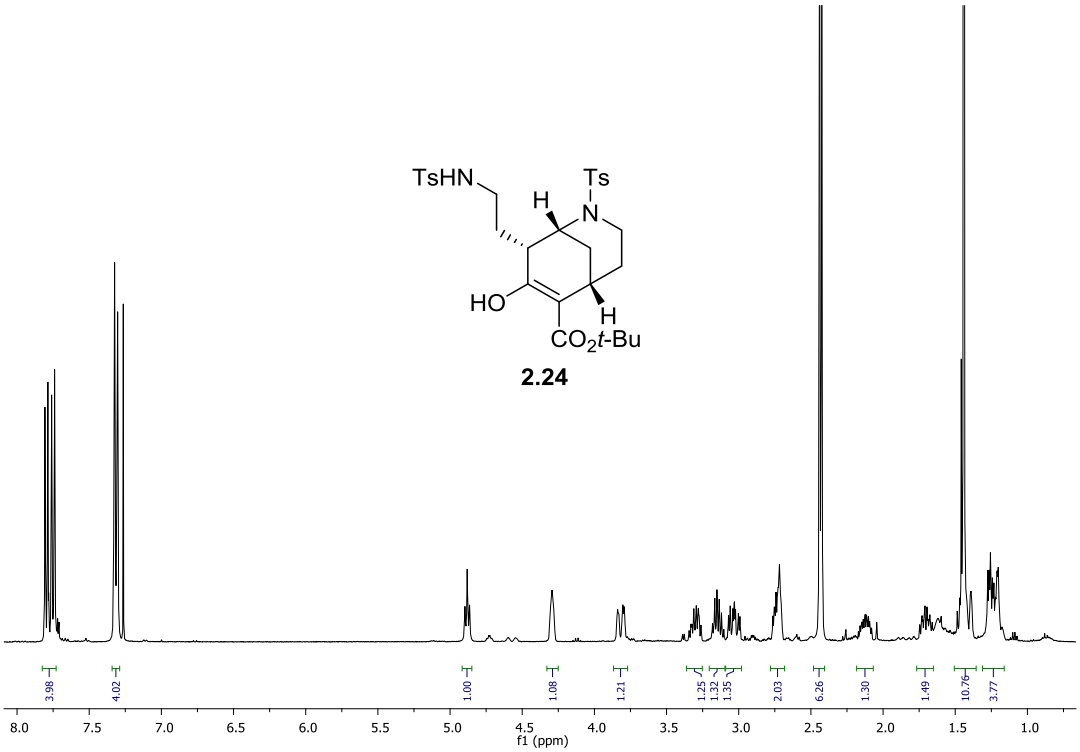

171.851
170.068
143.792
134.296
129.946
127.610
103.298
82.291
77.478
77.160
76.843
61.428
55.066
48.009
41.582
37.572
32.247
31.076
29.508
29.448
28.384
21.680
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

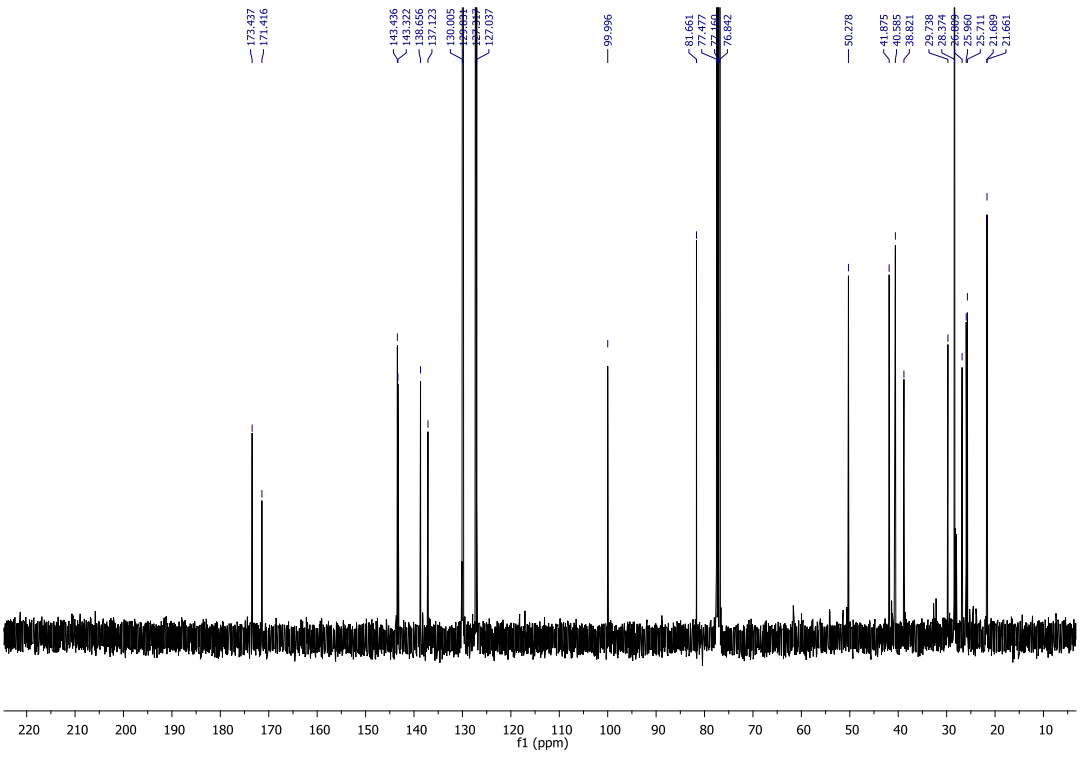
_N_-(2-((1_R_,5_S_,8_R_)-6-(_tert_-Butoxy)-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-en-8-yl)ethyl)-4-methylbenzenesulfonamide. (2.24)



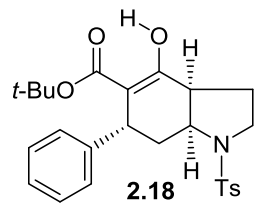
2.24

Enal **3.4** (45 mg, 0.179 mmol), β-keto ester **2.2** (58 mg, 0.163 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (8 mg, 0.016 mmol) and LiOAc (5 mg, 0.082 mmol) in toluene (0.6 mL) were stirred at 0 ºC for 24 h. The solvent was evaporated *in vacuo* and $LiOH \cdot H_2O$ (7 mg, 0.163 mmol), H_2O (29 mg, 1.63 mmol) and *i*PrOH (7 mL) were added and the resulting mixture was stirred at room temperature for 16 h. Purification by chromatography (0→10→25→50% EtOAc/hexane) gave **2.24** (54 mg, 59%) as a white solid. ^{1}H NMR (400 MHz, COSY) δ 1.20-1.27 (m, 3H, C8-CH_2 and H-9), 1.37-1.40 (m, 1H, H-9), 1.44 (s, 9H, CH_3), 1.65-1.75 (m, 1H, H-4), 2.08-2.17 (m, 1H, H-4), 2.42 (s, 3H, $ArCH_3$), 2.44 (s, 3H, $ArCH_3$), 2.71-2.76 (m, 2H, H-8 and H-5), 3.03 (ddd, *J* = 16.4, 12.0, 4.8 Hz, 1H, H-3ax), 3.14 (td, *J* = 12.4, 6.4 Hz, 1H, CH_2-NH), 3.26-3.34 (m, 1H, CH_2-NH), 3.82 (dd, *J* = 14.8, 3.6 Hz, 1H, H-3eq), 4.29 (*br*, 1H, H-1), 4.88 (t, *J* = 6.4 Hz, 1H, NH), 7.31 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.75 (d, *J* = 8.0 Hz, 2H, *o*-Ts), 7.79 (d, 8.4 Hz, 2H, *o*-Ts); ^{13}C NMR (400 MHz, HSQC) δ 21.5 ($ArCH_3$), 25.5 (C-5), 25.8 (C-4), 26.6 (C-1') 28.2 (CH_3), 29.6 (C-9), 38.7 (C-3), 40.4 (C-8), 41.7 (C-2'), 50.1 (C-1), 81.5 (C), 99.8 (C-6), 126.9 (*o*-Ar), 127.2 (*o*-Ar), 129.7 (*m*-Ar), 129.8 (*m*-Ar), 137.0 (*p*-Ar), 138.5 (*p*-Ar), 143.2 (i*pso*-Ar), 143.3 (i*pso*-Ar), 171.3 (C-7), 173.3 (CO); HRMS calcd for $C_{29}H_{39}N_2O_7S_2$ $[M+H]^+$ 591.2207, found 591.2193.


TsHN
Ts
H
N
HO
H
CO2t-Bu
2.24
3.98
4.02
1.00
1.08
1.21
1.25
1.32
1.35
2.03
6.26
1.30
1.49
10.76
3.77
f1 (ppm)

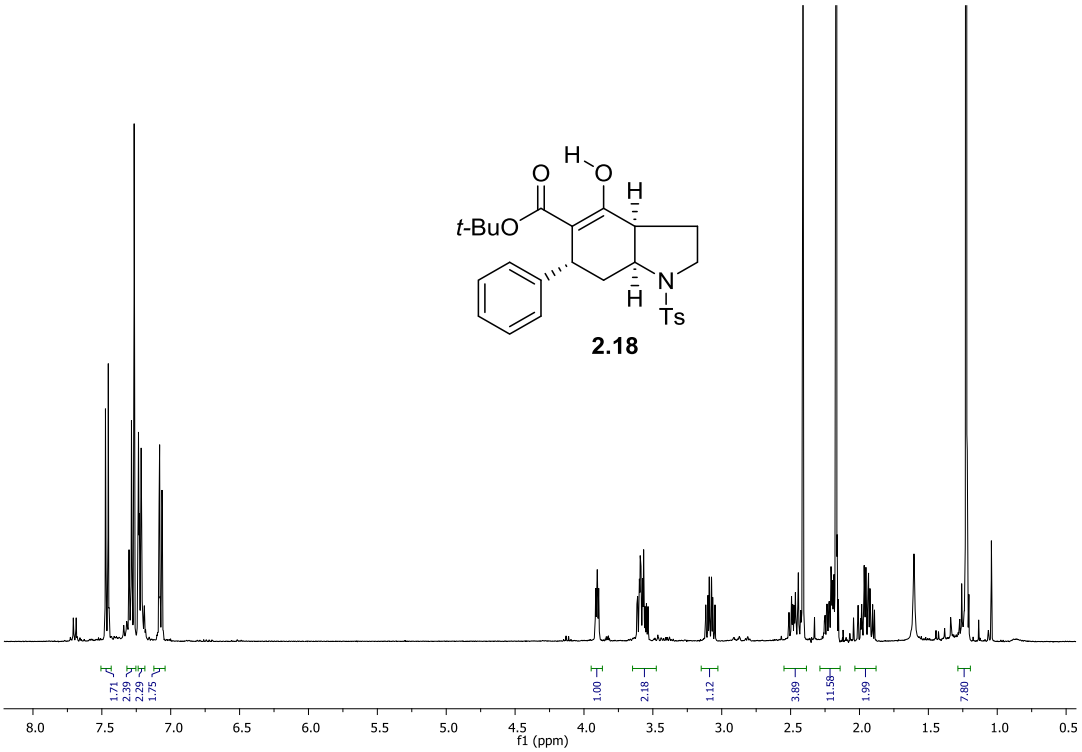

173.437
171.416
143.436
143.322
138.656
137.123
130.005
129.931
127.911
127.037
99.996
81.661
77.477
77.160
76.842
50.278
41.875
40.585
38.821
29.738
28.374
26.889
25.960
25.711
21.689
21.661
f1 (ppm)

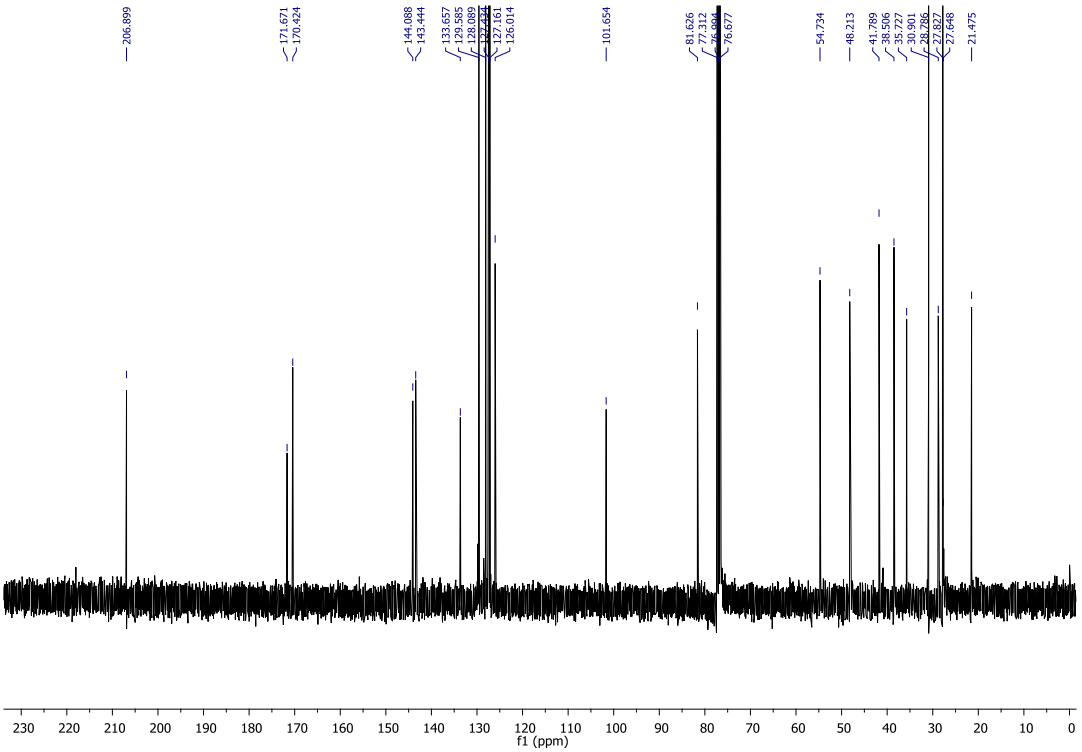
(3a*R*,6*R*,7a*R*)-*tert*-Butyl 4-Hydroxy-1-(4-methylphenylsulfonyl)-6-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.18)



2.18

This compound was prepared according to general method **C**: Cinnamaldehyde (23 mg, 0.176 mmol), β-keto ester **2.2** (57 mg, 0.160 mmol), bis-phenyl-OSiPh$_3$-pyrrolidine organocatalyst **2.16** (8 mg, 0.016 mmol) and LiOAc (5 mg, 0.080 mmol) in toluene (0.5 mL) were stirred at 0ºC for 24 h. The solvent removed *in vacuo* and *i*PrOH (0.6 mL) was added followed by Pd/C (5 mg) and the flask fitted with a hydrogen balloon. After 3 h, the flask was purged with argon, PS-BEMP (73 mg, 0.160 mmol) was added and the resulting mixture stirred for 72 h. Filtration through celite, concentration *in vacuo* and purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.18** (36 mg, 41%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.23 (s, 9H, CH_3), 1.89-1.97 (m, 1H, H-7ax), 1.90-1.98 (m, 1H, H-3β), 2.17-2.20 (m, 1H, H-7eq), 2.90-2.26 (m, 1H, H-3α), 2.41-2.51 (m, 1H, H-3a), 2.41 (s, 3H, $ArCH_3$), 3.08 (td, *J* = 10.1, 6.6 Hz, 1H, H-2α), 3.54-3.58 (m, 1H, H-7a), 3.58 (ddd, *J* = 12.0, 9.6, 7.6, 2.0 Hz, 1H, H-2β), 3.90 (t, *J* = 8.8 Hz, 1H, H-6eq), 7.07 (d, *J* = 7.2 Hz, 2H, *m*-Ph), 7.22 (d, *J* = 8.0 Hz, 2H, *o*-Ph), 7.28 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.60 (d, *J* = 8.4 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 21.5 ($ArCH_3$), 27.8 (CH_3), 28.8 (C-3), 35.7 (C-7), 38.5 (C-6), 41.8 (C-3a), 48.2 (C-2), 54.7 (C-7a) 81.6 (C), 101.7 (C-5), 126.0 (*o*-Ph), 127.2 (*m*-Ph), 127.4 (*o*-Ar), 128.1 (*p*-Ph) 129.6 (*m*-Ar), 133.7 (*p*-Ar), 143.4 (i*pso*-Ar), 144.1 (*ipso*-Ph), 170.7 (C-4), 171.7 (CO); HRMS calcd for $C_{26}H_{32}NO_5S$ $[M+H]^+$ 470.2001, found 470.1996.


H
O
O
H
t-BuO
H
N
Ts
2.18
1.71
2.39
2.29
1.75
1.00
2.18
1.12
3.89
11.58
1.99
7.80
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


206.899
171.671
170.424
144.088
143.444
133.657
129.585
128.089
127.444
127.161
126.014
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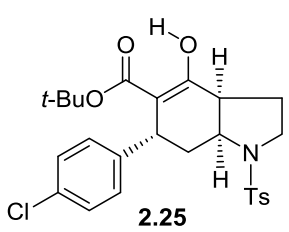
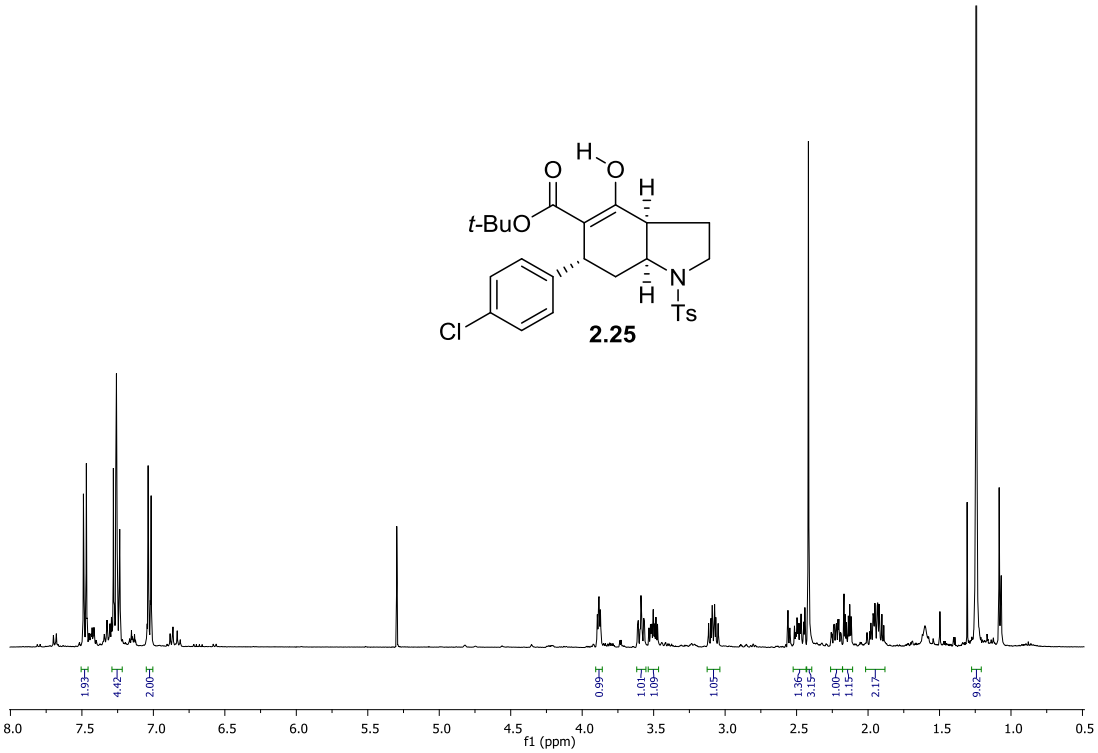
81.626
77.312
76.677
54.734
48.213
41.789
38.506
35.727
30.901
28.286
27.827
27.648
21.475
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

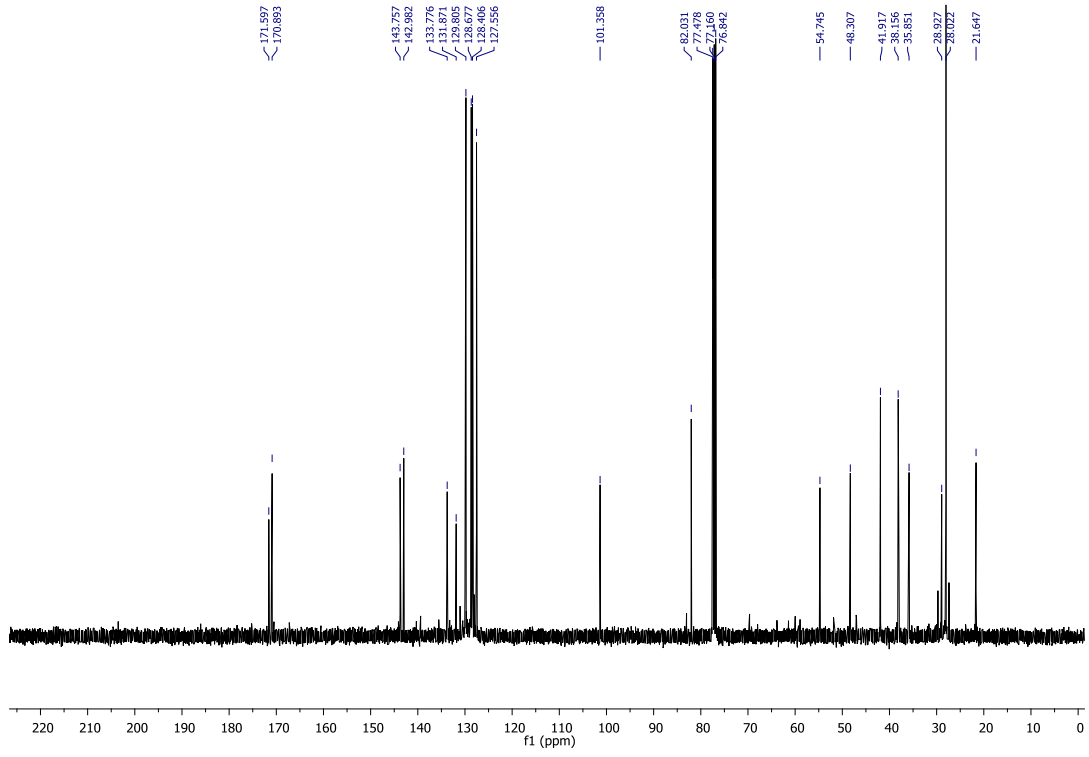
(3a*S*,6*R*,7a*S*)-*tert*-Butyl-6-(4-Chlorophenyl)-4-hydroxy-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.25)



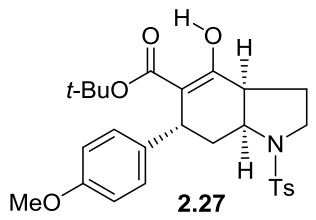
2.25

This compound was prepared according to the above general procedure **C**: 4-Chlorocinnamaldehyde (33 mg, 0.198 mmol), β-keto ester **2.2** (64 mg, 0.180 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (9 mg, 0.018 mmol) and LiOAc (6 mg, 0.090 mmol) were stirred in toluene (0.7 mL) at 0 ºC for 24 h. The solvent was evaporated, the residue dissolved in *i*PrOH (0.7 mL), Pd/C (7 mg) was added and the flask was fitted with a hydrogen balloon. After 3 h the reaction was purged with argon and PS-BEMP (82 mg, 0.180 mmol) as added and the resulting mixture was stirred at room temperature for 72 h. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.25** (39 mg, 43%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.24 (s, 9H, CH_3), 1.89-2.00 (m, 2H, H-7ax, H-3β), 2.14 (dt, *J* = 7.6, 3.6 Hz, 1H, H-7eq), 2.22 (dtd, *J* = 13.6, 8.8, 6.8 H, H-3α), 2.42 (s, 3H, $ArCH_3$), 2.44-2.52 (m, 1H, H-3a), 3.08 (dt, *J* = 10.0, 6.4 Hz, 1H, H-2α), 3.47-3.53 (m, 1H, H-6), 3.88 (t, *J* = 4.8 Hz, 1H, H-2β), 7.03 (d, *J* = 8.4 Hz, 2H, *o*-Ar), 7.25 (d, *J* = 8.8 Hz, 2H, *m*-Ar), 7.27 (d, *J* = 6.4 Hz, 2H, *o*-Ph), 7.48 (d, *J* = 8.0 Hz, 2H, *m*-Ph); ^{13}C NMR (400 MHz, HSQC) δ 21.6 ($ArCH_3$), 28.0 (CH_3), 28.9 (C-3), 35.9 (C-7), 38.2 (C-7a), 41.9 (C-3a), 48.3 (C-2), 54.7 (C-6), 82.0 (C), 101.4 (C-5), 127.6 (*o*-Ar), 128.4 (*o*-Ph), 128.7 (*m*-Ph), 129.8 (*m*-Ar), 131.9 (*p*-Ph), 133.8 (*p*-Ar), 143.0 (i*pso*-Ar), 143.8 (i*pso*-Ph), 170.9 (C-4), 171.6 (CO); HRMS calcd for $C_{26}H_{31}ClNO_5S$ $[M+H]^+$ 504.1606, found 504.1609.


H
O
O
H
t-BuO
N
H
Ts
Cl
2.25
1.93
4.42
2.00
0.99
1.01
1.09
1.05
1.36
3.15
1.00
1.15
2.17
9.82
f1 (ppm)

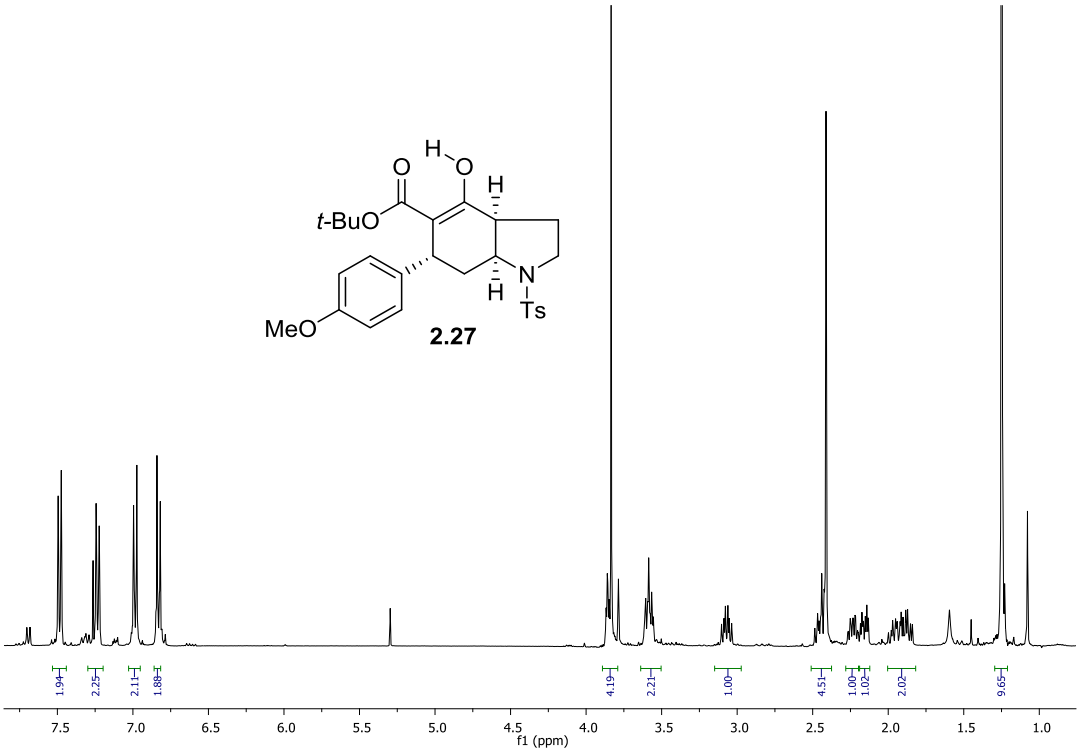

171.597
170.893
143.757
142.982
133.776
131.871
129.805
128.677
128.466
127.556
101.358
82.031
77.478
77.160
76.842
54.745
48.307
41.917
38.156
35.851
28.927
28.022
21.647
f1 (ppm)

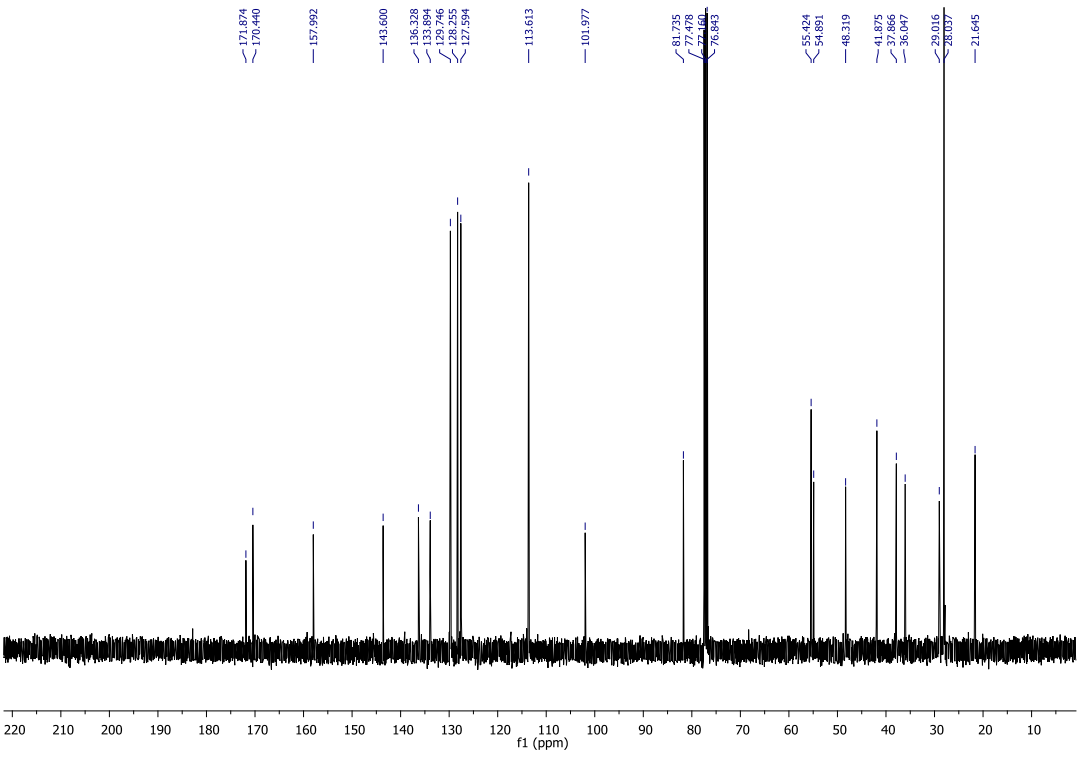
(3a*R*,6*R*,7a*R*)-*tert*-Butyl 4-Hydroxy-6-(methoxyphenyl)-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.27)



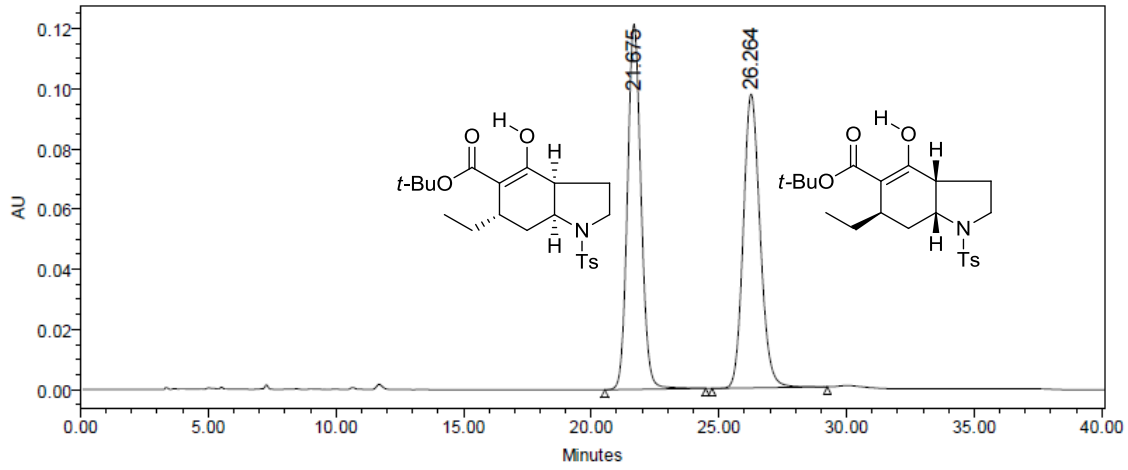
2.27

This compound was prepared according to the above general procedure **C**: *trans*-4-methoxycinnamaldehyde (29 mg, 0.179 mmol), β-keto ester **2.2** (58 mg, 0.163 mmol), bis-phenyl-OSiPh$_3$-pyrrolidine organocatalyst **2.16** (8 mg, 0.016 mmol) and LiOAc (5 mg, 0.082 mmol) were stirred in toluene (0.5 mL) at 0 ºC for 24 h. The solvent was removed *in vacuo*, the residue dissolved in *i*PrOH (0.7 mL), Pd/C (7 mg) was added and the flask was fitted with a hydrogen balloon. After 3 h the reaction was purged with argon and PS-BEMP (74 mg, 0.163 mmol) as added and the resulting mixture was stirred at room temperature for 72 h. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.27** (32 mg, 40%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.25 (s, 9H, CH_3), 1.87 (td, *J* = 12.8, 7.6 Hz, 1H, H-7ax), 1.90-2.00 (m, 1H, H-3β), 2.16 (dt, *J* = 8.0, 4.0 Hz, 1H, H-7eq), 2.23 (ddd, *J* = 14.0, 8.4, 6.8 H, H-3α), 2.41 (s, 3H, ArCH_3), 2.42-2.49 (m, 1H, H-3a), 3.07 (dt, *J* = 10.0, 6.4 Hz, 1H, H-2α), 3.56-3.62 (m, 2H, H-6 and H-2β), 3.83 (s, 3H, CH_3), 3.86 (dd, *J* = 5.2, 2.8 Hz, 1H, H-7a), 6.83 (d, *J* = 8.8 Hz, 2H, *o*-Ph), 6.99 (d, *J* = 8.8 Hz, 2H, *o*-Ar), 7.23 (d, *J* = 8.0 Hz, 2H, *m*-Ar), 7.48 (d, *J* = 8.4 Hz, 2H, *m*-Ph), ^{13}C NMR (400 MHz, HSQC) δ 21.5 (ArCH_3), 27.9 (CH_3), 28.9 (C-3), 35.9 (C-7), 37.7 (OCH_3), 41.7 (C-3a), 48.2 (C-2), 54.7 (C-6), 55.3 (C-7a), 81.6 (C), 101.8 (C-5), 113.5 (*o*-Ph), 127.4 (*o*-Ar), 128.1 (*m*-Ph), 129.6 (*m*-Ar), 133.7 (*p*-Ar), 136.2 (*p*-Ph), 143.4 (i*pso*-Ar), 157.8 (*ipso*-Ph), 170.3 (C-4), 171.7 (CO); HRMS calcd for $C_{27}H_{34}NO_6S$ $[M+H]^+$ 500.2103, found 500.2101.


H
O
O
H
t-BuO
N
H
Ts
MeO
2.27
1.94
2.25
2.11
1.88
4.19
2.21
1.00
4.51
1.00
1.02
2.02
9.65
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


171.874
170.440
157.992
143.600
136.328
133.894
129.746
128.255
127.594
113.613
101.977
81.735
77.478
77.160
76.843
55.424
54.891
48.319
41.875
37.866
36.047
29.016
28.037
21.645
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

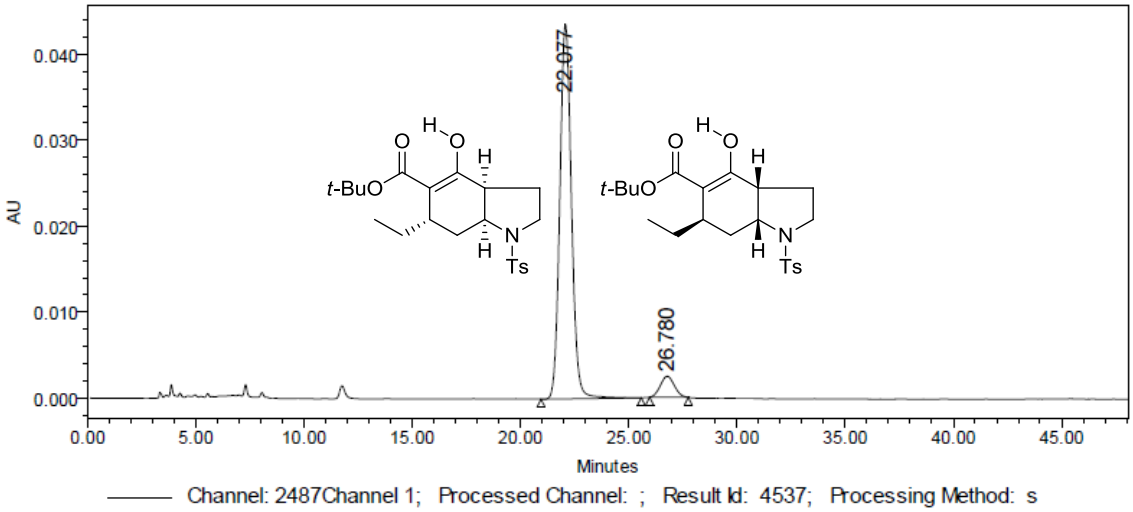
HPLC of Racemic reaction mixture (2.20)



Processed Channel Descr.:

	RT	Area	% Area	Height
1	21.675	4481958	50.03	121315
2	26.264	4476688	49.97	97659

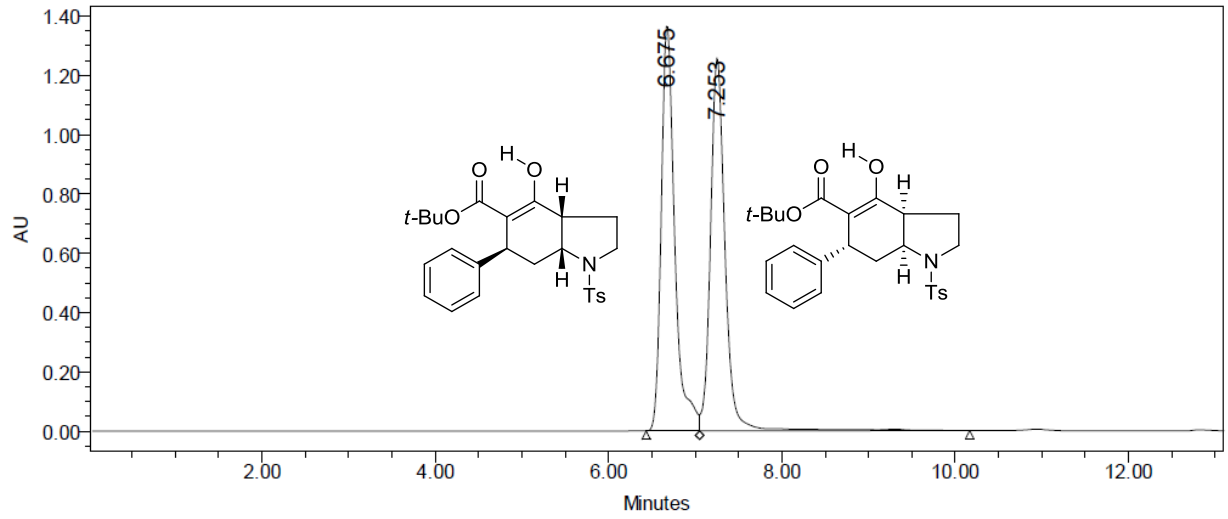
HPLC of organocatalysed reaction mixture (2.20)



Processed Channel Descr.:

	RT	Area	% Area	Height
1	22.077	1624514	93.65	43573
2	26.780	110158	6.35	2455

HPLC of Racemic reaction mixture (2.18)

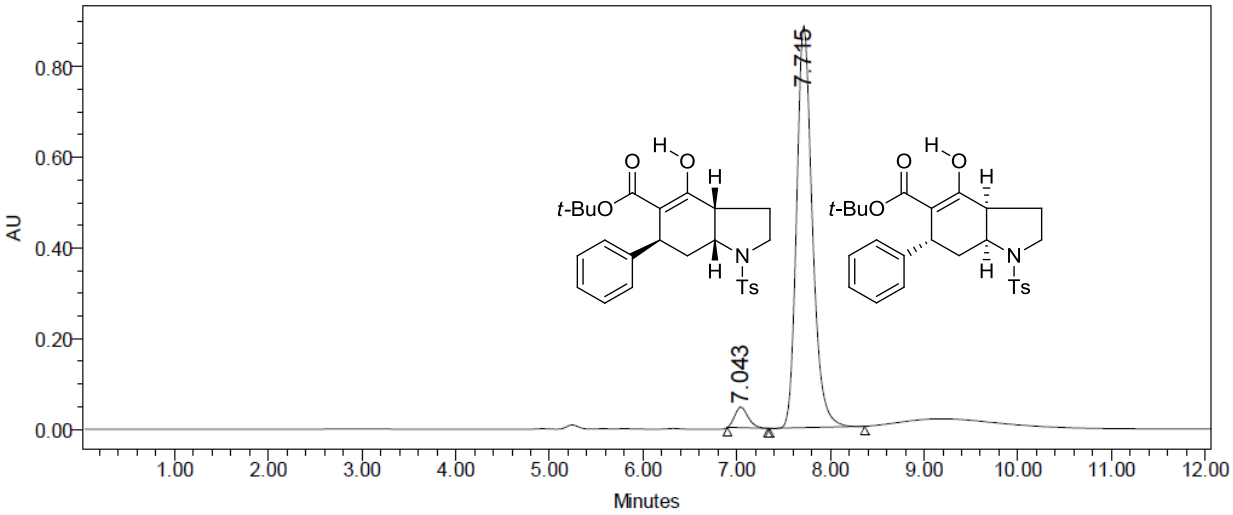


Channel: 2487Channel 1; Processed Channel: ; Result Id: 4870; Processing Method: I

Processed Channel Descr.:

	RT	Area	% Area	Height
1	6.675	14855977	50.03	1373245
2	7.253	14838663	49.97	1257118

HPLC of organocatalysed reaction mixture (2.18)

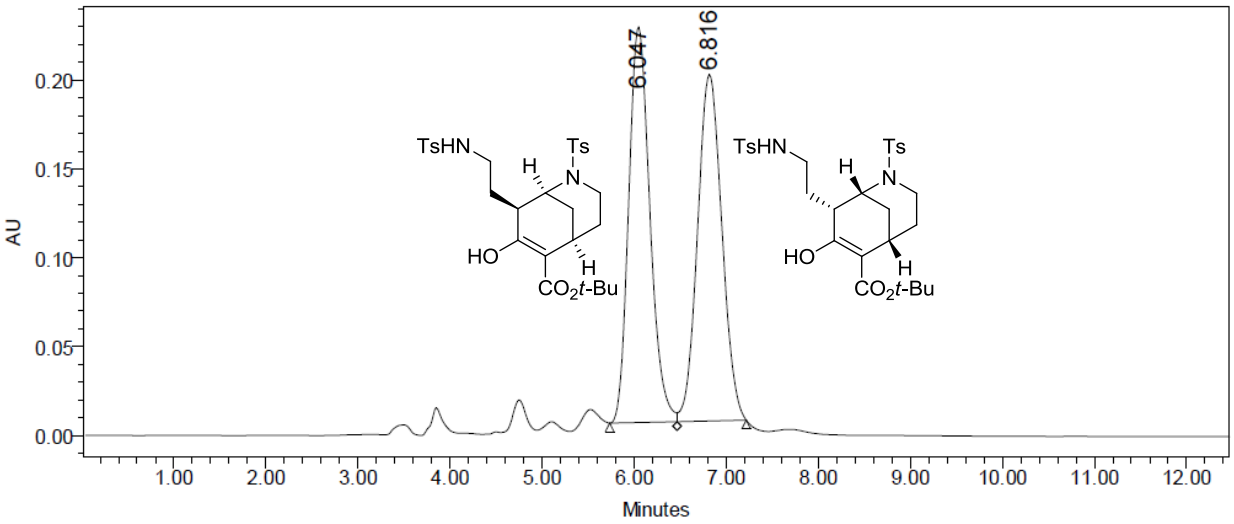


Channel: 2487Channel 1; Processed Channel: ; Result Id: 4921; Processing Method: a

Processed Channel Descr.:

	RT	Area	% Area	Height
1	7.043	449801	4.16	45130
2	7.715	10351495	95.84	886321

HPLC of Racemic reaction mixture (2.24)

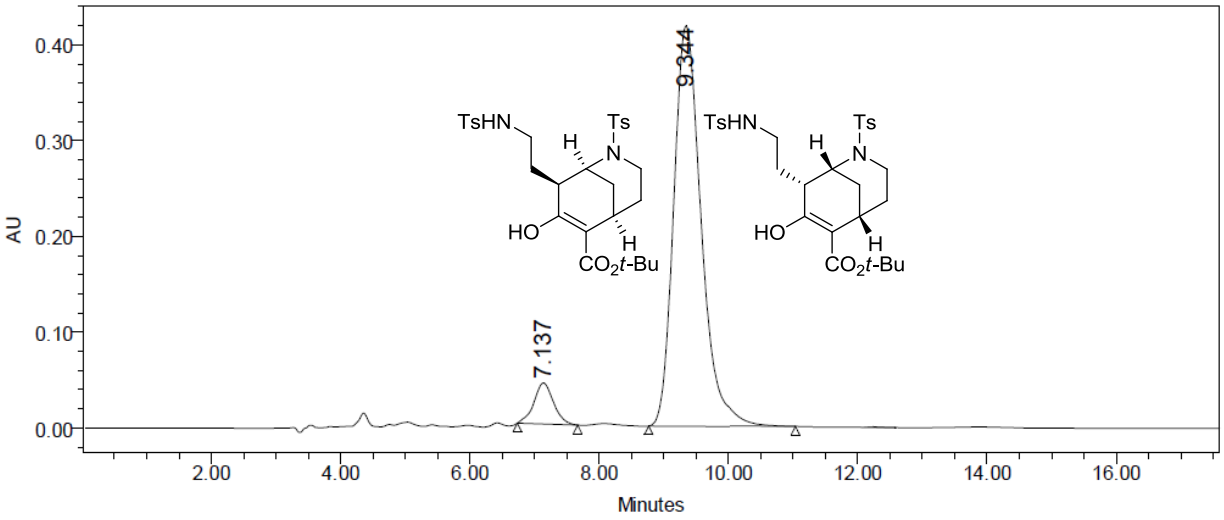


Channel: 2487Channel 1; Processed Channel: ; Result Id: 4704; Processing Method: a

Processed Channel Descr.:

	RT	Area	% Area	Height
1	6.047	3560896	49.82	222923
2	6.816	3587044	50.18	195120

HPLC of organocatalysed reaction mixture (2.24)

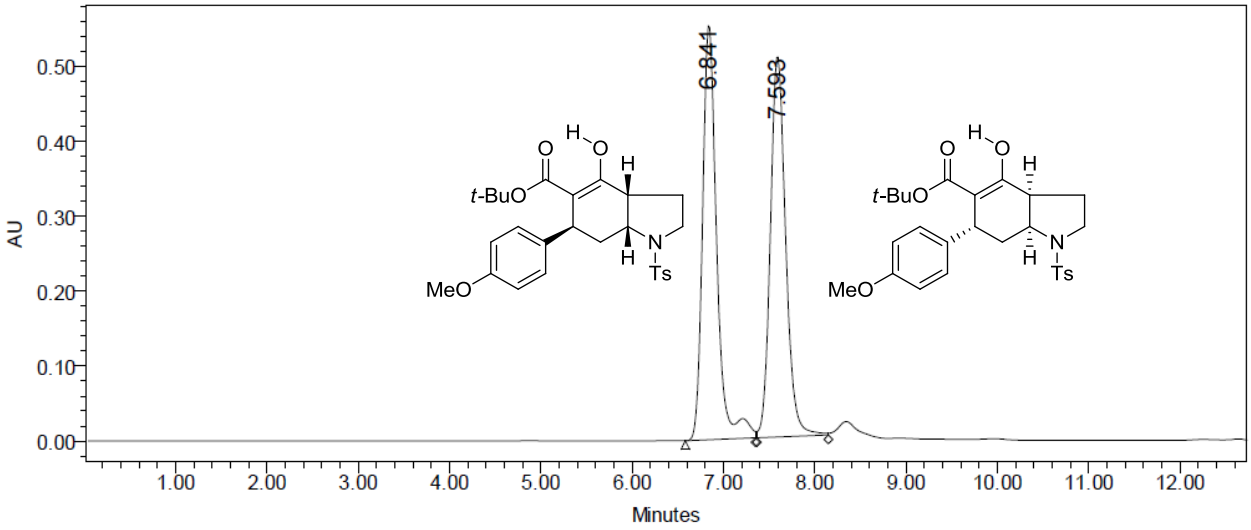


Channel: 2487Channel 1; Processed Channel: ; Result Id: 5112; Processing Method: s

Processed Channel Descr.:

	RT	Area	% Area	Height
1	7.137	904239	5.69	42762
2	9.344	14976224	94.31	418033

HPLC of Racemic reaction mixture (2.27)

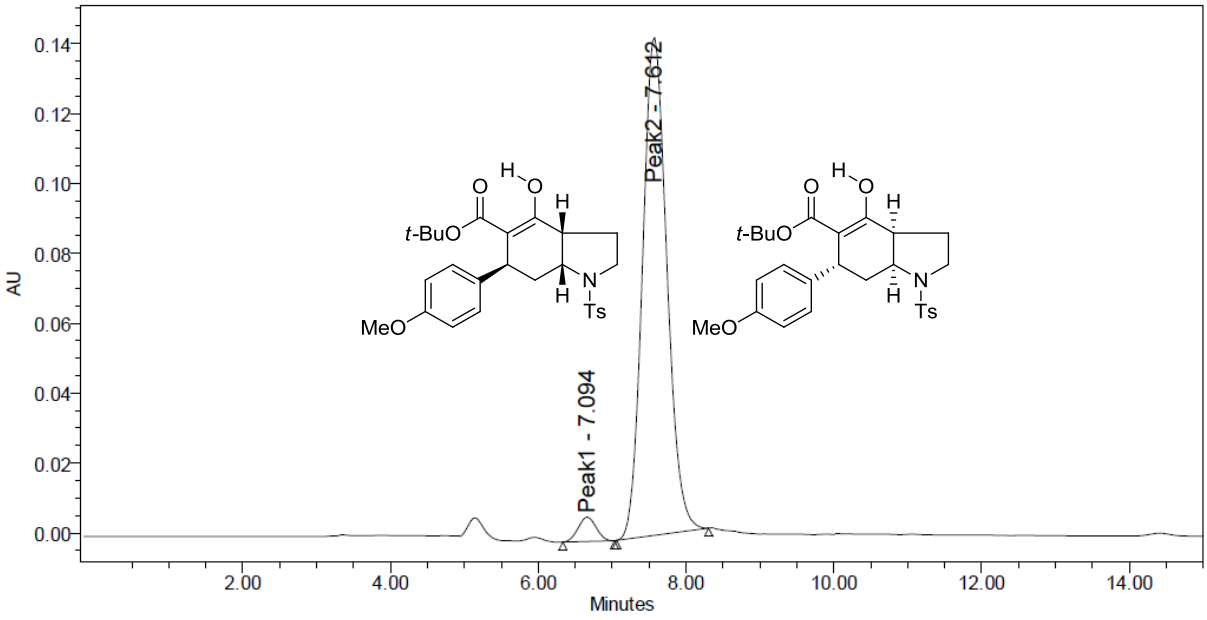


Channel: 2487Channel 1; Processed Channel: ; Result Id: 4881; Processing Method: a

Processed Channel Descr.:

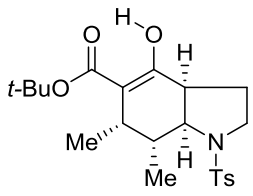
	RT	Area	% Area	Height
1	6.841	5938860	50.00	554940
2	7.593	5938019	50.00	508586

HPLC of organocatalysed reaction mixture (2.27)



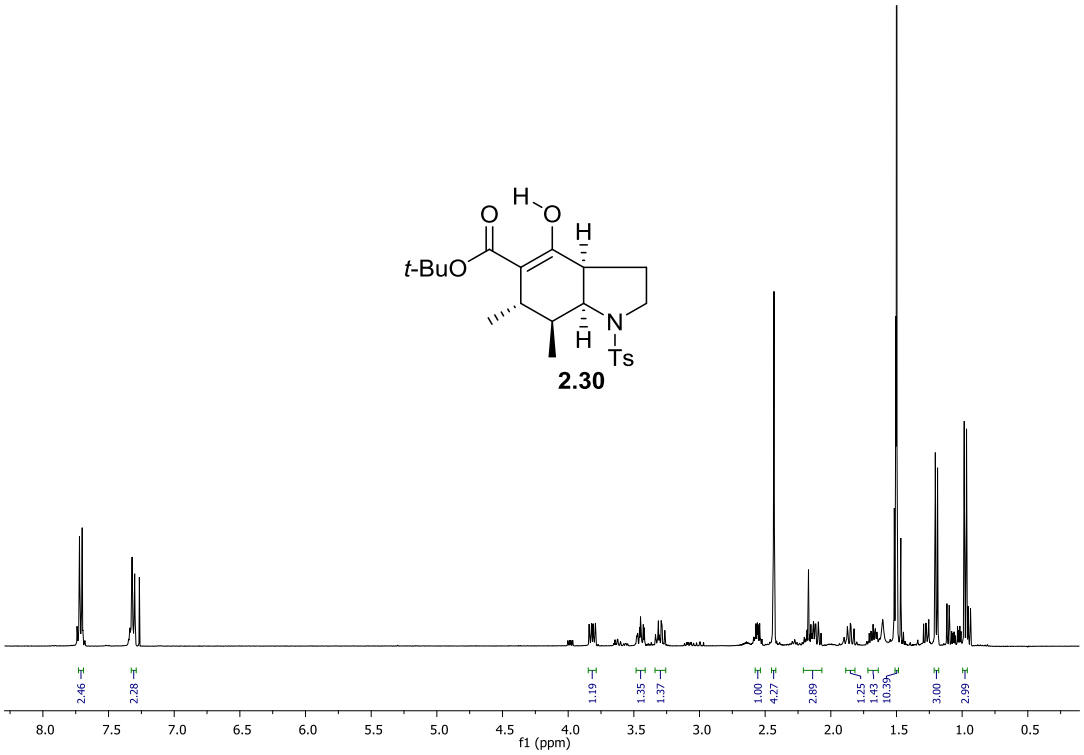
	RT	Area	% Area	Height
1	7.094	47992	2.62	5606
2	7.612	1785543	97.38	130628

(3a*R*,6*R*,7a*R*)-*tert*-Butyl 6,7-Dimethyl-4-hydroxy-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.28)

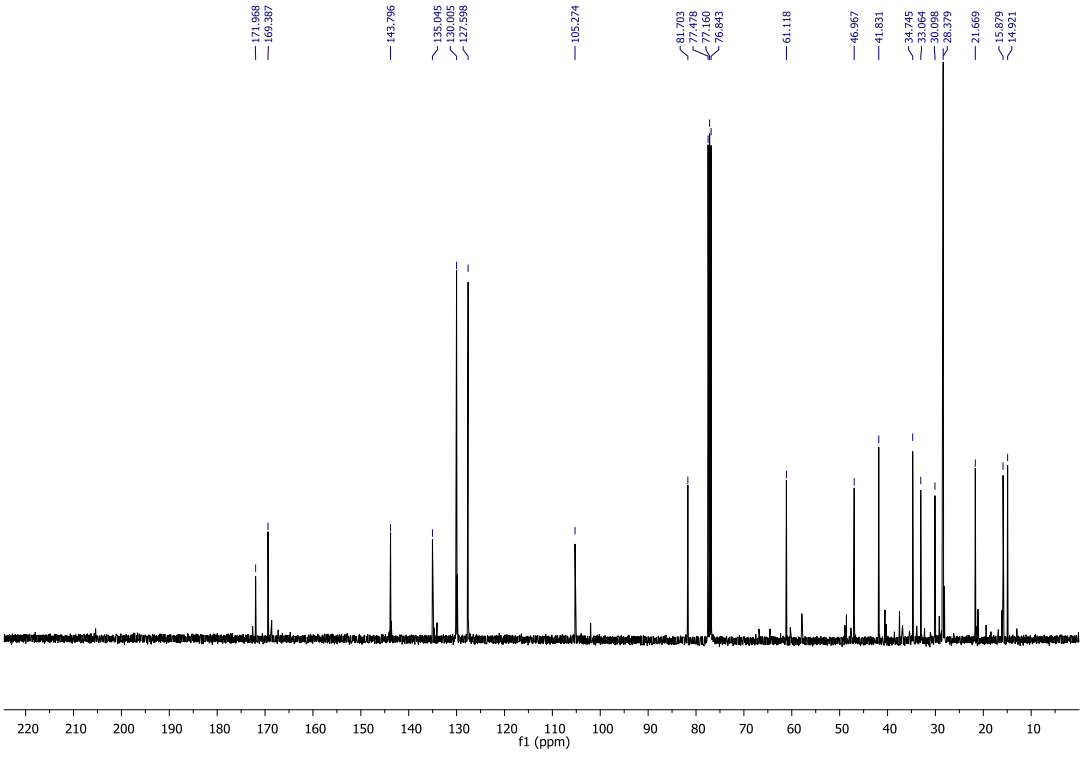


rac-2.28

This compound was prepared according to general method **A** using *trans*-2-methyl-2-butenal (16 mg, 0.186 mmol), β-keto ester **2.2** (60 mg, 0.169 mmol), PS-BEMP (77 mg, 0.169 mmol) and *i*-PrOH (0.7 mL) was stirred at room temperature for 16 h. Purification by column chromatography (0→25→50→100% EtOAc/hexane) gave octahydroindole ***rac*-2.28** (25 mg, dr 84:16, 35%) as a white solid.^{1}H NMR (400 MHz, COSY) δ ^{1}H NMR (400 MHz, COSY) δ 0.98 (d, *J* = 6.8 Hz, 3H, H6-CH_3), 1.20 (d, *J* = 6.8 Hz, 3H, H7-CH_3), 1.50 (s, 9H, CH_3), 1.68 (dqd, *J* = 11.0, 6.8, 4.4 Hz, 1H, H-7ax), 1.85 (td, *J* = 11.2, 9.2, 1.6 Hz, 1H, H-3), 2.07-2.20 (m, 2H, H-3, H-3a), 2.43 (s, 3H, $ArCH_3$), 2.56 (qd, *J* = 6.8, 4.4 Hz, 1H, H-6eq), 3.26-3.34 (m, 1H, H-2), 3.45 (ddd, *J* = 11.6, 8.8, 2.4 Hz, 1H, H-2), 3.82 (dd, *J* = 12.0, 7.2 Hz, 1H, H-7a), 7.31 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.71 (d, *J* = 8.0 Hz, 2H, *o*-ArH); ^{13}C NMR (400 MHz, HSQC) δ 14.9 (CH_3), 15.9 (CH_3), 21.7 ($ArCH_3$), 28.3 (CH_3), 30.1 (C-3), 33.1 (C-6), 34.7 (C-7), 41.8 (C-3a), 47.0 (C-2), 61.1 (C-7a), 81.7 (C), 105.3 (C-5), 127.6 (*o*-Ar), 130.0 (*m*-Ar), 135.0 (*p*-Ar), 143.8 (i*pso*-Ar), 169.4 (C-4), 172.0 (CO); HRMS calcd for $C_{22}H_{32}NO_5$ $[M+H]^+$ 422.2015, found 422.1995.


H
O
O
H
t-BuO
N
H
Ts
2.46
2.28
1.19
1.35
1.37
1.00
4.27
2.89
1.25
1.43
10.39
3.00
2.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

2.30


171.968
169.387
143.796
135.045
130.005
127.598
105.274
81.703
77.478
77.160
76.843
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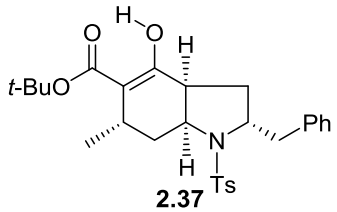
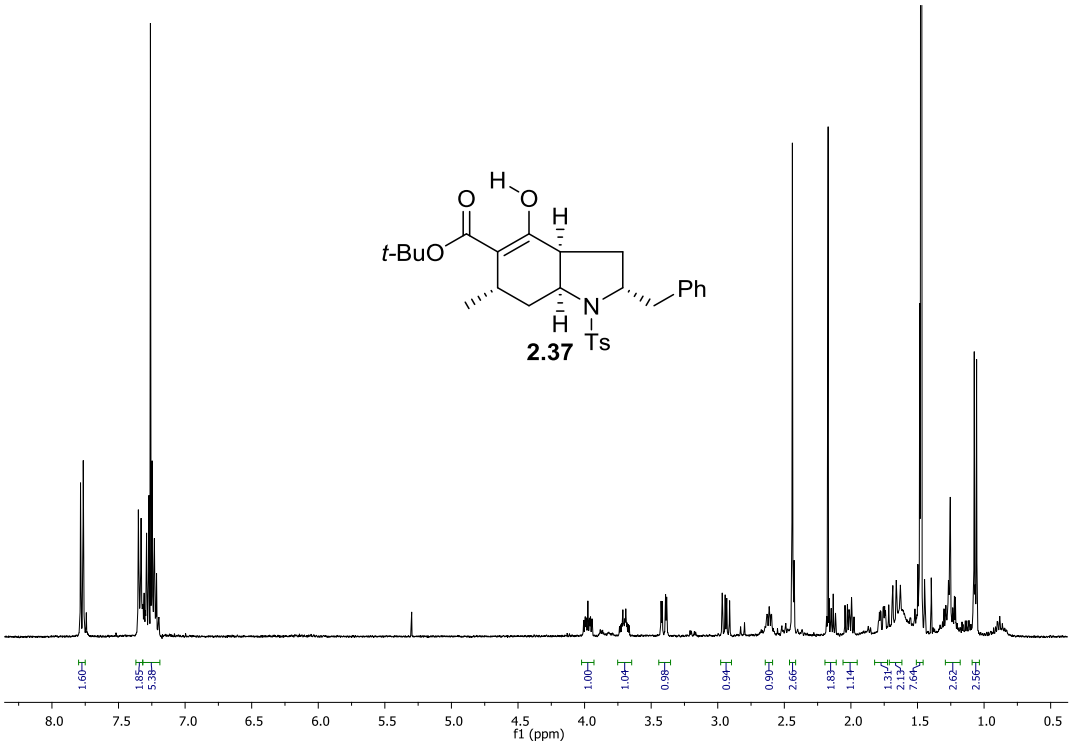
41.831
34.745
33.064
30.098
28.379
21.669
15.879
14.921
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

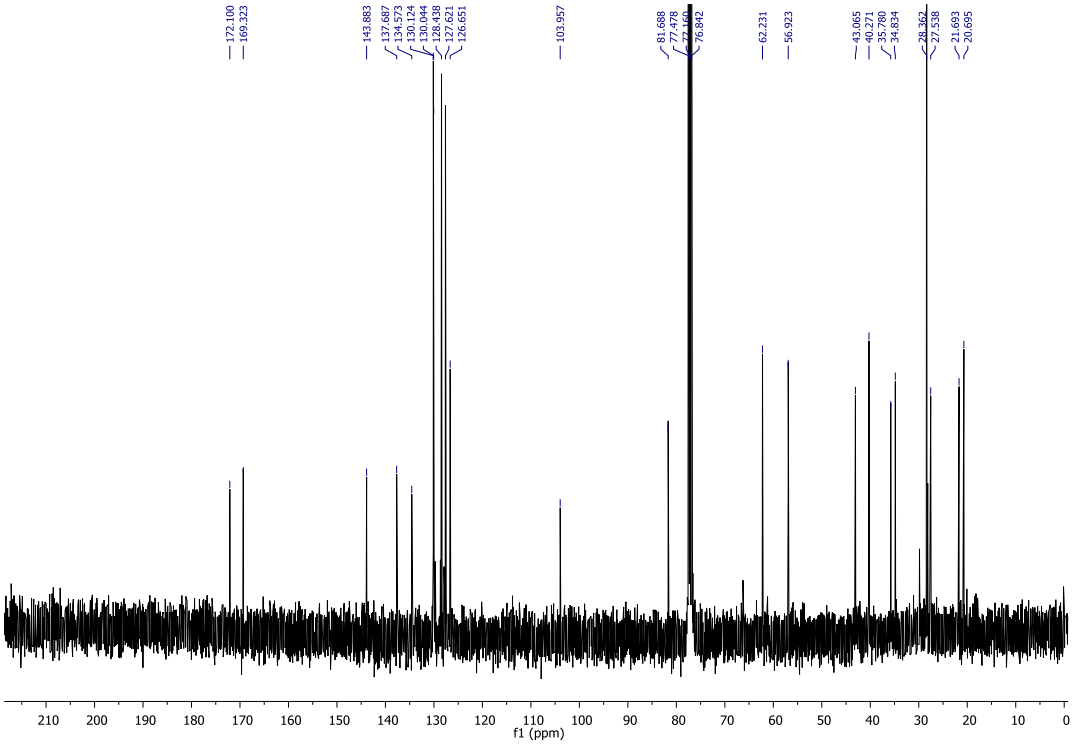
(2*R*,3a*S*,6*S*,7a*S*)-*tert*-Butyl 2-Benzyl-4-hydroxy-6-methyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a hexahydro-1*H*-indole-5-carboxylate (2.37)



2.37

This compound was prepared according to the general method **A** using β-keto ester **2.7** (190 mg, 0.426 mmol), crotonaldehyde (36 mg, 0.511 mmol), PS-BEMP (194 mg, 0.426 mmol) and *i*PrOH (2 mL). Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.37** (105 mg, 44%) as a white solid. ^{1}H NMR (400 MHz, COSY) δ 1.07 (d, *J* = 7.2 Hz, 3H, CH_3), 1.24-1.27 (m, 1H, H-7ax), 1.47 (s, 9H, CH_3), 1.62-1.72 (m, 1H, H-3), 1.77 (ddd, *J* = 13.2, 4.8, 2.0 Hz, 1H, H-7eq) 1.98-2.04 (m, 1H, H-3a), 2.12-2.18 (m, 1H, H-3), 2.44 (s, 3H, $ArCH_3$), 2.61 (qdd, *J* = 7.2, 5.6, 2.4 Hz, 1H, H-6), 2.94 (dd, *J* = 13.2, 8.8 Hz, 1H, CH_2Ph), 3.40 (dd, *J* = 13.2, 3.2 Hz, 1H, CH_2Ph), 3.67-3.74 (m, 1H, H-2), 3.98 (ddd, *J* = 12.5, 7.8, 4.8 Hz, 1H, H-7a), 7.21-7.35 (m, 7H, ArH), 7.78 (d, *J* = 8.3 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 20.7 (CH_3), 21.7 ($ArCH_3$), 27.5 (C-6), 28.4 (CH_3), 34.8 (C-7), 35.8 (C-3), 40.3 (C-3a), 43.1 (CH_2-Ph), 56.9 (C-7a), 62.2 (C-2), 81.7 (C), 104.0 (C-5), 126.7 (*o*-Ph), 127.6 (*o*-Ar), 128.4 (*m*-Ph), 130.0 (*m*-Ar), 130.1 (*p*-Ph), 134.6 (*p*-Ar), 137.7 (Ph), 143.9 (i*pso*-Ar), 169.3 (C-4), 172.1 (CO); HRMS calcd for $C_{28}H_{36}NO_5S$ $[M+H]^+$ 498.2309, found 498.2293.


H
O
O
H
t-BuO
Ph
N
H
Ts
2.37
1.60
1.85
5.38
1.00
1.04
0.98
0.94
0.90
2.66
1.83
1.14
1.31
2.13
7.64
2.62
2.56
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


172.100
169.323
143.883
137.687
134.573
130.124
130.044
128.438
127.621
126.651
103.957
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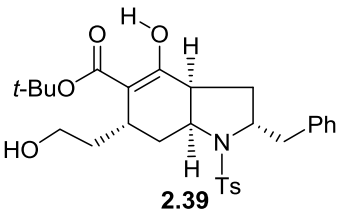
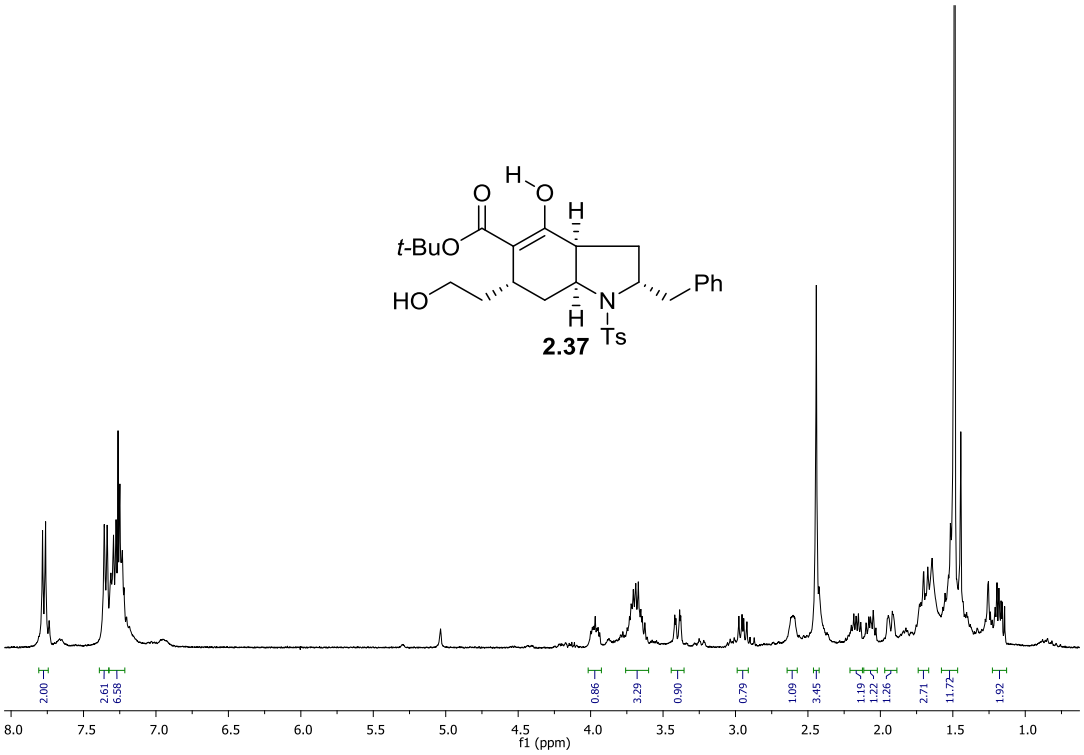
77.478
77.160
76.842
62.231
56.923
43.065
40.271
35.780
34.834
28.362
27.538
21.693
20.695
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

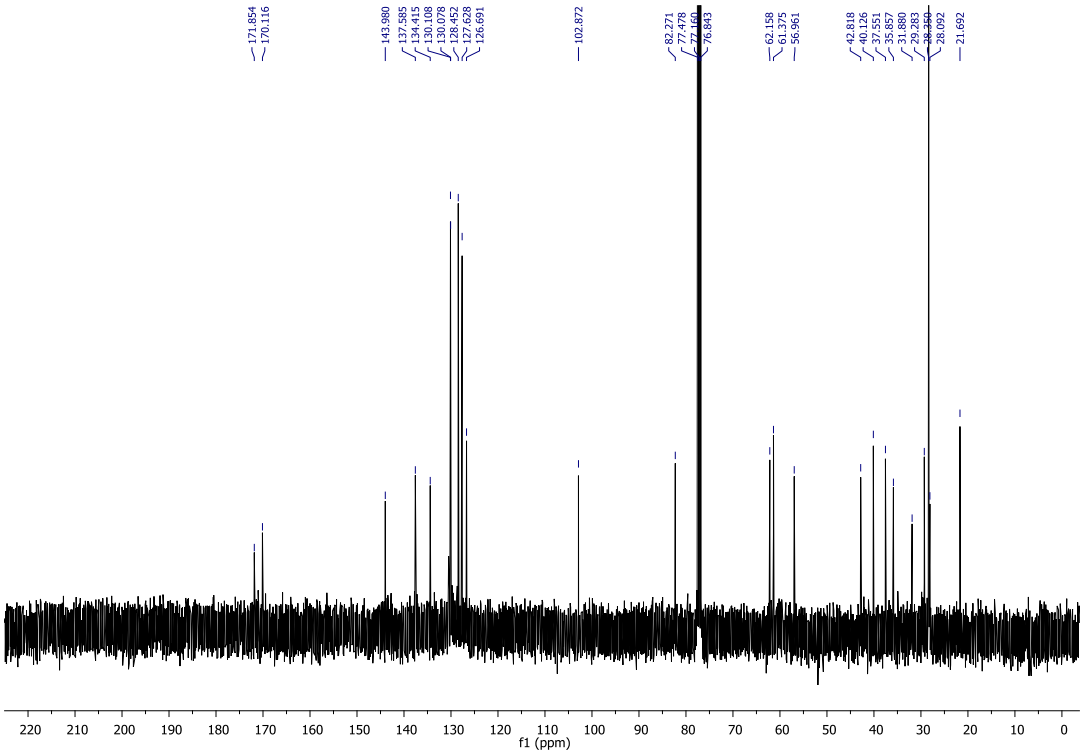
(2*R*,3a*S*,6*R*,7a*S*)-*tert*-Butyl 2-Benzyl-4-hydroxy-6-(2-hydroxyethyl)-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.39)



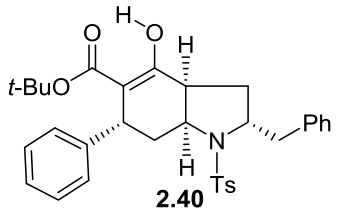
2.39

This compound was prepared according to the general method **A** using β-keto ester **2.7** (56 mg, 0.126 mmol), (*E*)-5-hydroxypent-2-enal (14 mg, 0.138 mmol), PS-BEMP (57 mg, 0.126 mmol) and *i*PrOH (0.5 mL). Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.39** (20 mg, 30%) as a white solid. ^{1}H NMR (400 MHz, COSY) δ 1.14.121 (m 1H, H-1'), 1.48-1.56 (m, 1H, H-3), 1.49 (s, 9H, CH_3), 1.64-1.74 (m, 1H, H-3), 1.91-1.95 (dm, 1H, H-1'), 2.04-2.10 (m, 1H, H-3a), 2.14-2.20 (m, 1H, H-7), 2.44 (s, 3H, $ArCH_3$), 2.60-2.62 (m, 1H, H-6), 2.95 (dd, *J* = 13.6, 8.8 Hz, 1H, CH_2Ph), 3.40 (dd, *J* = 13.6, 3.2 Hz, 1H, CH_2Ph), 3.61-3.75 (m, 3H, H-2, H-2'), 3.97 (ddd, *J* = 12.4, 7.2, 4.4 Hz, 1H, H-7a), 7.21-7.35 (m, 5H, ArH), 7.35 (d, *J* = 8.0 Hz, 2H, *o*-Ar), 7.77 (d, *J* = 8.0 Hz, 2H, *m*-Ar); ^{13}C NMR (400 MHz, HSQC) δ 21.7 ($ArCH_3$), 28.4 (CH_3), 29.3 (C-6), 31.9 (C-1'), 35.9 (C-7), 37.6 (C-3), 40.1 (C-3a), 42.8 (CH_2-Ph), 57.0 (C-7a), 61.4 (C-2'), 62.2 (C-2), 82.3 (C), 102.9 (C-5), 126.7, 127.6, 128.4, 130.1, 130.2, 134.4, 137.6, 144.0, 170.1 (C-4), 171.9 (CO); HRMS calcd for $C_{29}H_{38}NO_6S$ $[M+H]^+$ 528.2434, found 528.2414.


H
O
O
H
t-BuO
Ph
HO
N
H
Ts
2.37
2.00
2.61
6.58
0.86
3.29
0.90
0.79
1.09
3.45
1.19
1.22
1.26
2.71
11.72
1.92
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

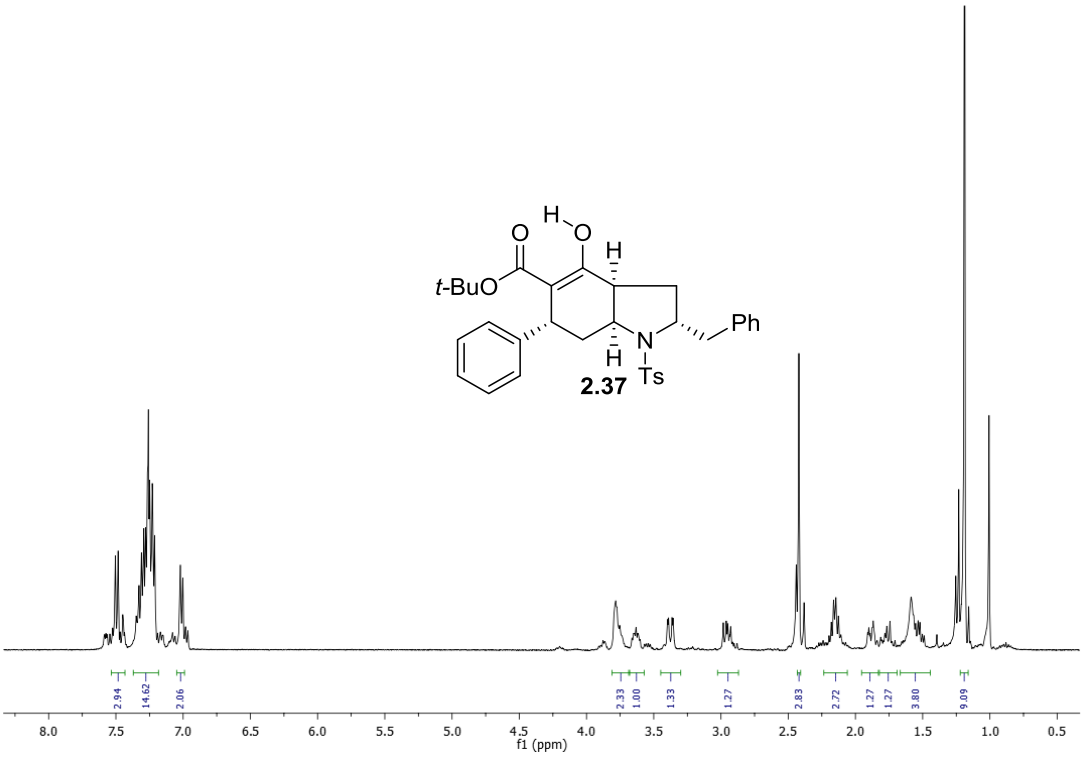

171.854
170.116
143.980
137.585
134.415
130.108
130.078
128.452
127.628
126.691
102.872
82.271
77.478
77.160
76.843
62.158
61.375
56.961
42.818
40.126
37.551
35.857
31.880
29.283
28.350
28.092
21.692
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

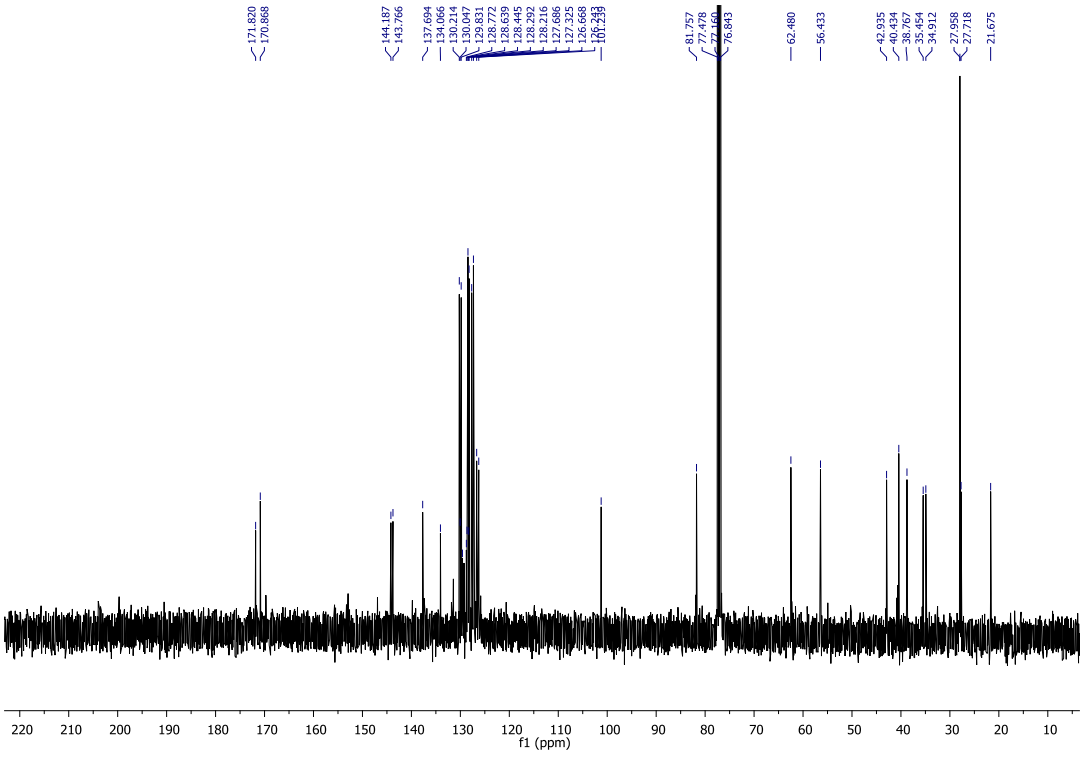
(2*R*,3a*S*,6*R*,7a*S*)-*tert*-Butyl 2-Benzyl-4-hydroxy-1-(4-methylphenylsulfonyl)-6-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole-5-carboxylate. (2.40)



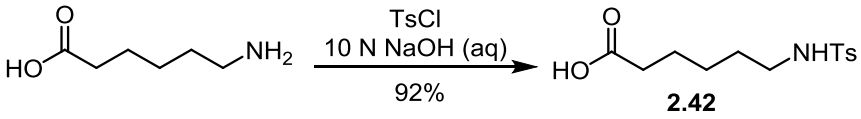
2.40

This compound was prepared according to the general method **A** using β-keto ester **2.7** (49 mg, 0.110 mmol), cinnamaldehyde (16 mg, 0.121 mmol), PS-BEMP (50 mg, 0.110 mmol) and *i*PrOH (0.4 mL). Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave octahydroindole **2.40** (26 mg, 43%) as a white solid. ^{1}H NMR (400 MHz, COSY) δ 1.19 (s, 9H, CH_3), 1.49-1.55 (m, 1H, H-3), 1.71-1.81 (m, 1H, H-7) 1.88 (dt, *J* = 13.2, 7.2, 3.2 Hz, 1H, H-3), 2.11-2.20 (m, 2H, H-7, H-3a), 2.42 (s, 3H, $ArCH_3$), 2.96 (dd, *J* = 13.2, 8.8 Hz, 1H, CH_2Ph), 3.38 (dd, *J* = 13.2, 2.8 Hz, 1H, CH_2Ph), 3.63 (ddd, *J* = 12.0, 7.6, 4.4 Hz, 1H, H-7a), 3.72-3.84 (m, 2H, H-2, H-6), 7.01 (d, *J* = 7.6 Hz, 2H, *o*-Ar), 7.21-7.35 (m, 10H, ArH), 7.49 (d, *J* = 8.0 Hz, 2H, *m*-Ar), ^{13}C NMR (400 MHz, HSQC) δ 21.7 ($ArCH_3$), 28.0 (CH_3), 34.9 (C-7), 35.5 (C-3), 38.8 (C-6), 40.4 (C-3a), 42.9 (CH_2-Ph), 56.4 (C-7a), 62.5 (C-2), 81.7 (C), 101.2 (C-5), 126.2, 126.7 127.3, 127.6 128.2, 128.3 128.6, 128.8, 129.8, 130.0, 130.2, 134.0, 137.7, 143.8, 144.2, 170.9 (C-4), 171.8 (CO); HRMS calcd for $C_{33}H_{38}NO_5S$ $[M+H]^+$ 560.2469, found 560.2465.


H
O
O
H
t-BuO
Ph
N
H
Ts
2.37
2.94
14.62
2.06
2.33
1.00
1.33
1.27
2.83
2.72
1.27
1.27
3.80
9.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


171.820
170.868
144.187
143.766
137.694
134.066
130.214
130.047
129.831
128.772
128.639
128.445
128.292
128.216
127.686
127.325
126.668
126.243
101.239
81.757
77.478
77.160
76.843
62.480
56.433
42.935
40.434
38.767
35.454
34.912
27.958
27.718
21.675
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

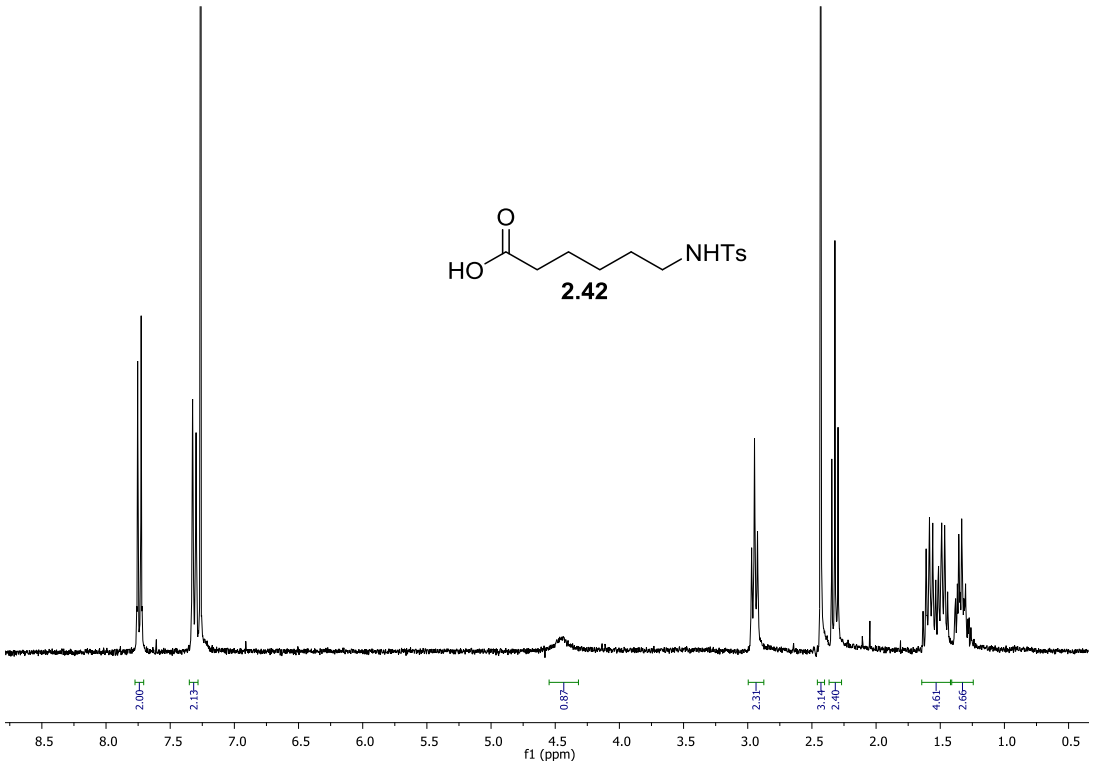
6-(4-Methylphenylsulfonamido) hexanoic acid. (2.42)

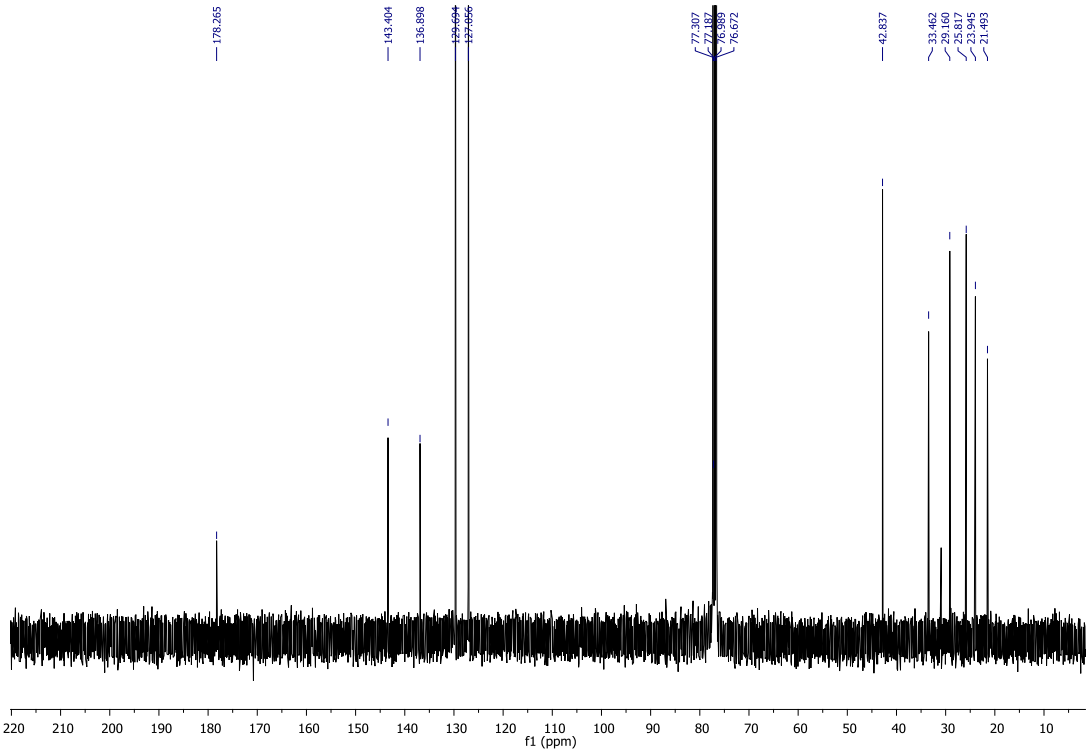


2.42

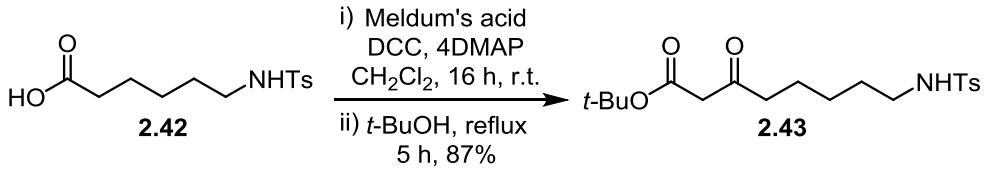
To a solution of 6-aminohexanoic acid (3.00 g, 22.9 mmol) in water (43 ml), was added solid NaOH (2.10 g, 52.6 mol) followed by tosyl chloride (4.36 g, 22.87 mol) in several portions over 15 minutes. The reaction mixture was then heated to 90 ºC and stirred for 3 h. After cooling to room temperature, the pH was adjusted to 5 with HCl (6N). The resulting precipitate was then filtered, washed with water, and dried to afford **2.42** as a white solid (6.05 g, 92%). Spectral data was identical to that previously reported.[150]

[150] Pavlidis, V. H.; Chan, E. D.; Pennington, L.; McParland, M.; Whitehead, M.; Coutts, I. G. C. *Synth. Commun.* **1988**, *18*, 1615-1624.


O
HO
NHTs
2.42
2.00
2.13
0.87
2.31
3.14
2.40
4.61
2.66
f1 (ppm)

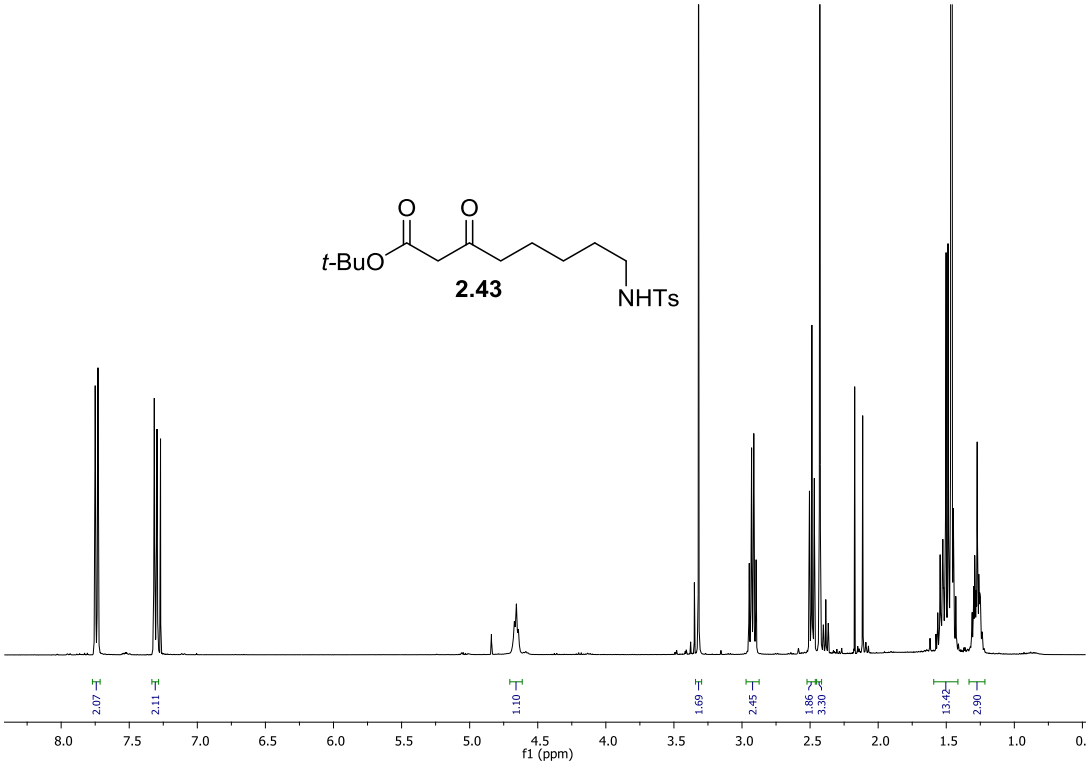

178.265
143.404
136.898
77.307
42.837
33.462
29.160
25.937
23.345
21.493
f1 (ppm)

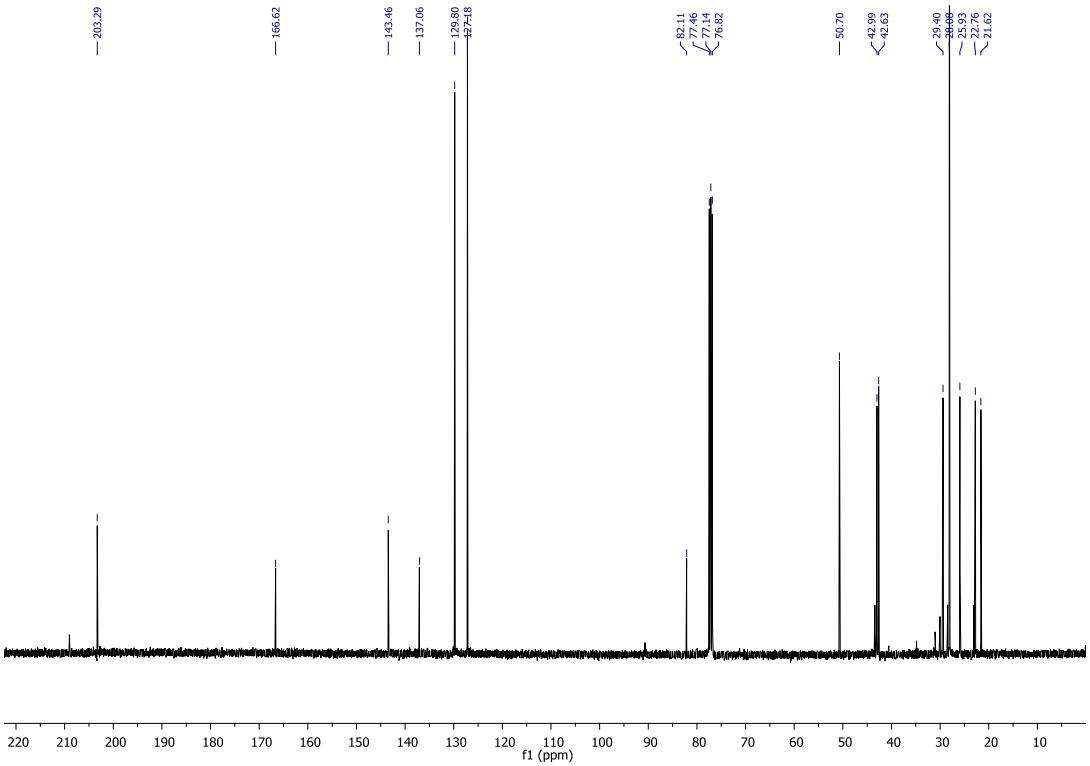
tert-Butyl 8-(4-Methylphenylsulfonamido)-3-oxooctanoate. (2.43)[151]



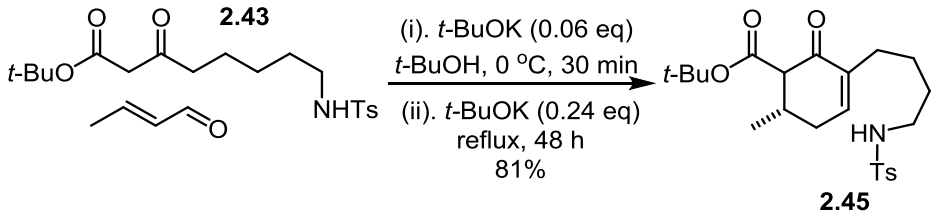
A solution of DCC (1.59 g, 7.71 mmol) in CH_2Cl_2 (7 mL) was added slowly to a stirred solution of Meldrum's acid (1.01 g, 7.01 mmol), protected amino acid **2.42** (2.00 g, 7.01 mmol) and DMAP (0.946 mg, 7.71 mmol) in dry CH_2Cl_2 (14 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 16 h and the precipitated solid was removed by filtration and washed with dichloromethane. The filtrate was washed subsequently with 1 M aq $NaHSO_4$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved *tert*-butanol (28 mL) and the solution was refluxed under argon for 5 h. Concentration *in vacuo* and purification by column chromatography (0→5→10→25% EtOAc/hexane) gave **2.43** (2.33 g, 87%): ^{1}H NMR (400 MHz, COSY) δ 1.24-1.30 (m, 2H, H-6), 1.45 (s, 9H, CH_3), 1.42-1.53 (m, 4H, H-5, H-7), 2.42 (3H, CH_3Ar), 2.48 (t, *J* = 2.48 Hz, 2H, H-4), 2.91 (q, *J* = 13.6, 7.2 Hz, 2H, H-8), 3.31 (s, 2H, H-2), 4.65 (t, *J* = 4.65 Hz, 1H, NH), 7.30 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.73 (d, *J* = 8.4 Hz, 2H, *o*-ArH). ^{13}C NMR (400 MHz, HSQC) δ 22.6 (ArCH_3). 22.9 (C-5), 25.8 (C-6), 27.9 (CH_3)$_3$, 29.3 (C-7), 42.5 (C-4), 42.8 (C-8), 50.5 (C-2), 82.0 (C), 127.0 (*o*-Ar), 129.7 (*m*-Ar), 136.9 (*p*-Ar), 143.3 (i*pso*-Ar), 166.5 (C-3), 203.2 (CO); HRMS calcd for $C_{15}H_{22}NO_5S$ $[M+H]^+$ 328.1213, found 328.1214.

[151] Friedrich M.; Grošelj U.; Kiraly-Potpara S.; Meden A.; Wagger J.; Dahmann G.; Stanovnik B.; Svete J.; Kralj, D. *Tetrahedron,* **2009**, *65*, 7151-7162.

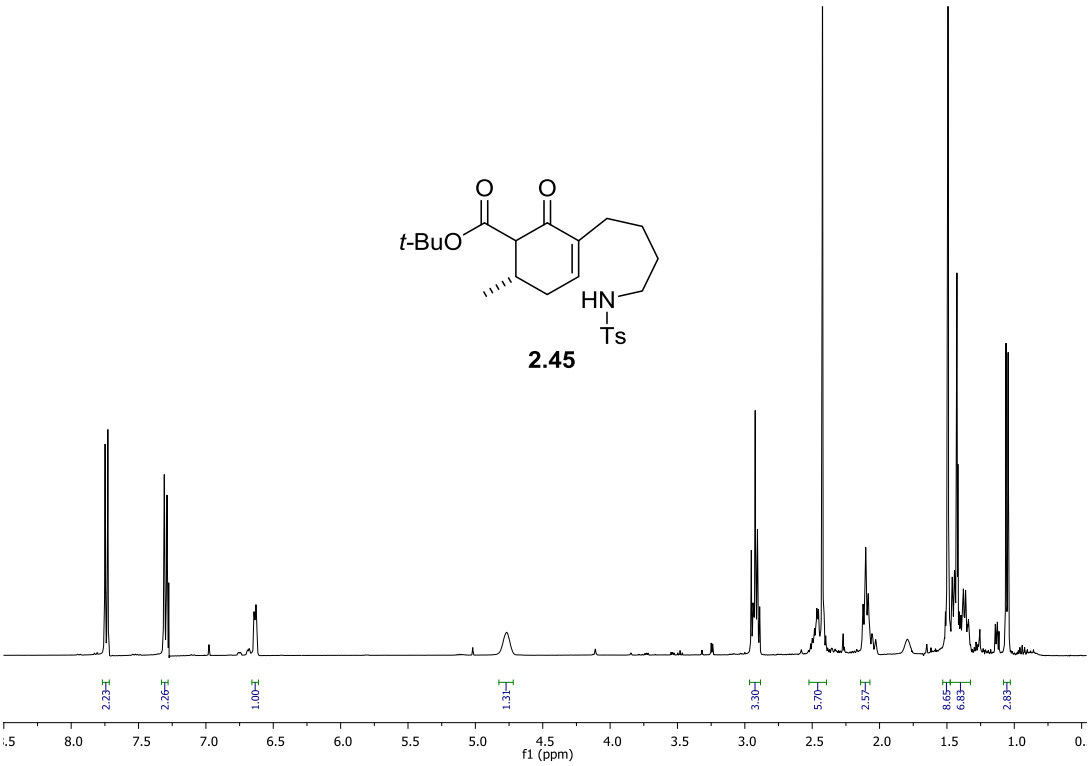

O
O
t-BuO
2.43
NHTs
2.07
2.11
1.10
1.69
2.45
1.86
3.30
13.42
2.90
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

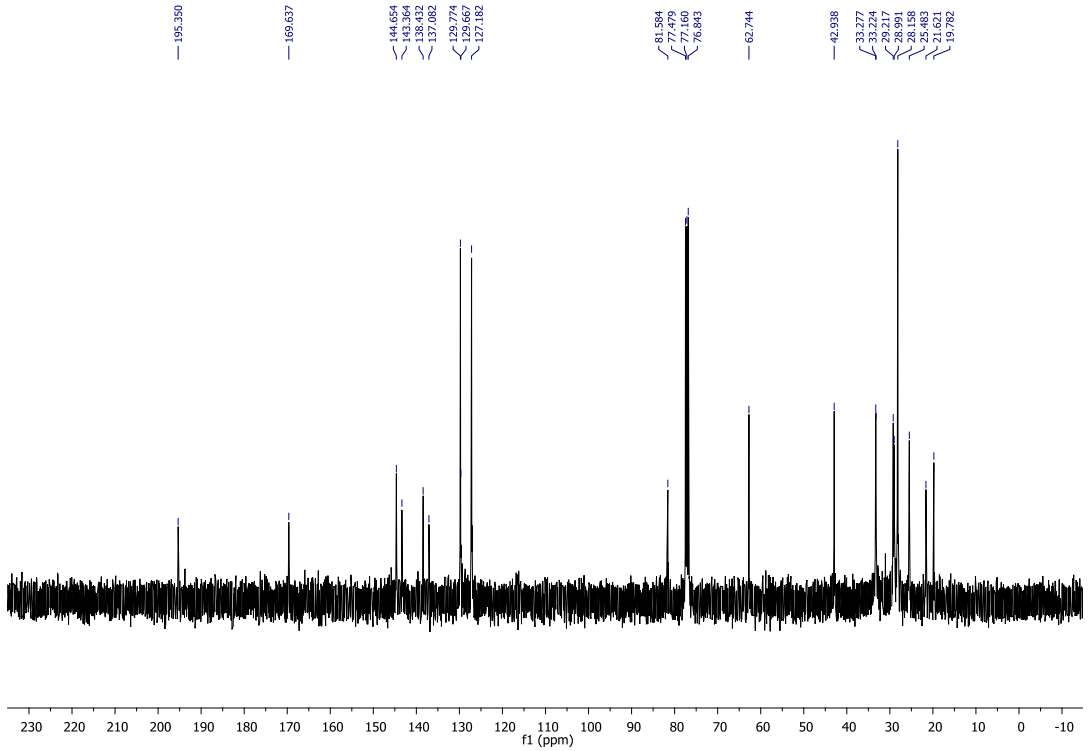

203.29
166.62
143.46
137.06
129.80
127.18
82.11
77.46
77.14
76.82
50.70
42.99
42.63
29.40
28.88
25.93
22.76
21.62
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

tert-Butyl-6-Methyl-2-oxo-3-(N-tosyl-4-aminobutyl)cyclohex-3-enecarboxylate. (2.45)

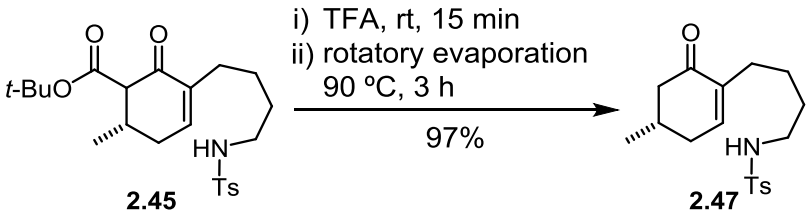


To a solution of β-keto ester **2.43** (550 mg, 1.43 mmol) in *tert*-butanol (67 mL) was added crotonaldehyde (110 mg, 1.58 mmol). The solution was cooled to 0 ºC and potassium *tert*-butoxide (10 mg, 0.06 equiv) was added. The reaction was stirred for 30 min at room temperature and a further portion of potassium *tert*-butoxide (39 mg, 0.24 equiv) was added. The reaction mixture was heated to reflux for 48 h, cooled to room temperature and quenched by the addition of sat NH_4Cl (aq) (1.5 mL/mmol), diluted with Et_2O (8.6 mL/mmol) and the phases separated. The organic phase was washed with brine (2 x 3 mL/mmol), dried ($MgSO_4$) and concentrated *in vacuo*. Purificacion by column chromatography (SiO_2, 10→25→50% EtOAc in hexane) gave cyclohexenone **2.45** (506 mg, 81%). ^{1}H NMR (400 MHz, COSY) δ 1.04 (d, *J* = 6.4 Hz, 3H, C6-CH_3), 1.30-1.45 (m, 6H, CH_2 sidechain), 1.48 (s, 9H, CH_3), 2.09 (t, *J* = 7.6 Hz, 2H, H-5), 2.41 (s, 3H, CH_3Ar), 2.44-2.46 (m, 1H, H-6), 2.87-2.89 (m, 2H, NCH_2), 2.91-2.94 (m, 1H, H-1), 4.76 (br, 1H, NH), 6.62 (dd, *J* = 6.0, 2.8 Hz, 1H, H-4), 7.28 (d, *J* = 7.6 Hz, 2H, *m*-ArH), 7.72 (d, *J* = 8.8 Hz, 2H, *o*-ArH), ^{13}C NMR (400 MHz, HSQC) δ 19.6 (C6-CH_3), 21.4 (ArCH_3), 25.3, 28.8, 29.1 (CH_2), 27.9 (CH_3), 28.9 (C-5), 33.1 (C-6), 42.8 (NCH_2), 62.6 (C-1), 81.4 (C), 127.0 (*o*-Ar), 129.6 (*m*-Ar), 136.9 (*p*-Ar), 138.3 (C-3), 143.2 (i*pso*-Ar), 144.5 (C-4), 169.5 (CO), 195.2 (C-2); HRMS calcd for $C_{23}H_{37}N_2O_5S$ $[M+NH_4]^+$ 453.2418, found 453.2415.

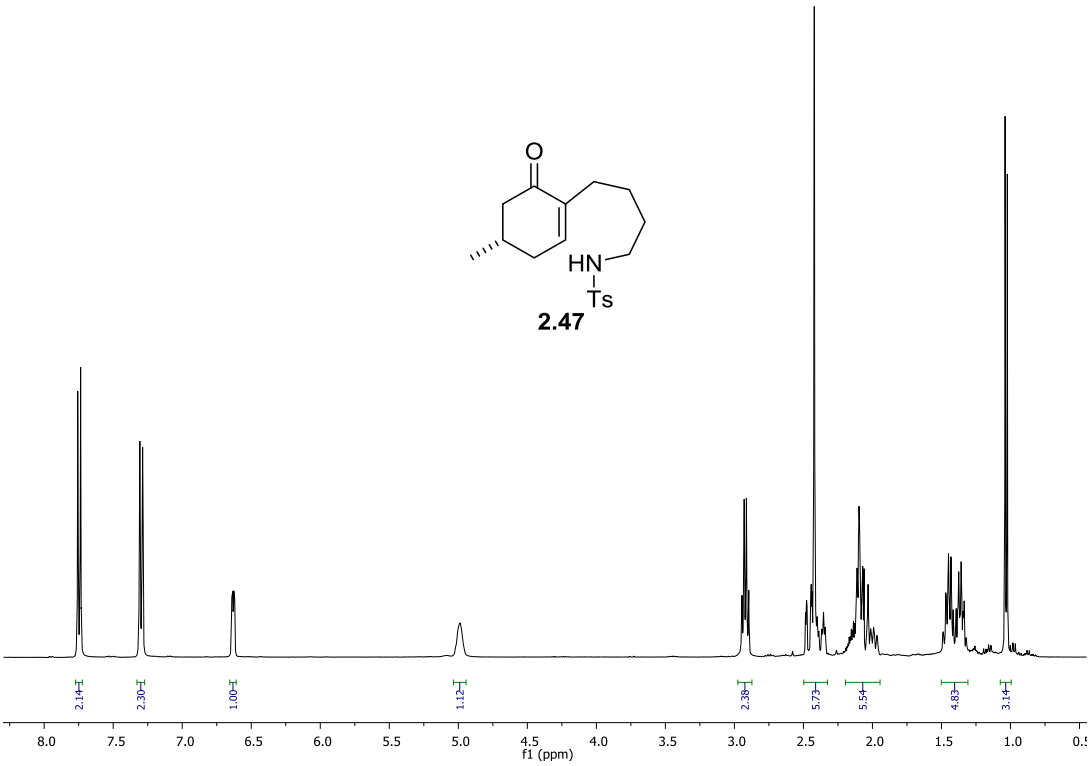

O
O
t-BuO
HN
Ts
2.45
2.23
2.26
1.00
1.31
3.30
5.70
2.57
8.65
6.83
2.83
f1 (ppm)

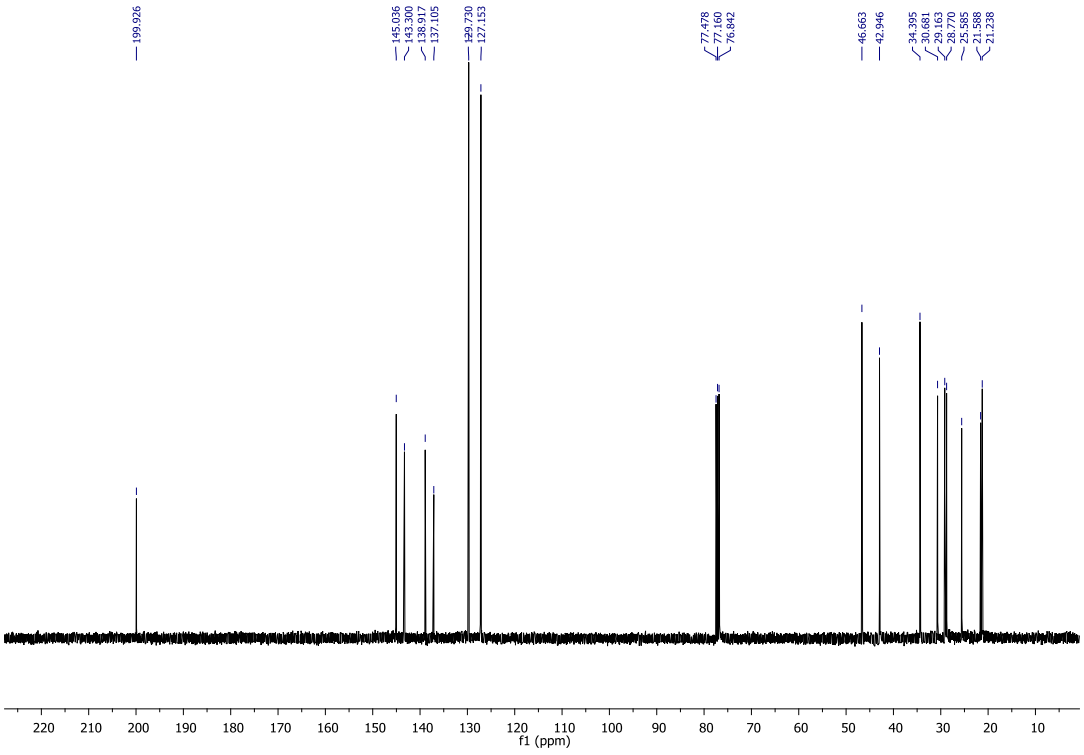

195.350
169.637
144.654
143.364
138.432
137.082
129.774
129.667
127.182
81.584
77.479
77.160
76.843
62.744
42.938
33.277
33.224
29.417
28.991
28.158
25.483
21.621
19.782
f1 (ppm)

(*S*)-4-Methyl-*N*-(4-(4-methyl-6-oxocyclohex-1-en-1-yl)-butyl) benzenesulfonamide (2.47)

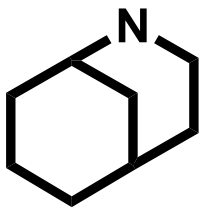


Cyclohexenone **2.45** (415 mg, 0.953 mmol) was dissolved in TFA (1 mL) and stirred for 15 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 2 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 90 ºC for 3 h to give the crude cyclohexenone **2.47** (310 mg, 97%) as a brown oil. ^{1}H NMR (400 MHz, COSY) δ 1.03 (d, *J* = 6.2 Hz, 2H, C6-CH_3), 1.32-1.39 (m, 2H, H-2'), 1.41-1.48 (m, 2H, H-3'), 1.98-2.03 (m, 1H, H-5), 2.13-2.17 (m, 4H, H-4, H-6), 2.34-2.48 (m, 2H, H-1'), 2.42 (s, 3H ArCH_3), 2.92 (q, *J* = 6.4 Hz, 2H, NCH_2), 4.98 (t, *J* = 6.0 Hz, 1H, NH), 6.63 (br, 1H, H-2), 7.29 (d, *J* = 8.0 Hz, 2H, *m*-Ar), 7.75 (d, *J* = 8.0 Hz, 2H, *o*-Ar); ^{13}C NMR (400 MHz, HSQC) δ 21.2 (C6-CH_3), 21.6 (ArCH_3), 25.6, 28.8, 29.2 (CH_2), 30.7 (C-5), 34.4 (C-6), 42.9 (NCH_2), 46.7 (C-1), 127.2 (*o*-Ar), 129.7 (*m*-Ar), 137.1 (*p*-Ar), 138.9 (C-3), 143.3 (i*pso*-Ar), 145.0 (C-4), 199.9 (C-2); HRMS calcd for $C_{18}H_{26}NO_3S$ $[M+H]^+$ 336.1628, found 336.1626.

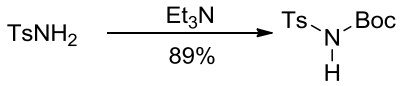

O
HN
Ts
2.47
2.14
2.30
1.00
1.12
2.38
5.73
5.54
4.83
3.14
f1 (ppm)


199.926
145.036
143.300
138.917
137.105
129.730
127.153
77.478
77.160
76.842
46.663
42.946
34.395
30.681
29.163
28.770
25.585
21.588
21.238
f1 (ppm)

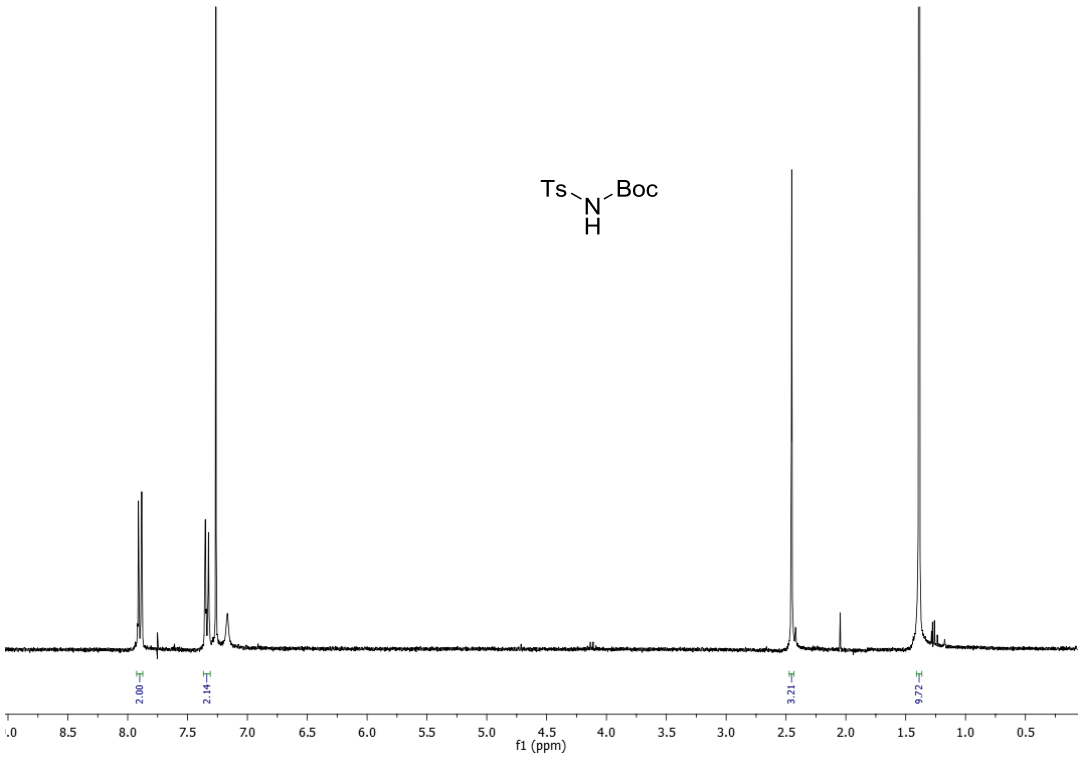
MORPHANS



tert-Butyl *N*-(4-Methylphenylsulfonyl)carbamate

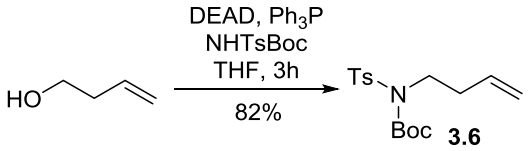


This compound was prepared according to the literature procedure[152] (9.69 g, 89%); ^{1}H NMR (400 MHz, COSY) δ 1.39 (s, 9H), 2.45 (s, 3H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, HSQC) δ 21.9, 28.1, 84.3, 128.5, 129.7, 136.1, 145.0.



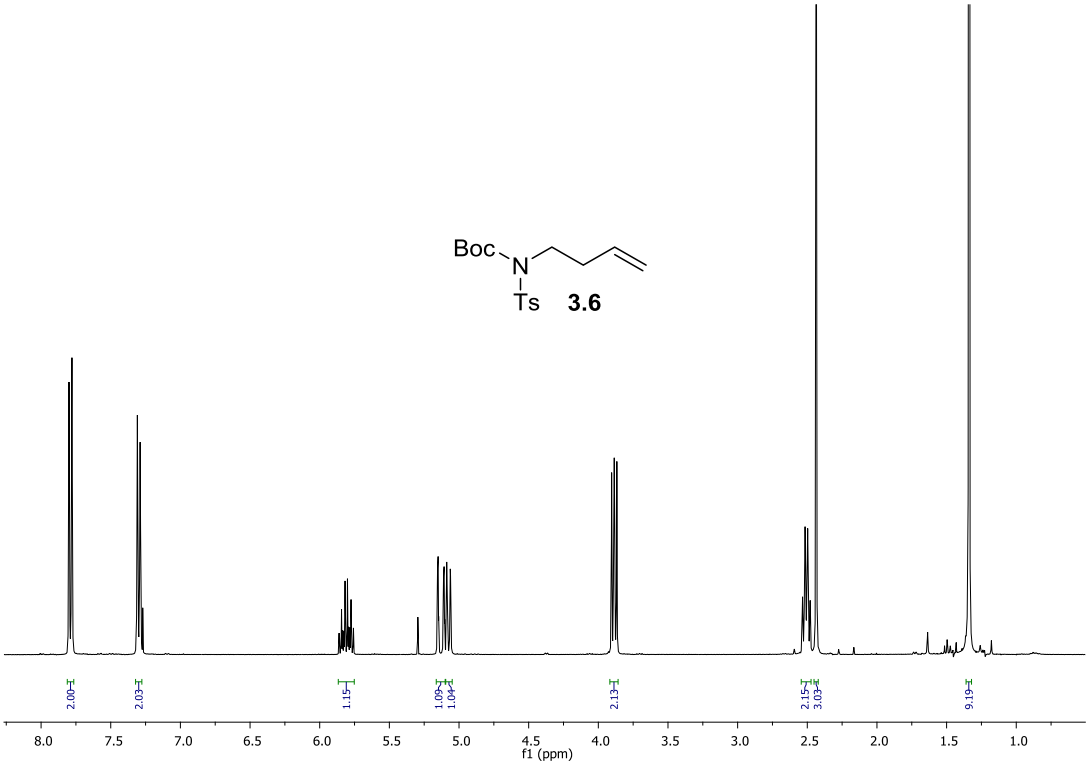
[152] Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379-380.

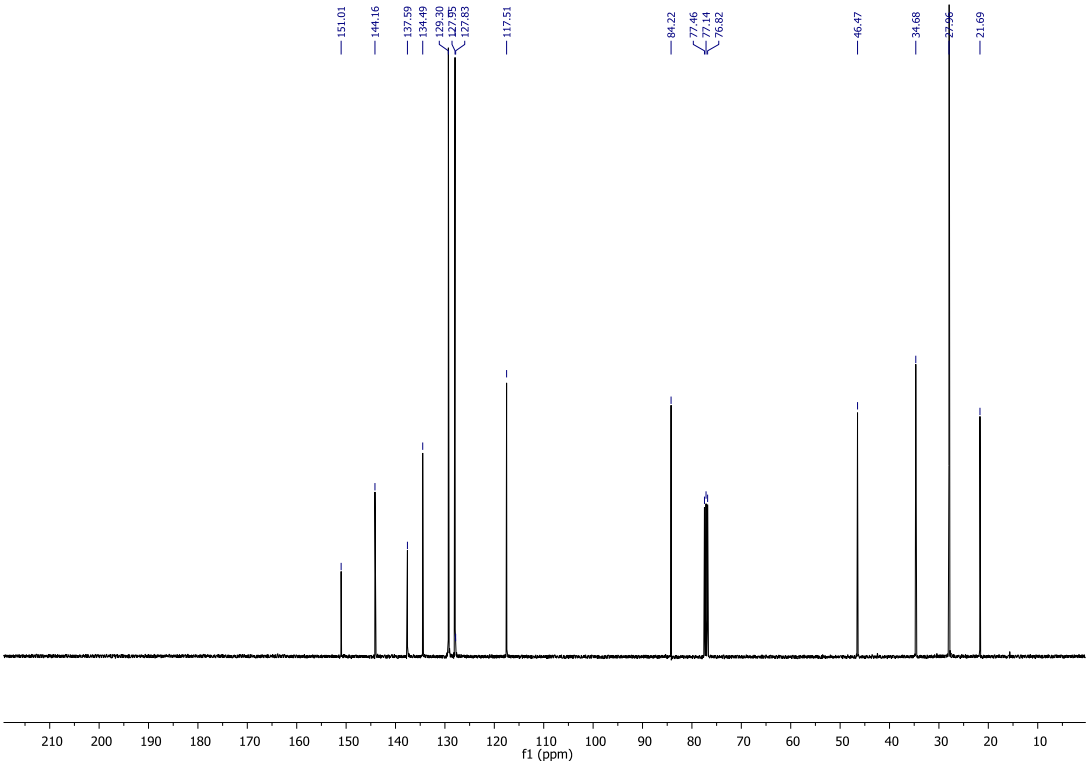
_N_-(But-3-en-1-yl)-_N_-(_tert_-Butoxycarbonyl)-4-methylbenzenesulfonamide. (3.6)



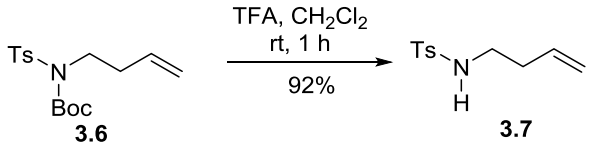
3.6

This compound was prepared according to the literature procedure[83] (4.91 g, 82%); ^{1}H NMR (400 MHz, COSY) δ 1.33 (s, 9H); 2.43 (s, 3H), 2.50 (q, *J* = 7.2 Hz, 2H, H-2), 3.88 (t, *J* = 7.2 Hz, 2H, H-1), 5.06 (d, *J* = 10.4 Hz, 1H, H-4), 5.12 (d, *J* = 17.2 Hz, 1H, H-4), 5.80 (ddt, *J* = 17.2, 10.4, 7.2 Hz, 1H, H-3), 7.29 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.78 (d, *J* = 8.4 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, HSQC) δ 21.5 ($ArCH_3$), 27.8 (CH_3), 34.5 (C-2), 46.3 (C-1), 84.1 (C), 117.4 (C-4), 127.8 (*o*-Ts), 129.2 (*m*-Ts), 134.4 (C-3), 137.5 (*p*-Ts), 144.0 (i*pso*-Ts), 150.9 (CO). HRMS calcd for $C_{12}H_{16}NO_4S$ $[M+{}^{t}Bu]^{+}$ 270.0795, found 270.0797.

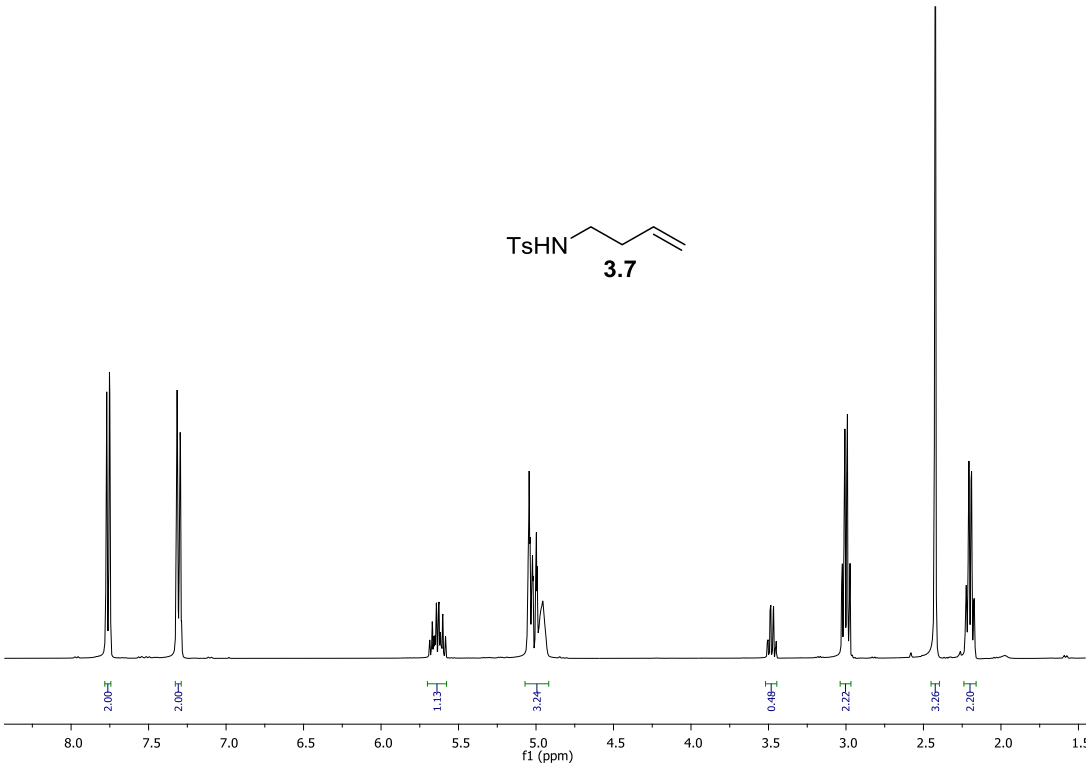

Boc
N
Ts
3.6
2.00
2.03
1.15
1.09
1.04
2.13
2.15
3.03
9.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

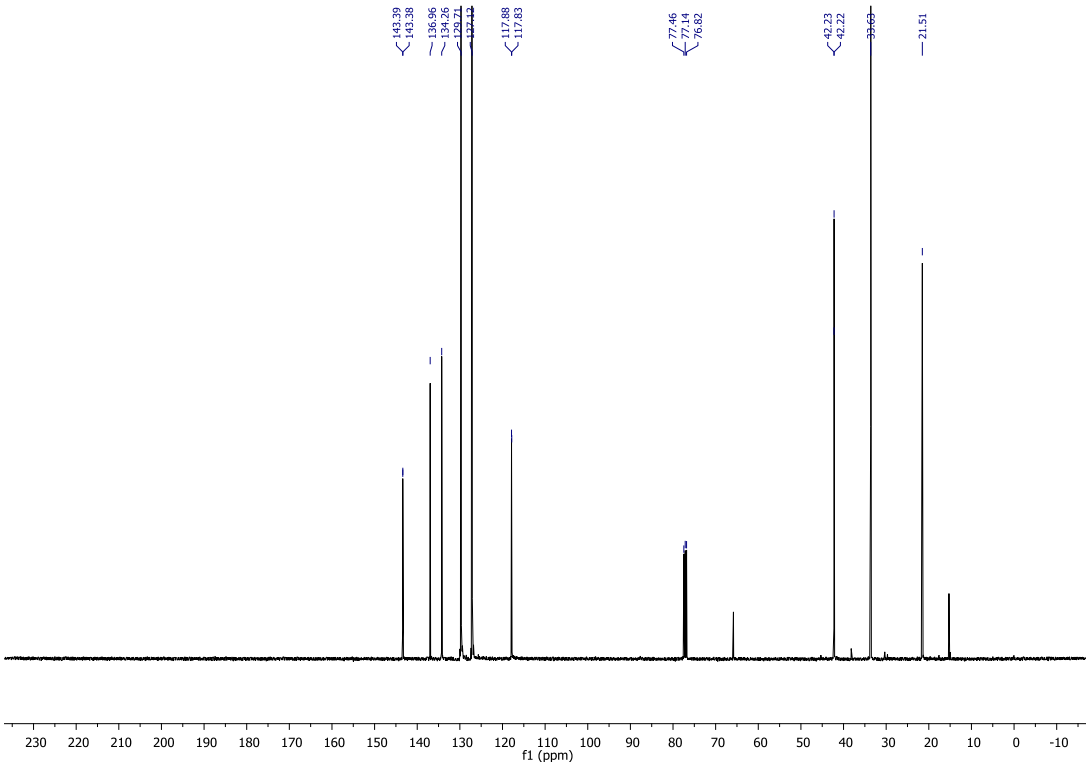

151.01
144.16
137.59
134.49
129.30
127.95
127.83
117.51
84.22
77.46
77.14
76.82
46.47
34.68
27.96
21.69
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

_N_-(But-3-en-yl)-4-methylbenzenesulfonamide. (3.7)

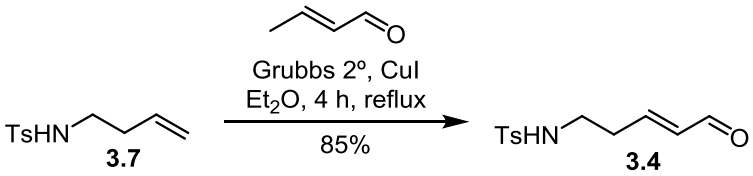


This product was prepared according to a literature procedure[83] (2.68 g, 92%); ^{1}H NMR (400 MHz, COSY) δ 2.19 (qd, *J* = 6.8, 1.2 Hz, 2H, H-2), 2.42 (s, 3H, CH_3), 3.00 (qd, *J* = 7.2, 1.8 Hz, 2H, H-1), 4.96 (br, 1H, NH), 5.02 (m, 2H, H-4), 5.64 (ddt, *J* = 17.2, 10.4, 6.8, 1H, H-3), 7.29 (d, *J* = 8.0 Hz, 2H, o-Ts), 7.75 (d, *J* = 8.2 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, HSQC) δ 21.4 ($ArCH_3$), 33.5 (C-2), 42.1 (C-1), 117.7 (C-4), 127.0 (*o*-Ts), 129.6 (*m*-Ts), 134.1 (C-3), 136.8 (*p*-Ts), 143.3 (*ipso*-Ts).

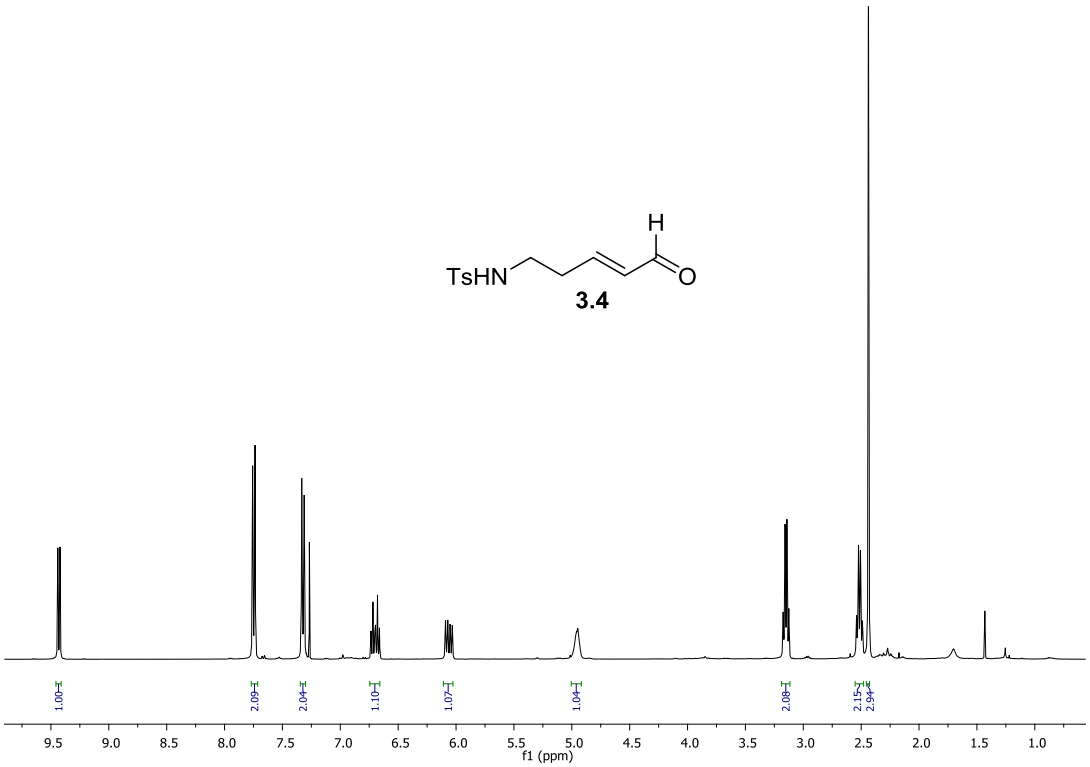

TsHN
3.7
2.00
2.00
1.13
3.24
0.40
2.22
3.26
2.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

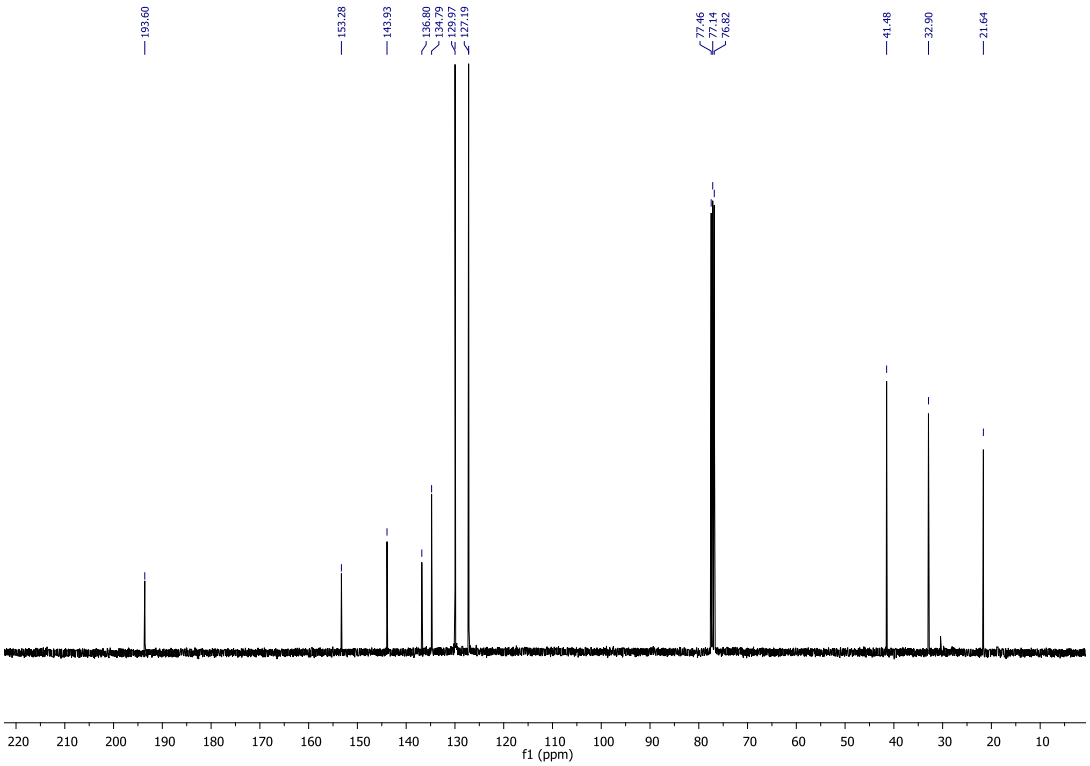

143.39
143.38
136.96
134.26
129.71
127.12
117.88
117.83
77.46
77.14
76.82
42.23
42.22
33.63
21.51
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(*E*)-5-*N*-(4-Methylphenylsulfonyl) aminopent-3-enal. (3.4)

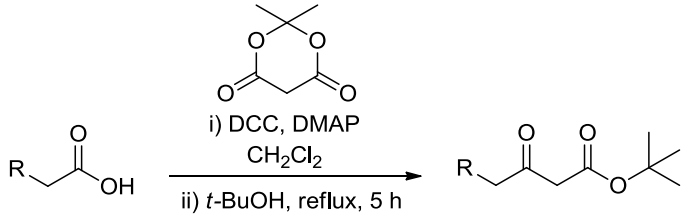


To a solution of alkene **3.7** (118 mg, 0.524 mmol) and crotonaldehyde (110 mg, 1.57 mmol) in diethyl ether (5 mL) was added Grubbs-2nd generation catalyst (4.0 mg, 5.2 µmol), and CuI (1.5 mg, 7.9 µmol) and the mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (0→10→25→50% EtOAc/hexane) to give **3.4** (112 g, 85%) as a brown oil. ^{1}H NMR (400 MHz, COSY) δ 2.43 (s, 3H, $ArCH_3$), 2.51 (q, *J* = 6.7 Hz, 2H, H-4), 3.14 (q, *J* = 6.7 Hz, 2H, H-5), 4.95 (br, 1H, NH), 6.05 (dd, *J* = 16.0, 7.6 Hz, 1H, H-2), 6.69 (dt, *J* = 16.0, 6.7 Hz, 1H, H-3), 7.29 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.75 (d, *J* = 8.0 Hz, 2H, *o*-Ts), 9.42 (d, *J* = 7.6 Hz, 1H, CHO); ^{13}C NMR (100 MHz, HSQC) δ 21.5 ($ArCH_3$), 32.8 (C-4), 41.3 (C-5), 127.1 (*o*-Ts), 129.8 (*m*-Ts), 134.7 (*p*-Ts), 136.7 (C-2), 143.8 (i*pso*-Ts), 153.1 (C-3), 193.5 (C-1). HRMS calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$ 254.0845, found 254.0848.


H
TsHN
O
3.4
1.00
2.09
2.04
1.10
1.07
1.04
2.08
2.15
2.94
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

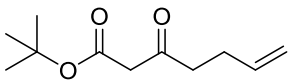

193.60
153.28
143.93
136.80
134.79
129.97
127.19
77.46
77.14
76.82
41.48
32.90
21.64
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

General Procedure A: Synthesis of β-keto esters 3.13a-h



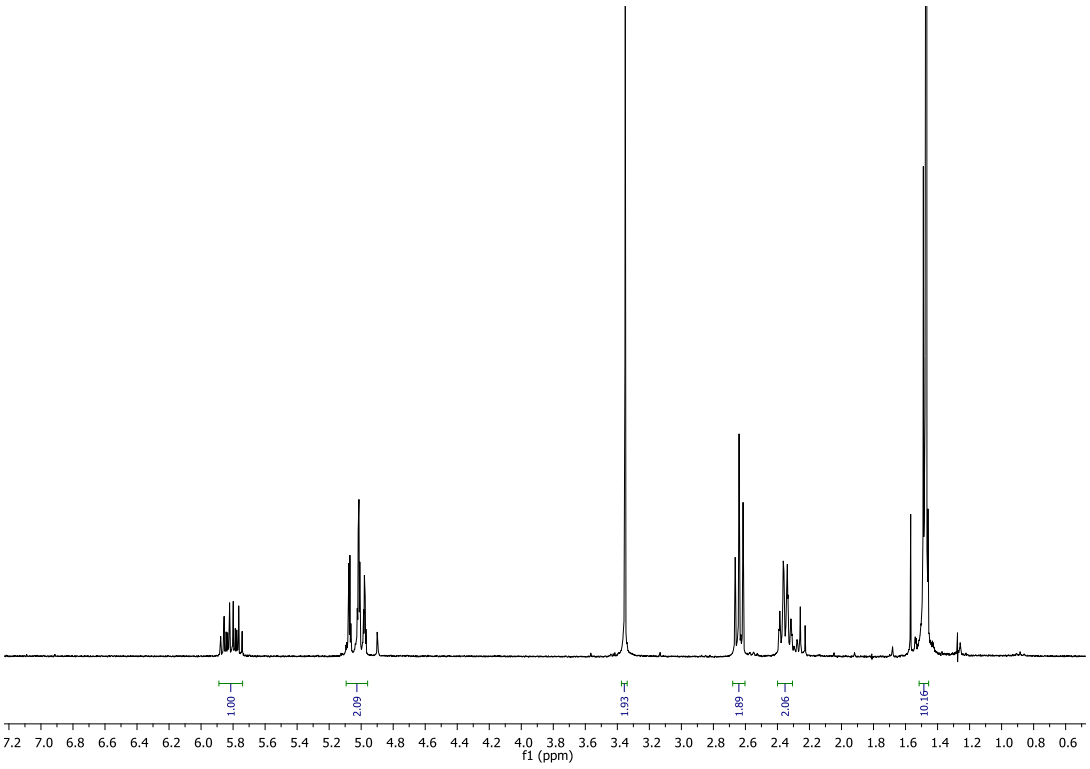
A solution of DCC (1.1 equiv) in CH_2Cl_2 (1 mL/mmol) was added slowly to a stirred solution of Meldrum's acid (1 equiv), the corresponding carboxylic acid compound (1 equiv), and DMAP (1.1 equiv) in CH_2Cl_2 (5 mL/mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 16 h and the precipitated solid was removed by filtration and washed with CH_2Cl_2. The filtrate was washed with 1 M aq $NaHSO_4$, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved *tert*-butanol (4 mL/mmol) and the solution was refluxed under argon for 5 h. Concentration *in vacuo* and purification by column chromatography gave the corresponding β-keto ester product.

***tert*-Butyl 3-Oxohept-6-enoate (3.13a)**[153]



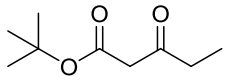
3.13a

This compound was prepared according to the above general procedure using DCC (1.13 g, 5.49 mmol), Meldrum's acid (0.72 g, 4.99 mmol), 4-pentenoic acid (0.50 g, 4.99 mmol), and DMAP (0.67 g, 5.49 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave keto ester **3.13a** (0.83 g, 84%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9 H, CH_3), 2.35 (q, *J* = 7.8 Hz, 2H, H-5), 2.63 (t, *J* = 7.8 Hz, 2H, H-4), 3.35 (s, 2H, H-2), 5.06 (d, *J* = 10.4 Hz, 1H, H-7), 5.12 (d, *J* = 17.2 Hz, 1H, H-7), 5.80 (ddt, *J* = 17.2, 10.4, 7.4 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (C-5), 27.9 (CH_3), 41.8 (C-4), 50.6 (C-2), 81.8 (C), 115.3 (C-7), 136.6 (C-6), 166.3 (C-1), 202.3 (C-3).



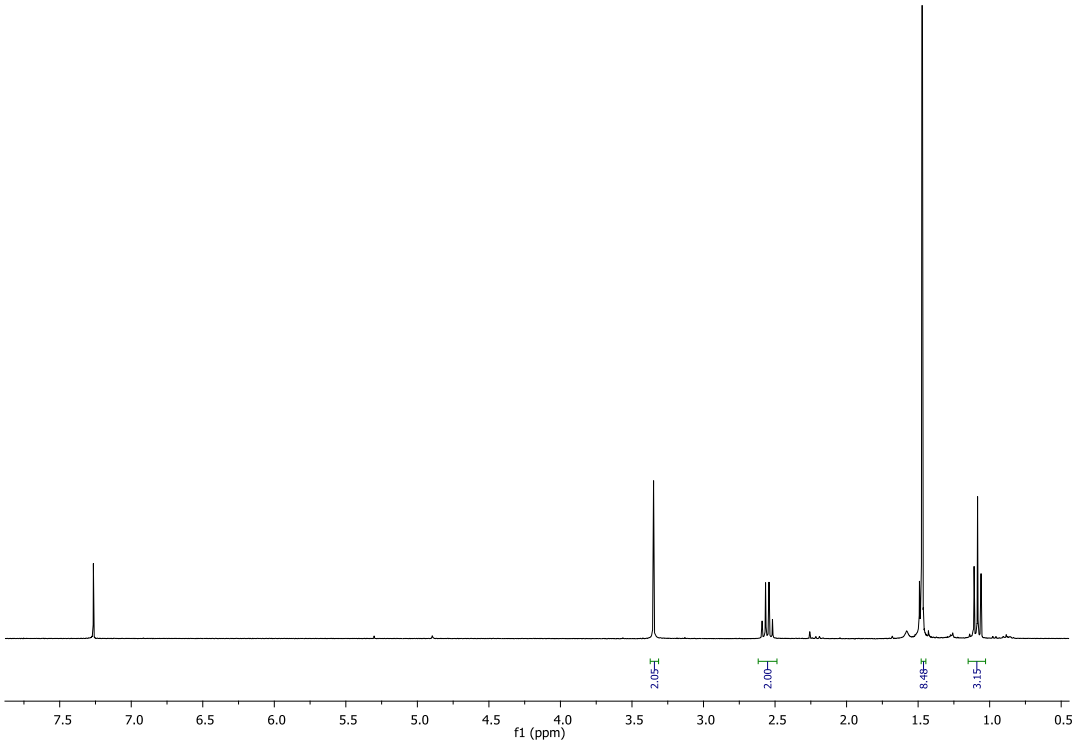
[153] Lanners, S.; Norouzi-Arasi, H.; Khiri, N.; Hanquet, G. *Eur. J. Org. Chem.* **2007**, *24*, 4065-4075.

tert-Butyl 3-Oxopentanoate (3.13b)[154]



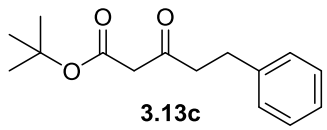
3.13b

This compound was prepared according to the above general procedure using DCC (1.53 g, 7.42 mmol), Meldrum's acid (0.97 g, 6.75 mmol), propionic acid (0.50 g, 6.75 mmol), and DMAP (0.91 g, 7.42 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave keto ester **3.13b** (0.90 g, 75%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, *J* = 7.2 Hz, 3H, H-5). 1.47 (s, 9H, CH_3), 3.34 (s, 2H, H-2), 2.34 (q, 2H, *J* = 7.2 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.4 (C-5), 27.8 (CH_3), 36.0 (C-4), 50.2 (C-2), 81.7 (C), 166.5 (C-1), 203.7 (C-3).



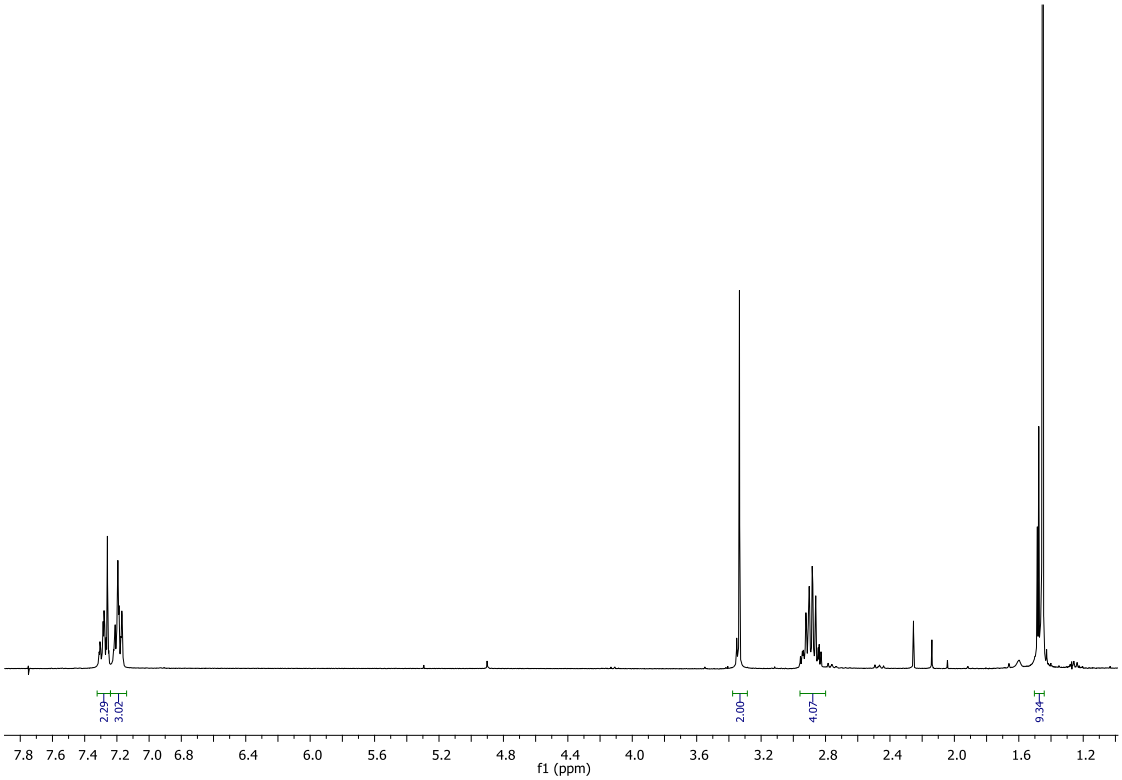
[154] Tabuchi, H.; Hamamoto, T.; Ichihara, A. *Synlett* **1993**, *9*, 651-652.

tert-Butyl 3-Oxo-5-phenylpentanoate (3.13c)[155,156]



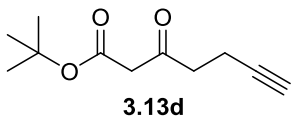
3.13c

This compound was prepared according to the above general procedure using DCC (1.51 g, 7.32 mmol), Meldrum's acid (0.96 g, 6.66 mmol), 3-phenylpropionic acid (1.00 g, 6.66 mmol), and DMAP (0.89 g, 7.32 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave keto ester **3.13c** (1.02 g, 62%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 9H, CH_3), 2.79 and 2.80 (2t, *J* =7.0 Hz, 2H each, H-4 and H-5), 3.24 (s, 2H, H-2), 7.10-7.16 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.9 (CH_3), 29.4 (C-5), 44.3 (C-4), 50.7 (C-2), 81.9 (C), 126.1 (*o*-Ar), 128.2 (*m*-Ar), 128.5 (*p*-Ar), 140.6 (*ipso*-Ar), 166.3 (C-1), 202.2 (C-3).



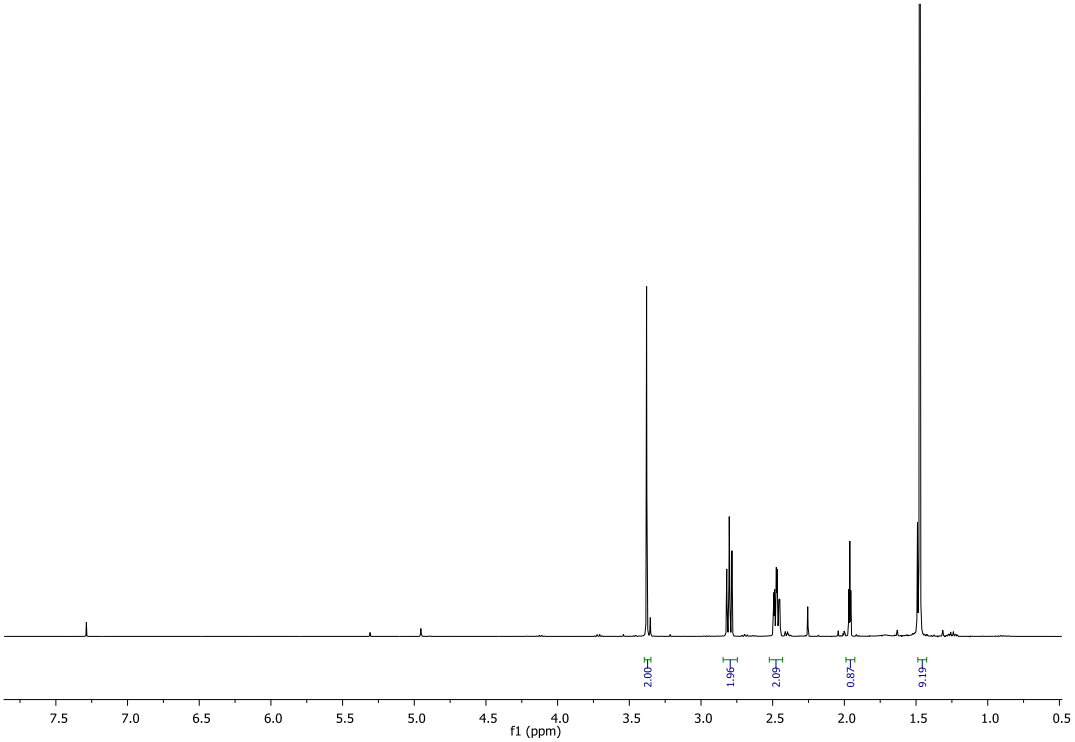
[155] Trotter, B. W.; Bell, I. M.; *PCT Int. Appl., 2003035616*, **2003.**
[156] For an alternative procedure, see: Langer, P.; Bellur, E. *J. Org. Chem*, **2003**, *68*, 9742-9746.

tert-Butyl 3-Oxohept-6-ynoate (3.13d)

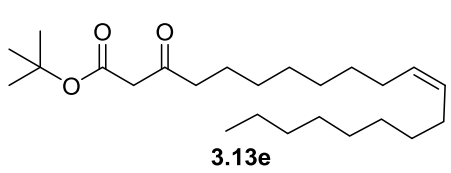


3.13d

This compound was prepared according to the above general procedure using DCC (2.31 g, 11.21 mmol), Meldrum's acid (1.47 g, 10.19 mmol), 4-pentynoic acid (1.00 g, 10.19 mmol), and DMAP (1.37 g, 11.21 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave keto ester **3.13d** (1.15 g, 58%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.45 (s, 9H, CH_3), 1.94 (t, J = 2.4 Hz, 1H, H-7), 2.45 (td, J = 7.6, 2.4 Hz, 2H, H-5), 2.78 (t, J = 7.6 Hz, 2H, H-4), 3.35 (s, 2H, H-2); ^{13}C NMR (100 MHz, HSQC) δ 12.7 (C-5), 27.9 (CH_3), 41.4 (C-4), 50.4 (C-2), 68.8 (C-7), 82.1 (C-6), 82.6 (C), 166.1 (C-1), 200.9 (C-3). HRMS calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1172, found 197.1171.

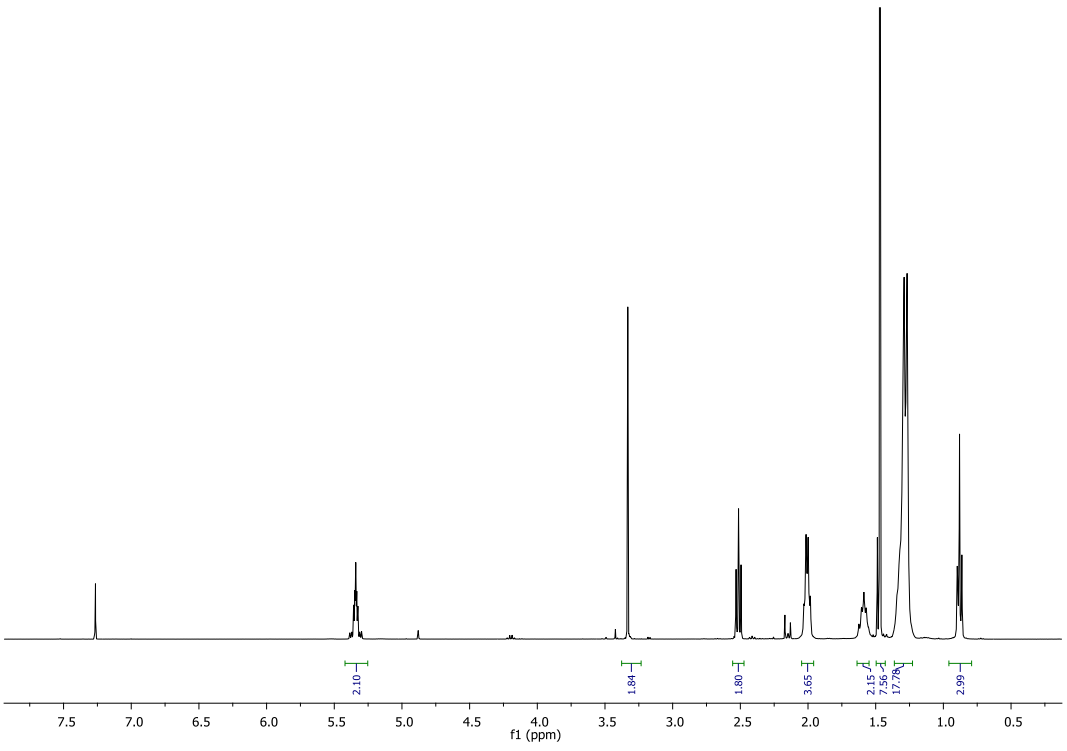


***(Z)-tert*-butyl 3-Oxoicos-11-enoate (3.13e)**

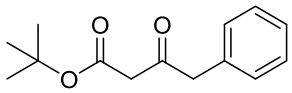


3.13e

This compound was prepared according to the above general procedure using DCC (0.80 g, 3.89 mmol), Meldrum's acid (0.51 g, 3.54 mmol), oleic acid (1.00 g, 3.54 mmol), and DMAP (0.48 g, 3.89 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave keto ester **3.13e** (0.98 g, 76%) as a yellow oil ^{1}H NMR (400 MHz, COSY) δ 0.87 (t, J = 6.4 Hz, 3H, H-20), 1.25-1.35 (m, H), 1.46 (s, 9H, CH_3), 1.58 (quint, J = 7.4 Hz, 2H, H-5), 2.00 (dd, *J* = 7.0, 3.5 Hz, 4H, H-10 and H-13), 2.51 (t, *J* = 7.2 Hz, 2H, H-4), 3.32 (s, 2H, H-2), 5.33 (quint, *J* = 3.5 Hz, 2H, H-11 and H-12); ^{13}C NMR (100 MHz, HSQC) δ 14.1 (C-20), 22.7, 23.4, 27.1, 27.2, 27.9 (CH_3), 29.0, 29.1, 29.2, 29.3, 29.5, 29.7, 29.8, 31.9, 42.9 (C-4), 50.6 (C-2), 82.1 (C-6), 81.8 (C), 129.7 and 130.0 (=CH), 166.5 (C-1), 203.4 (C-3). HRMS calcd for $C_{24}H_{44}NaO_3$ $[M+Na]^+$ 403.3183, found 403.3171.

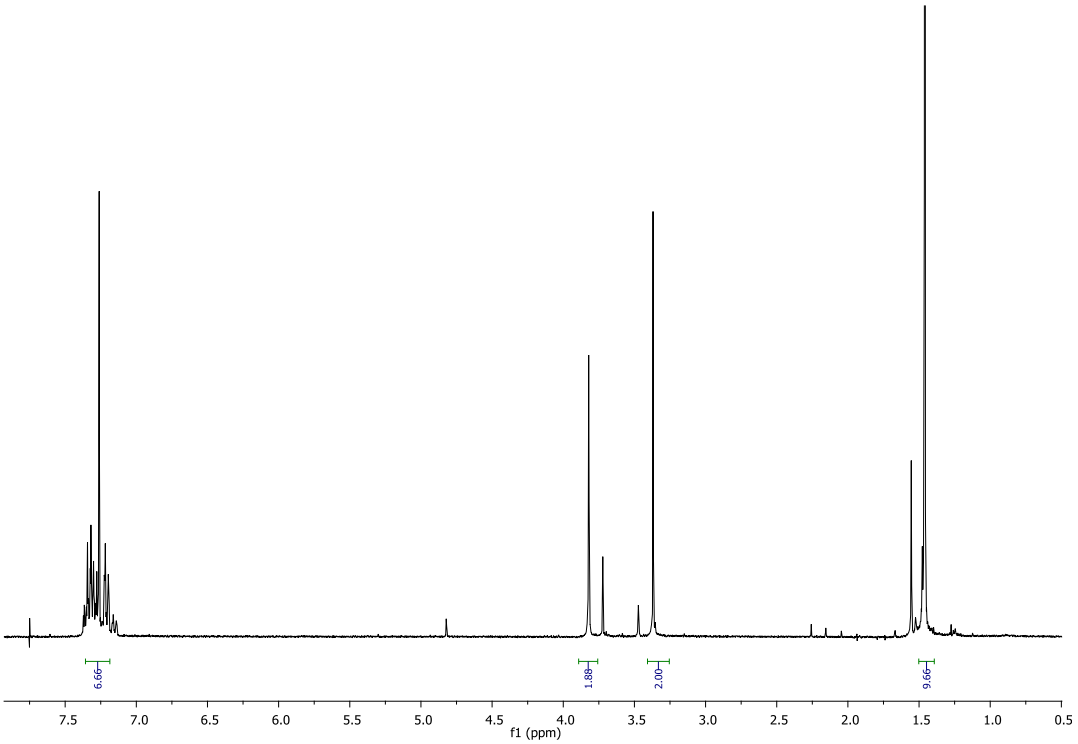


tert-Butyl 3-Oxo-4-phenylbutanoate (3.13f)[157]



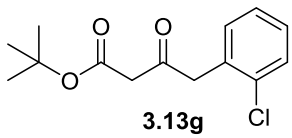
3.13f

This compound was prepared according to the above general procedure using DCC (1.00 g, 4.84 mmol), Meldrum's acid (0.64 g, 4.41 mmol), phenylacetic acid (0.60 g, 4.41 mmol), and DMAP (0.59 g, 4.84 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave keto ester **3.13f** (0.78 g, 76%) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H, CH_3), 3.37 (s, 2H, H-2), 3.82 (s, 2H, H-4), 7.14-7.37 (m, 5H, *o*-ArH, *p*-ArH, *m*-ArH) ^{13}C NMR ($CDCl_3$,100 MHz) δ 28.0 (CH_3), 49.6 (C-4), 49.9 (C-2), 82.0 (C), 127.3 (*o*-Ar), 128.8 (*m*-Ar), 129.6 (*p*-Ar), 133.4 (i*pso*-Ar), 166.3 (C-1), 200.9 (C-3).



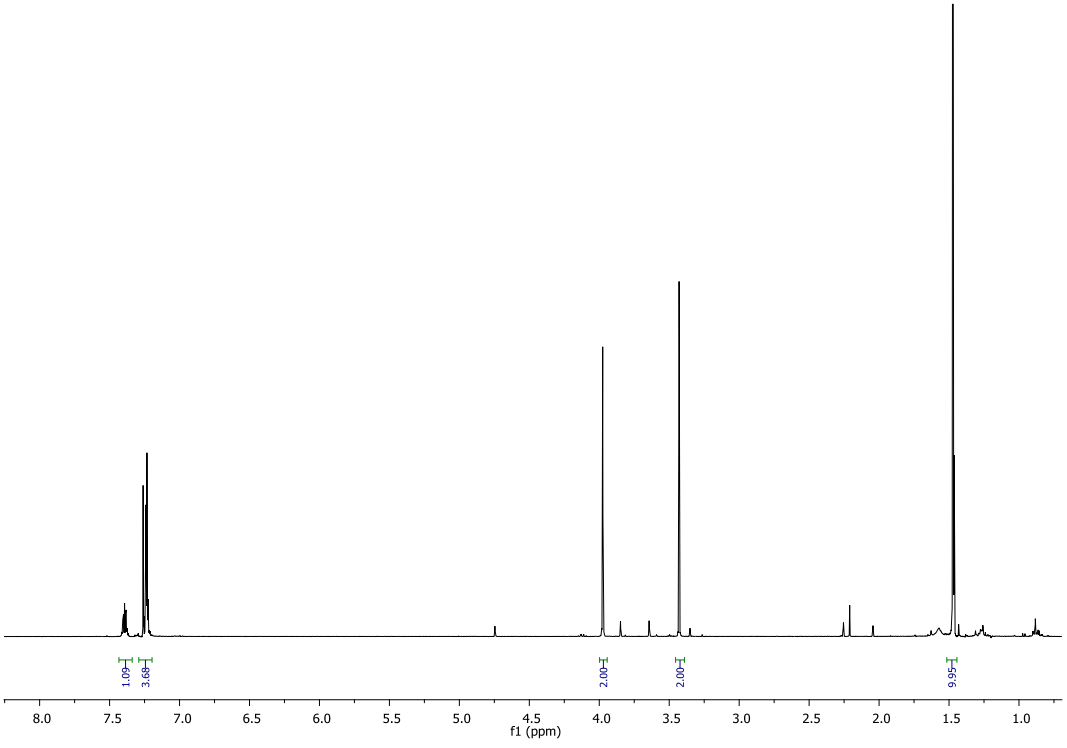
[157] Knobloch, E.; Brückner, R. *Synthesis* **2008**, *14*, 2229-2246.

tert-Butyl 4-(2-Chlorophenyl)-3-oxobutanoate (3.13g)

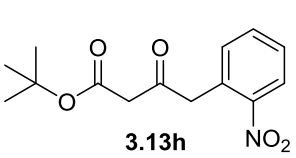


3.13g

This compound was prepared according to the above general procedure using DCC (0.79 g, 3.82 mmol), Meldrum's acid (0.50 g, 3.47 mmol), 2-chlorophenylacetic acid (0.59 g, 3.47 mmol), and DMAP (0.47 g, 3.82 mmol). Purification by column chromatography (0→1→2.5→5% EtOAc/hexane) gave keto ester **3.13g** (830 mg, 89%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.47 (s, 9H, CH_3), 3.43 (s, 2H, H-2), 3.97 (s, 2H, H-4), 7.25 (m, 3H, ArH), 7.39 (dd, *J* = 7.5, 3.2 Hz, 1H, ArH-3´) ^{13}C NMR (100 MHz, HSQC) δ 27.9 (CH_3), 47.5 (C-4), 50.1 (C-2), 82.1 (C), 127.0 (Ar-5´), 128.9 (Ar-4´), 129.5 (Ar-3´), 131.8 (Ar-6´), 134.5 (Ar-1´), 137.5 (Ar-2´), 166.2 (C-1), 199.5 (C-3). HRMS calcd for $C_{14}H_{17}ClNaO_3$ $[M+Na]^+$ 291.0758, found 291.0762.

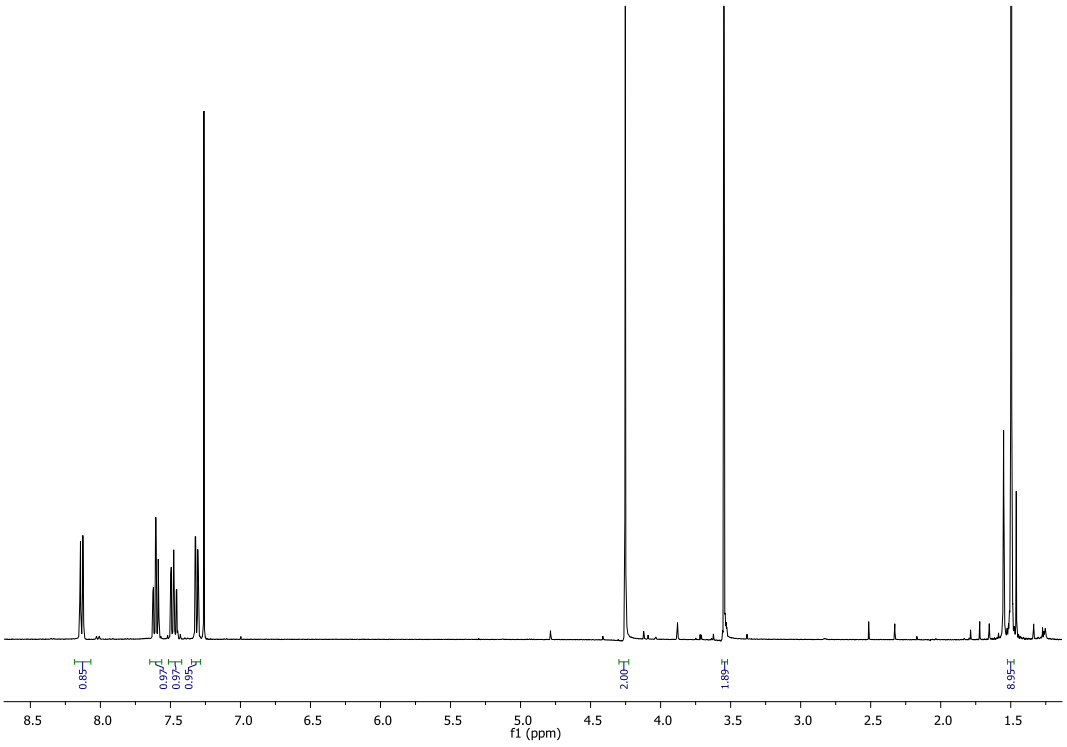


tert-Butyl 4-(2-Nitrophenyl)-3-oxobutanoate (3.13h)

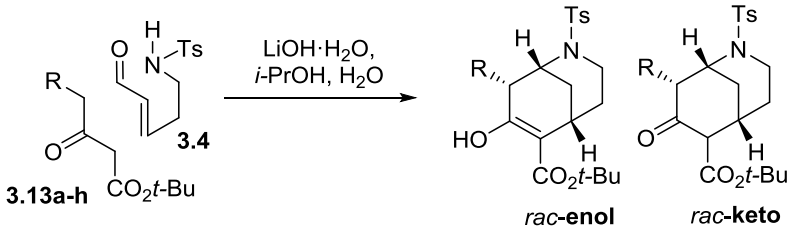


3.13h

This compound was prepared according to the above general procedure using DCC (0.88 g, 4.25 mmol), Meldrum's acid (0.56 g, 3.86 mmol), 2-nitrophenylacetic acid (0.70 g, 3.86 mmol), and DMAP (0.52 g, 4.25 mmol). Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave **3.13h** (1.03 g, 96%) as an amorphous solid. ^{1}H NMR (400 MHz, COSY) δ 1.50 (s, 9H, CH_3), 3.55 (s, 2H, H-2), 4.25 (s, 2H, H-4), 7.31 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-6´), 7.47 (td, *J* = 8.0, 1.6 Hz, 1H, ArH-4´), 7.60 (td, *J* = 7.6, 1.6 Hz, 1H, ArH-5´), 8.13 (dd, *J* = 8.4, 1.2 Hz, 1H, ArH-3´); ^{13}C NMR (100 MHz, HSQC) δ 28.0 (CH_3), 47.7 (C-4), 50.6 (C-2), 82.3 (C), 125.3 (Ar-3´), 128.6 (Ar-4´), 129.8 (Ar-5´), 133.7 (Ar-6´), 166.2 (C-1), 198.6 (C-3). HRMS calcd for $C_{14}H_{17}NNaO_5$ $[M+Na]^+$ 302.0999, found 302.10099.



General Procedure B: Synthesis of Morphans – racemic version



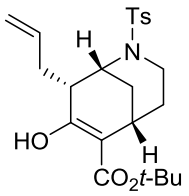
To a solution of β-keto ester (1.0 equiv) in *i*PrOH (1 mL/mmol) was added enal **3.4** (1.1 equiv), H_2O (10 equiv), followed by $LiOH{\cdot}H_2O$ (1 equiv). The reaction mixture was stirred for 16 h at room temperature, quenched with sat. aq. NH_4Cl (15 mL/mmol) solution and the product was extracted with EtOAc (3 x 20 mL/mmol). The combined organic layers were dried and concentrated *in vacuo*. Purification by column chromatography gave the corresponding morphan products.

Table 1: Reaction in racemic form of modified C-8 substituted morphans

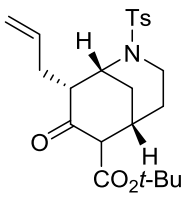
Entry	-R	Yield[a]	Ratio[a]
1	$CH_2CH{=}CH_2$	71%	1.6:1
2	H	40%	1:0
3	CH_3	47%	1:0
4	CH_2Ph	64%	1:1
5	$CH_2C{\equiv}CH$	63%	1.6:1
6	$(CH_2)_6CH{=}CH(CH_2)_7CH_3$	38%	5:1
7	Ph	53%	9:1
8	*o*-ClPh	56%	3:1

[a]mixture enol/keto forms

(1*RS*,5*SR*,8*SR*)-*tert*-Butyl 8-Allyl-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (*rac*-3.14) and *(*1*RS*,5*SR*,6*SR*,8*SR*)-*tert*-Butyl 8-allyl-2-(4-methylphenylsulfonyl)-7-oxo-2-azabicyclo[3.3.1]nonane-6-carboxylate (*rac*-3.15)



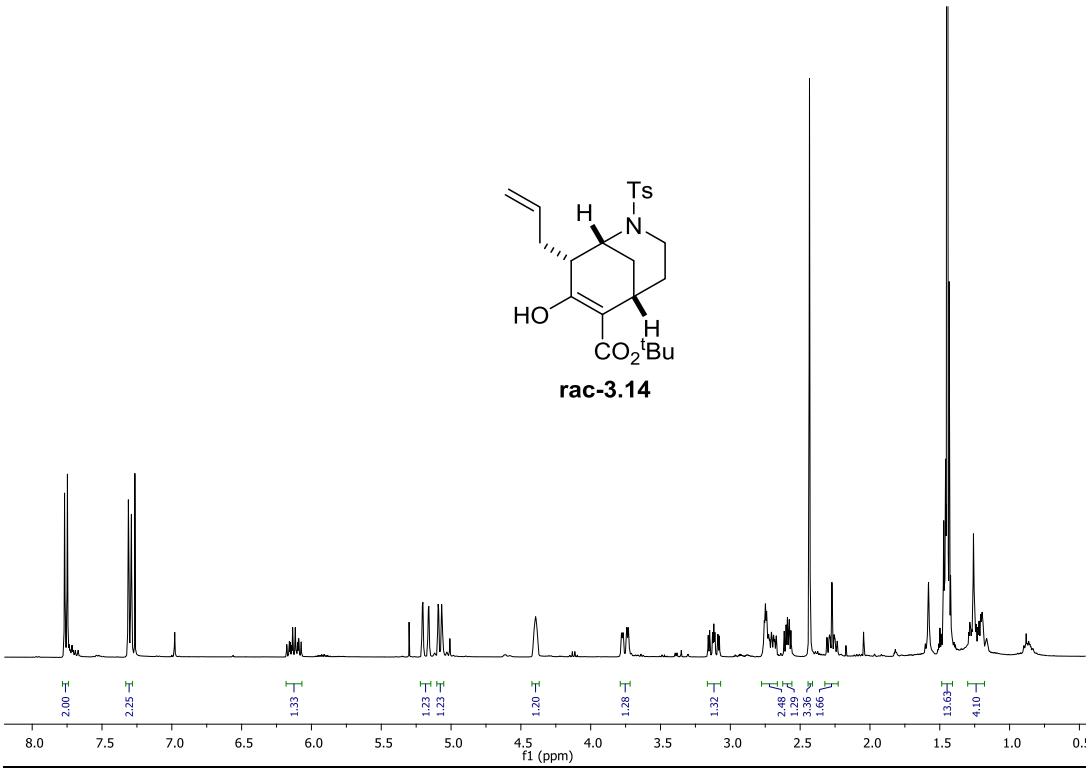
rac-**3.14**

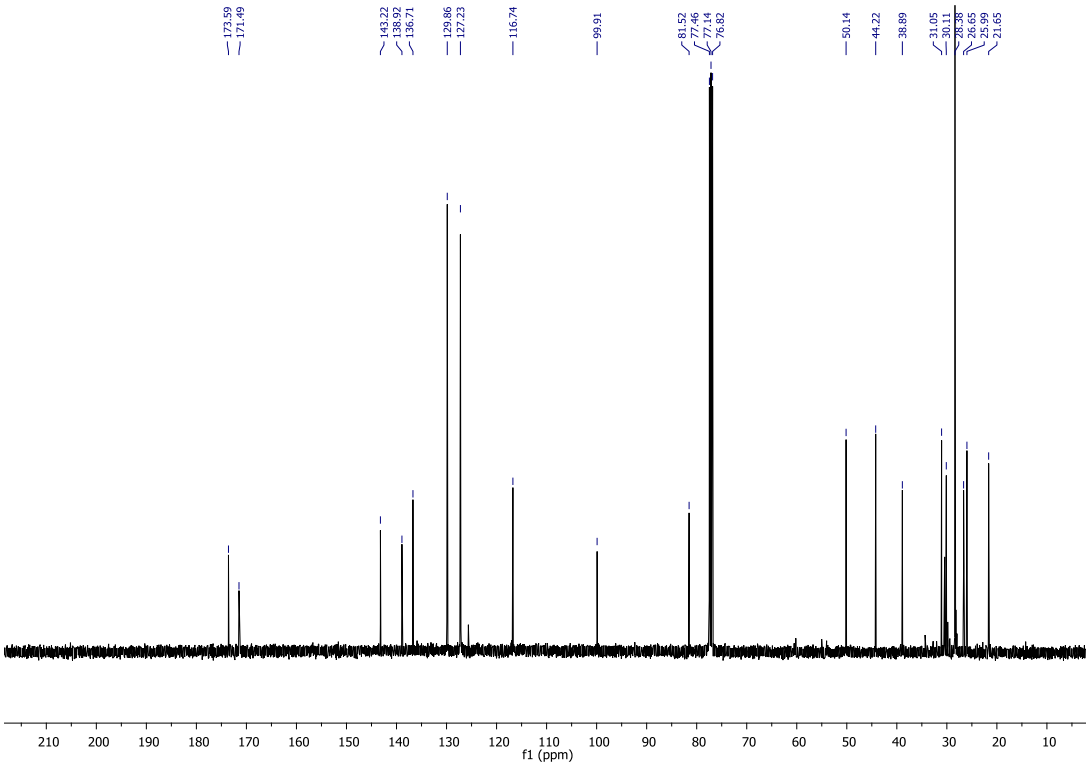


rac-**3.15**

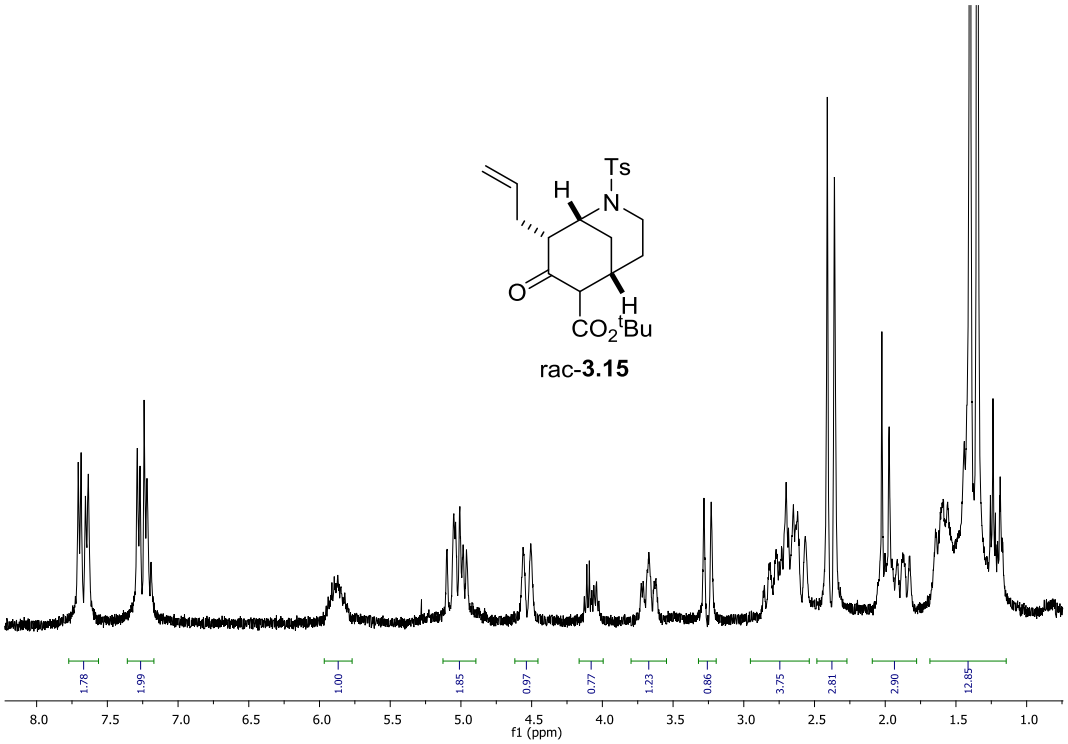
Operating as the above general method **B** and starting from β-keto ester **3.13a** (450 mg, 2.84 mmol), a 1.6:1 mixture of ***rac*-3.14** and its tautomer ***rac*-3.15** was obtained. Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave ***rac*-3.14** (544 mg, 44%) and ***rac*-3.15** (334 mg, 27%), with a 71% overall yield.

Compound ***rac*-3.14**: ^{1}H NMR (400 MHz, COSY) δ 1.20 (m, 2H, H-4), 1.44 (s, 9H, CH_3), 1.45 (masked, 2H, H-9), 2.27 (ddd, *J* = 14.4, 7.6, 6.8 Hz, 1H, 8-CH_2), 2.43 (s, 3H, ArCH_3), 2.59 (ddd, *J* = 9.5, 5.5, 4.5 Hz, 1H, H-8ax), 2.70 (m, 1H, 8-CH_2), 2.74 (t, *J* = 3.2 Hz, 1H, H-5), 3.11 (ddd, *J* = 13.0, 12.4, 4.0 Hz, 1H, H-3ax), 3.75 (dd, *J* = 13.0, 4.2 Hz, 1H, H-3eq), 4.39 (*br*, 1H, H-1), 5.08 (dt, *J* = 10.8, 0.8, 0.4 Hz, 1H, =CH_2), 5.20 (dd, *J* = 16.8, 1.6 Hz, 1H, =CH_2), 6.11 (dddd, *J* = 16.8, 10.8, 7.6, 6.4 Hz, 1H, =CH), 7.29 (d, *J* = 8.0, 2H, *m*-ArH), 7.75 (d, *J* = 8.0, 2H, *o*-ArH), ^{13}C NMR (100 MHz, HSQC) δ 21.5 (ArCH_3), 25.8 (C-5), 26.5 (C-4), 28.2 (CH_3), 30.0 (C-9), 30.9 (8-CH_2), 38.8 (C-3), 44.1 (C-8), 50.0 (C-1), 81.4 (C), 99.8 (C-6), 116.6 (=CH_2), 127.1 (*o*-Ts), 129.7 (*m*-Ts), 136.6 (=CH), 138.8 (*p*-Ts), 143.1 (i*pso*-Ts), 171.4 (C-7), 173.5 (CO). HRMS calcd for $C_{23}H_{32}NO_5S$ $[M+H]^+$ 434.1996, found 434.1996.

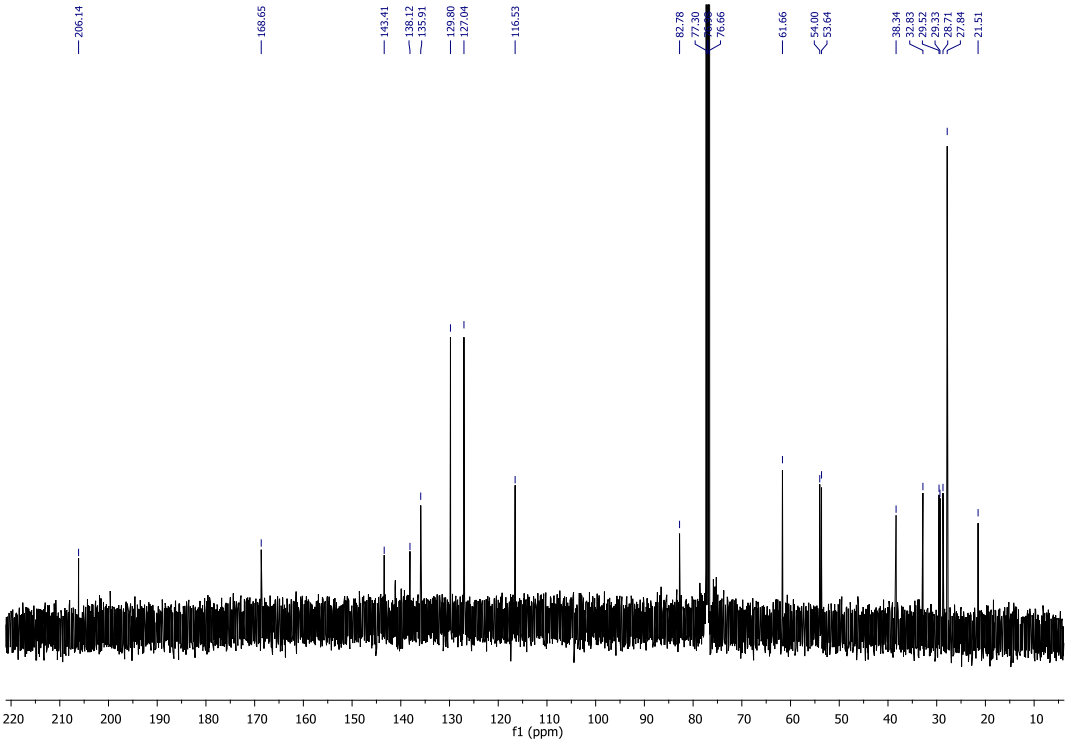

Ts
H
N
HO
H
CO2tBu
rac-3.14
2.00
2.25
1.33
1.23
1.23
1.20
1.28
1.32
2.48
1.29
3.36
1.66
13.63
4.10
f1 (ppm)


173.59
171.49
143.22
138.92
136.71
129.86
127.23
116.74
99.91
81.52
77.46
77.14
76.82
50.14
44.22
38.89
31.05
30.11
28.38
26.65
25.99
21.65
f1 (ppm)

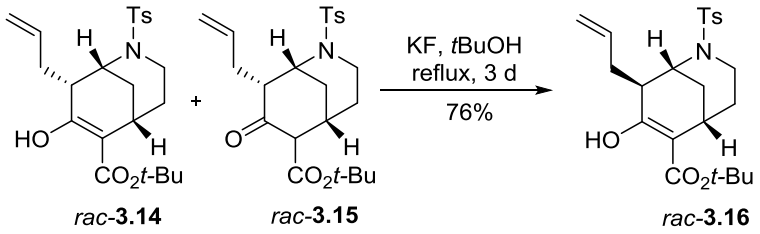
Compound ***rac*-3.15**: ^{1}H NMR (400 MHz, COSY) δ 1.38 (masked, 1H, H-4), 1.40 (s, 9H, CH_3), 1.55 (masked, 1H, H-4), 1.62 (dm, *J* = 12 Hz, 1H, H-9), 1.90 (d, *J* = 14 Hz, H-9), 2.04 (m, 1H, 8-CH_2), 2.41 (s, 3H, ArCH_3), 2.62 (br, 1H, H-5), 2.67-2.75 (m, 2H, H-8 and 8-CH_2), 2.82 (td, *J* = 16.0, 3.6 Hz, 1H, H-3ax), 3.28 (s, 1H, H-6), 3.70 (dd, *J* = 16.0, 5.6 Hz, 1H, H-3eq), 4.56 (*br* s, 1H, H-1), 5.03 (d, *J* = 16.0 Hz, 1H, =CH_2), 5.08 (dd, *J* = 10.4, 1.0 Hz, 1H, =CH_2), 5.68 (m, 1H, =CH), 7.30 (d, *J* = 7.6 Hz, 2H, *m*-Ts), 7.72 (d, *J* = 7.6 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, HSQC) δ 21.5 (ArCH_3), 27.8 (CH_3), 28.7 (C-9), 29.3 (C-4), 29.5 (8-CH_2), 32.8 (C-5), 38.4 (C-3), 53.7 (C-8), 54.0 (C-1), 61.7 (C-6), 82.8 (C), 116.6 (=CH_2), 127.1 (*o*-Ts), 129.8 (*m*-Ts), 135.9 (=CH), 138.2 (*p*-Ts), 143.4 (i*pso*-Ts), 168.7 (CO), 206.2 (C-7). HRMS calcd for $C_{23}H_{32}NO_5S$ $[M+H]^+$ 434.1996, found 434.1999.


Ts
H
N
O
H
CO2tBu
1.78
1.99
1.00
1.85
0.97
0.77
1.23
0.86
3.75
2.81
2.90
12.85
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

rac-**3.15**

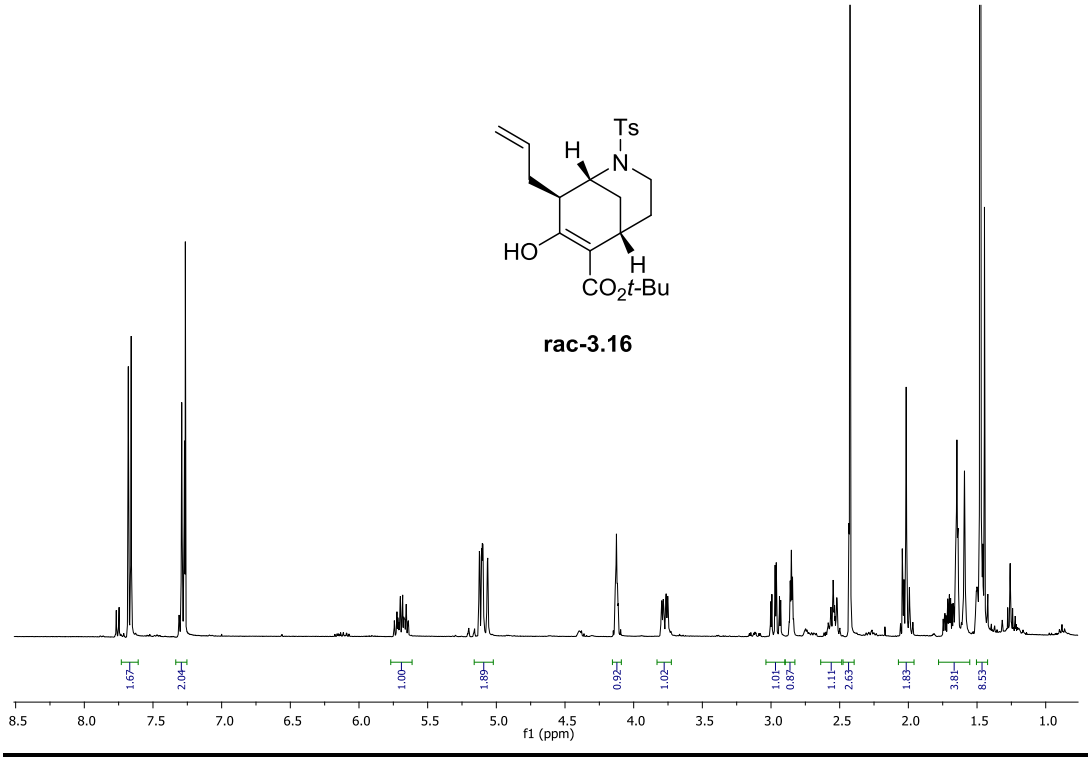

206.14
168.65
143.41
138.12
135.91
129.80
127.04
116.53
82.78
77.30
76.66
61.66
54.00
53.64
38.34
32.83
29.52
29.33
28.71
27.84
21.51
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

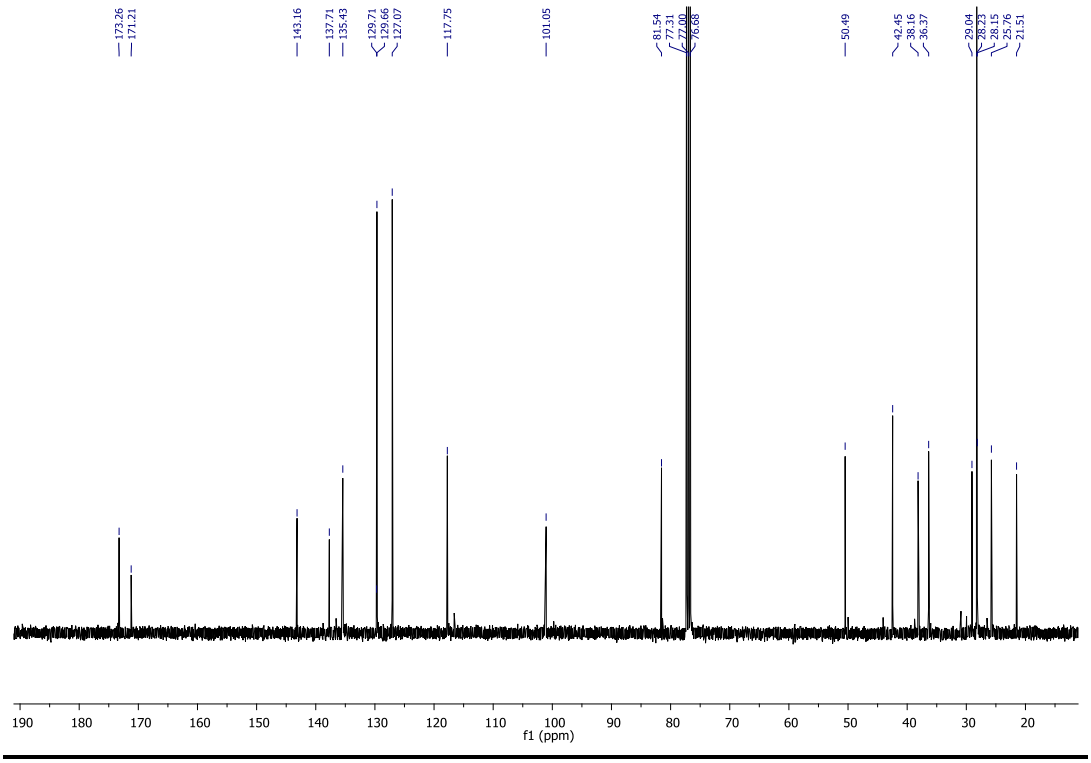
(1*RS*,5*SR*,8*SR*)-*tert*-Butyl 8-Allyl-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (*rac*-3.16)



rac-**3.14** *rac*-**3.15** *rac*-**3.16**

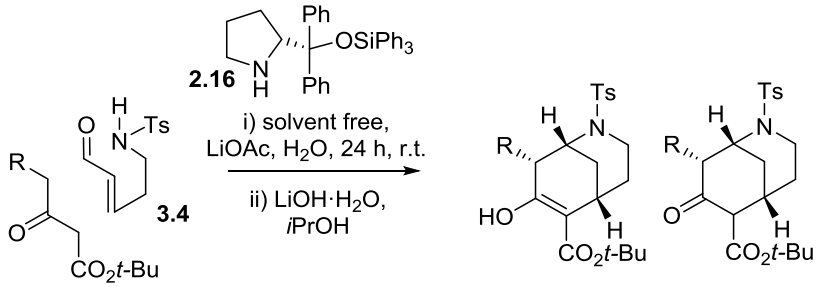
To a mixture of *rac*-**3.14** and *rac*-**3.15** (87 mg, 0.20 mmol) in *t*-BuOH (9 mL), was added potassium fluoride (175 mg, 3.02 mmol), and the resulting mixture was heated at reflux for 3 d. After the reaction was cooled to room temperature, the mixture was partitioned between water and CH_2Cl_2 (15 mL), and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were washed with brine, dried, and concentrated *in vacuo.* Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave *rac*-**3.16** (66 mg, 76%) as an amorphous solid. ^{1}H NMR (400 MHz, COSY) δ 1.50 (masked, 1H, H-4eq), 1.64 (br t, *J* = 3.2 Hz, 2H, H-9), 1.70 (tdd, *J* = 12.8, 4.8, 3.2 Hz, 1H, H-4ax), 2.00 (masked, 1H, H-8eq), 2.01 (m, 1H, 8-CH_2), 2.54 (m, 1H, 8-CH_2), 2.85 (q, *J* = 3.2 Hz, 1H, H-5), 2.96 (td, *J* = 12.8, 3.2 Hz, 1H, H-3ax), 3.77 (dd, *J* = 12.8, 4.8 Hz, 1H, H-3eq), 4.12 (*br s*, 1H, H-1), 5.08 (dt, *J* = 10.8, 0.8, 0.4 Hz, 1H, CH_2=), 5.10 (dd, *J* = 16.8, 1.6 Hz, 1H, CH_2=), 5.68 (m, 1H, =CH), 7.28 (d, *J* = 8.0, 2H, *m*-Ts), 7.67 (d, *J* = 8.0, 2H, *o*-Ts); ^{13}C NMR (100 MHz, HSQC) δ 21.5 ($ArCH_3$), 25.8 (C-5), 28.2 (CH_3), 28.3 (C-9), 29.0 (C-4), 36.4 (8-CH_2), 38.2 (C-3), 42.6 (C-8), 50.5 (C-1), 81.5 (C), 101.1 (C-6), 117.8 (=CH_2), 127.1 (*o*-Ts), 129.7 (*m*-Ts), 135.4 (=CH), 137.7 (*p*-Ts), 143.2 (i*pso*-Ts), 171.2 (C-7), 173.3 (CO). HRMS calcd for $C_{23}H_{32}NO_5S$ $[M+H]^+$ 434.1996, found 434.1992.


Ts
H
N
HO
H
CO2t-Bu
rac-3.16
1.67
2.04
1.00
1.89
0.92
1.02
1.01
0.87
1.11
2.63
1.83
3.81
8.53
f1 (ppm)


173.26
171.21
143.16
137.71
135.43
129.71
129.66
127.07
117.75
101.05
81.54
77.31
77.00
76.68
50.49
42.45
38.16
36.37
29.04
28.23
28.15
25.76
21.51
f1 (ppm)

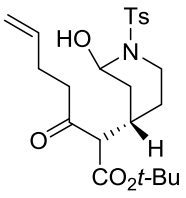
Asymmetric procedure:

General Method C: Synthesis of Morphans - enantioselective version



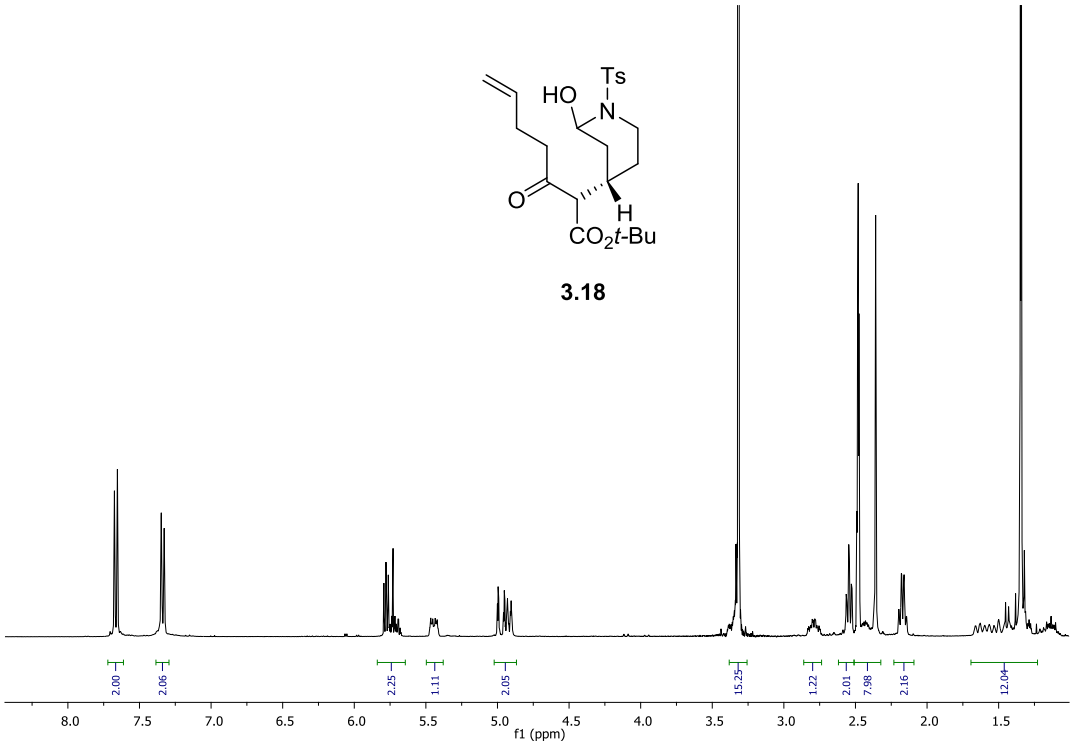
To β-keto ester (2 equiv) and enal **3.4** (1 equiv), was added H_2O (10 equiv) and LiOAc (0.1 eq) followed by bis-phenyl-$OSiPh_3$-pyrrolidine **2.16** (0.1 equiv) and the resulting mixture was stirred for 24 h at room temperature. *i*PrOH (1 mL/mmol of enal), and $LiOH{\cdot}H_2O$ (3 equiv) was added, and the resulting solution was stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (15 mL/mmol) solution and the product was extracted with EtOAc (3 x 20 mL/mmol). The combined organic layers were dried and concentrated *in vacuo*. The crude material was purified by column chromatography to give the corresponding enantioenriched morphan.

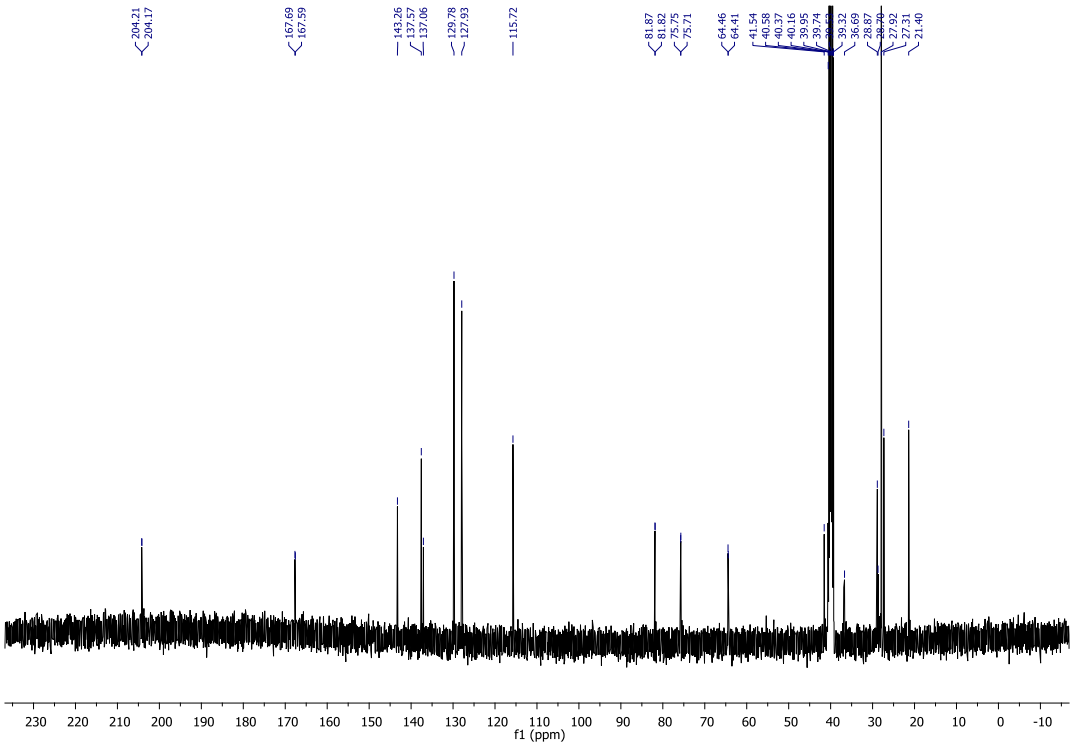
***(2S)-tert*-Butyl 2-(Hydroxy-1-(4-methylphenylsulfonyl)piperidin-4-yl)-3-oxohept-6-enoate (3.18)**



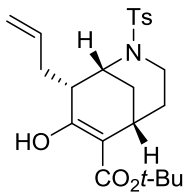
3.18

Following the general method **C** (part i) and purification of the intermediate by column chromatography (0→5→10→25% EtOAc/hexane) provided an analytical sample of **3.18** as a yellow oil: ^{1}H NMR (dmso-d_6, 400 MHz, COSY) δ 1.12-1.20 (m, 2H, H-5´), 1.36 (s, 9H, CH_3), 1.55-1.68 (m, 2H, H-3´), 2.18 (q, J = 7.5 Hz, 2H, H-5), 2.37 (s, 3H, CH_3Ar), 2.45 (m, 1H, H-4´), 2.56 (dt, J = 7.6, 2.0 Hz, 2H, H-4), 2.80 (m, 2H, H-6´), 3.35 (s, 1H, H-2), 4.92-5.02 (m, 2H, $=CH_2$), 5.43-5.48 (m, 1H, H-2´) 5.70-5.76 (m, 1H, =CH), 7.35 (d, J = 8.4 Hz, 2H, *m*-Ts), 7.67 (d, J = 8.4 Hz, 2H, *o*-Ts), ^{13}C NMR (100 MHz, HSQC) δ 21.9 ($ArCH_3$), 27.8 (C-5´), 28.4 (CH_3), 29.2 (C-3´), 29.4 (C-5), 39.8 (C-6´), 40.3 (C-4´), 42.0 (C-4), 64.9 (C-2), 76.2 (C-2´), 82.3 (C), 116.2 ($=CH_2$), 128.4 (*o*-Ts), 130.3 (*m*-Ts), 137.6 (=CH), 138.1 (*p*-Ts), 143.8 (i*pso*-Ts), 168.1 (C-1), 204.7 (C-3). HRMS calcd for $C_{46}H_{66}N_2NaO_{12}S_2$ $[2M+Na]^+$ 925.3949, found 925.3963.

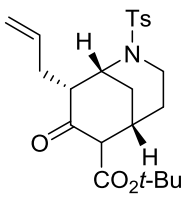

Ts
HO
N
O
H
CO2t-Bu
3.18
2.00
2.06
2.25
1.11
2.05
15.25
1.22
2.01
7.98
2.16
12.04
f1 (ppm)


204.21
204.17
167.69
167.59
143.26
137.57
137.06
129.78
127.93
115.72
81.87
81.82
75.75
75.71
64.46
64.41
41.54
40.58
40.37
40.16
39.95
39.74
39.32
36.69
28.87
27.92
27.31
21.40
f1 (ppm)

(1*R*,5*S*,8*S*)-*tert*-Butyl 8-Allyl-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.14) and *(1R,5S,8S)-tert*-butyl-8-allyl-2-(4-methylphenylsulfonyl)-7-oxo-2-azabicyclo[3.3.1]nonane-6-carboxylate (3.15)



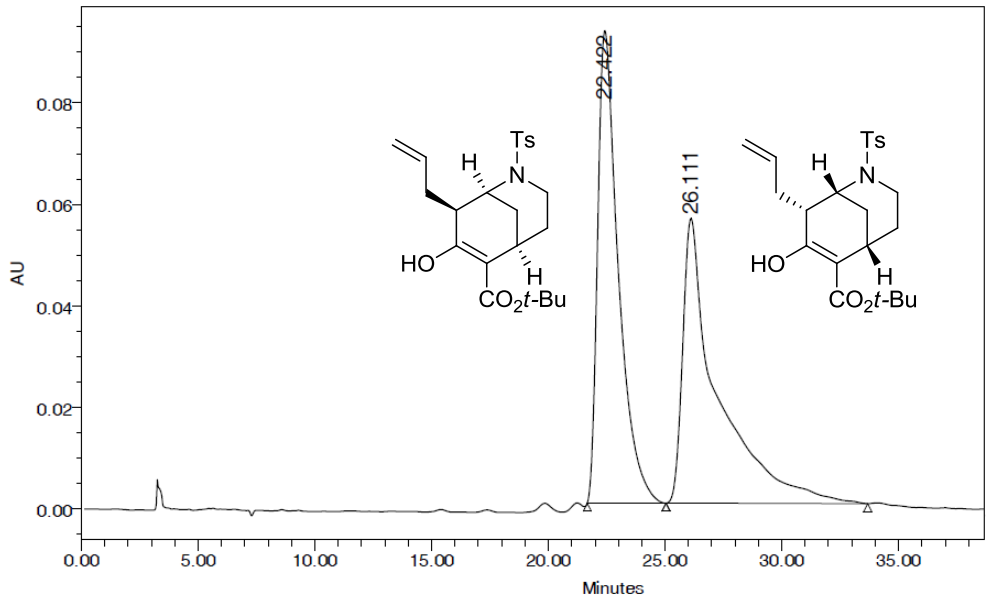
3.14



3.15

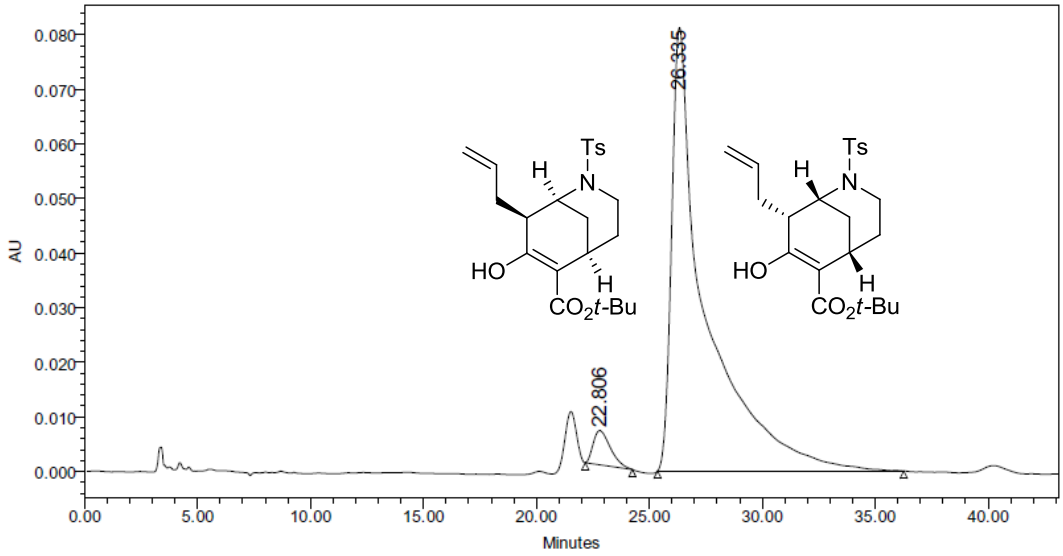
These compounds were prepared according to the general above procedure using β-keto ester **3.13a** (79 mg, 0.40 mmol), enal (47 mg, 0.20 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (10 mg, 0.02), LiOAc (1.3 mg, 0.02 mmol) and H_2O (36 mg, 2.0 mmol). *i*PrOH (0.8 mL) and $LiOH{\cdot}H_2O$ (25 mg, 0.60 mmol). Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave **3.14** (31 mg, 36%) and **3.15** (18 mg, 20%), both as an amorphous solids. For their NMR data, see above ***rac*-3.14** and ***rac*-3.15**.

HPLC of Racemic reaction mixture (3.14)



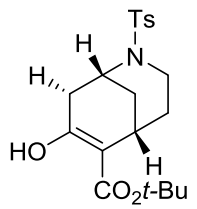
	RT	Area	% Area	Height
1	22.422	5751719	49.53	93101
2	26.111	5860210	50.47	56088

HPLC of organocatalysed reaction mixture (3.14)



	RT	Area	% Area	Height
1	22.806	334909	3.78	6298
2	26.335	8514293	96.22	81242

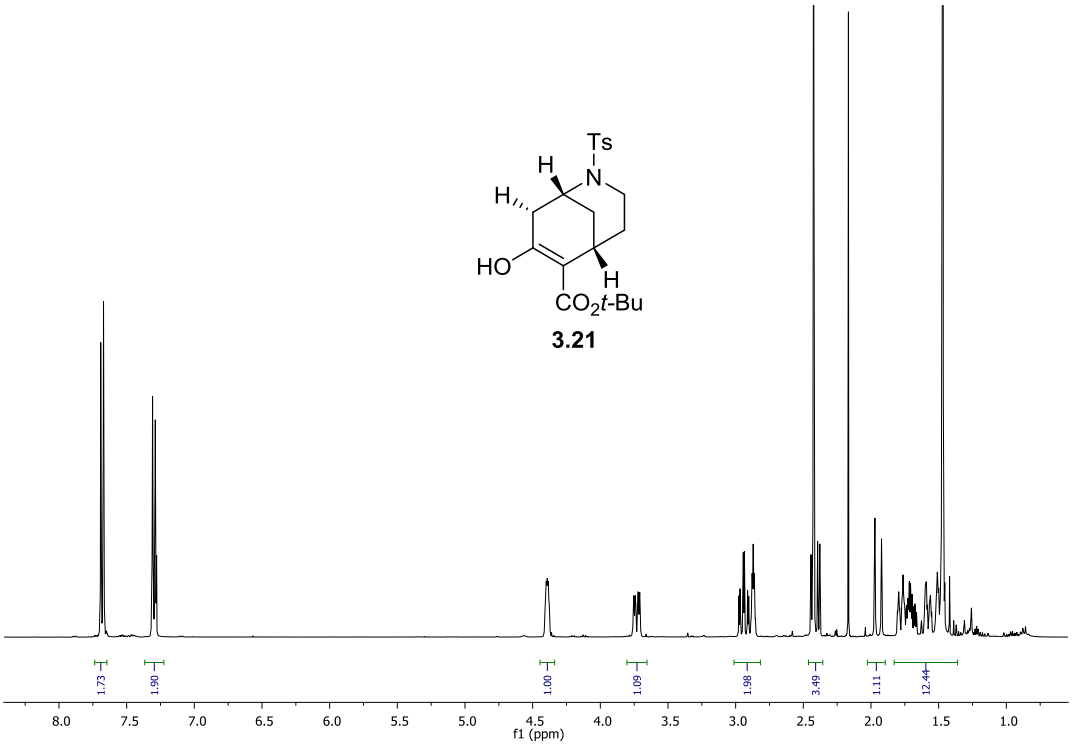
(1*R*,5*S*)-*tert*-Butyl 7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate. (3.21)



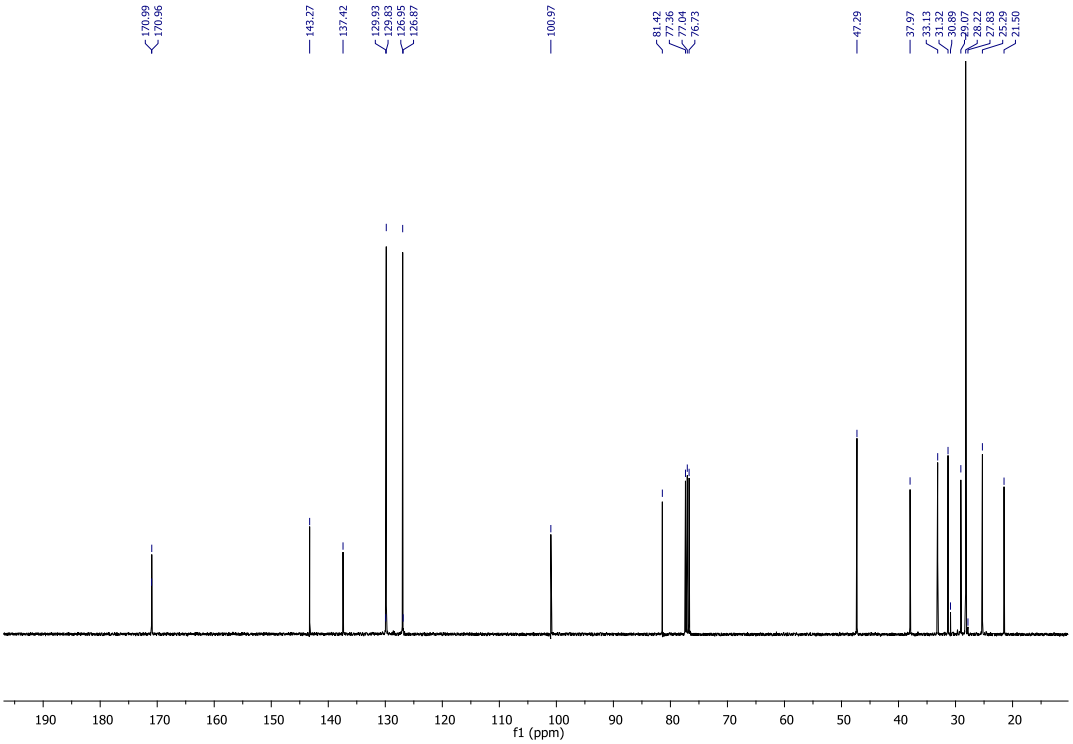
3.21

This compound was prepared according to general method **C**[158] using commercially available *tert*-butyl acetoacetate (108 mg, 0.68 mmol), enal (86 mg, 0.34 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (17 mg, 0.034), LiOAc (2.2 mg, 0.034 mmol) and H_2O (61 mg, 3.41 mmol). *i*PrOH (1.4 mL) and $LiOH \cdot H_2O$ (43 mg, 1.02 mmol). Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave **3.21** (50 mg, 37%) as a off-white solid. ^1H NMR (400 MHz, COSY) δ 1.45 (s, 9H, CH_3), 1.48 (dm, *J* = 12.4 Hz, 1H, H-4eq), 1.56 (dm, *J* = 12.6 Hz, 1H, H-9), 1.68 (tt, *J* = 12.6, 3.4 Hz, 1H, H-4ax), 1.76 (dm, *J* = 12.6 Hz, 1H, H-9),1.93 (d, *J* = 20.0 Hz, 1H, H-8eq), 2.39 (dd, *J* = 19.6, 6.0 Hz, 1H, H-8ax), 2.41 (s, 3H, $ArCH_3$), 2.85 (quint, *J* = 3.2 Hz, 1H, H-5), 2.92 (td, *J* = 12.4, 3.2 Hz, 1H, H-3ax), 3.71 (dd, *J* = 12.8, 4.8 Hz, 1H, H-3eq), 4.37 (dt, *J* = 5.6, 2.8 Hz, 1H, H-1), 7.28 (d, *J* = 8.0, 2H, *m*-ArH), 7.66 (d, *J* = 8.4, 2H, *o*-ArH), ^{13}C NMR (100 MHz, HSQC) δ 21.4 ($ArCH_3$), 25.2 (C-5), 28.2 (CH_3), 29.0 (C-4), 31.3 (C-9), 33.1 (C-8), 37.9 (C-3), 47.2 (C-1), 81.4 (C), 100.9 (C-6), 126.9 (*o*-Ts), 129.8 (*m*-Ts), 137.4 (*p*-Ts), 143.2 (i*pso*-Ts), 170.9 (C-7), 171.0 (CO). HRMS calcd for $C_{20}H_{28}NO_5S$ $[M+H]^+$ 394.1683, found 394.1688.

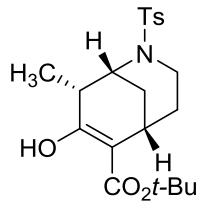
[158] Step ii required 48 h to reach completion.


Ts
H
N
H
HO
H
CO2t-Bu
1.73
1.90
1.00
1.09
1.98
3.49
1.11
12.44
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

3.21

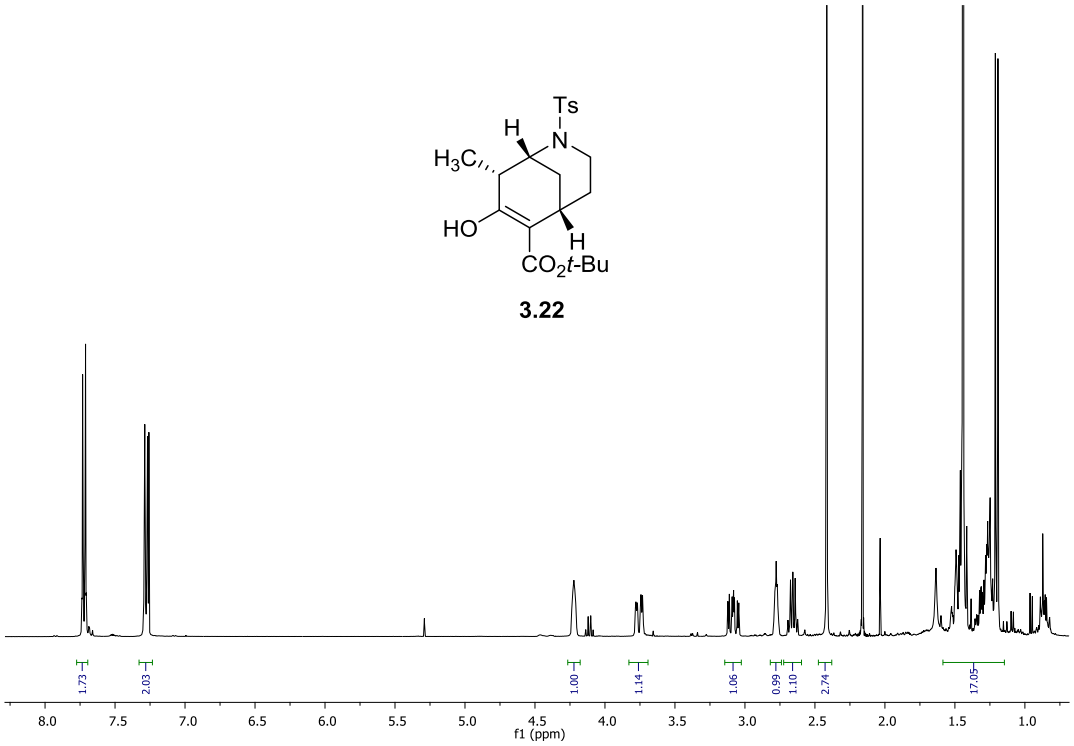

170.99
170.96
143.27
137.42
129.93
129.83
126.95
126.87
100.97
81.42
77.36
77.04
76.73
47.29
37.97
33.13
31.32
30.89
29.07
28.22
27.83
25.29
21.50
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

(1*R*,5*S*,8*S*)-*tert*-Butyl 7-Hydroxy-8-methyl-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.22)

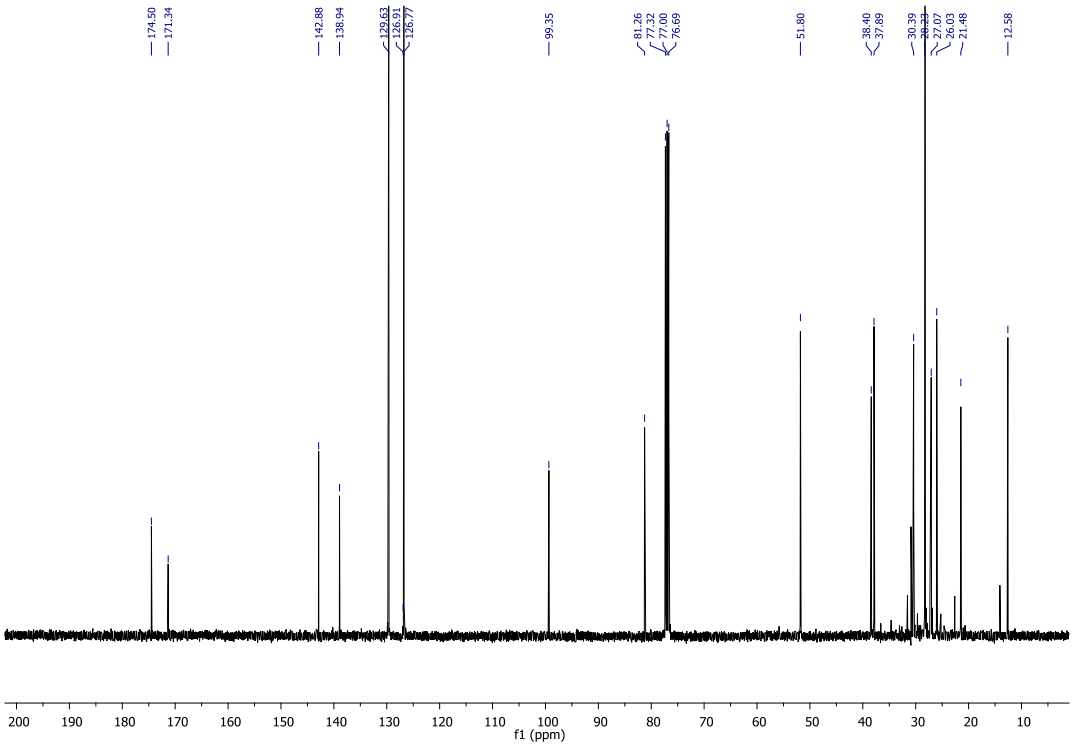


3.22

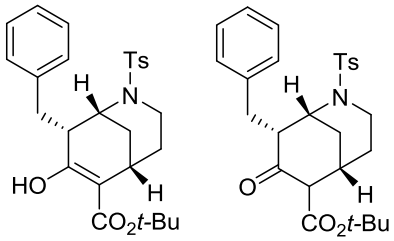
This compound was prepared according to general method **C** using β-keto ester **3.13b** (107 mg, 0.60 mmol), enal (77 mg, 0.30 mmol), bis-phenyl-OSiPh$_3$-pyrrolidine organocatalyst **2.16** (15 mg, 0.030), LiOAc (2.0 mg, 0.030 mmol) and H_2O (54 mg, 3.0 mmol). *i*PrOH (1.2 mL) and LiOH·H_2O (38 mg, 0.91 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave **3.22** (87 mg, 70%) as a off-while solid: ^{1}H NMR (100 MHz, COSY) δ 1.20 (d, *J* = 7.5 Hz, 3H, 8-CH_3), 1.23-1.29 (m, 2H, H-4), 1.44(s, 9H, CH_3), 1.44 (masked, 1H, H-9), 1.52 (dm, *J* = 12.6 Hz, 1H, H-9), 2.42 (s, 3H, ArCH_3), 2.66 (quint, *J* = 6.4 Hz, 1H, H-8), 2.78 (t, *J* = 3.2 Hz, 1H, H-5), 3.08 (ddd, *J* = 14.8, 12.4, 4.0 Hz, 1H, H-3ax), 3.76 (dd, *J* = 14.4, 4.0 Hz, 1H, H-3eq), 4.22 (*br*, 1H, H-1), 7.28 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.72 (d, *J* = 8.4 Hz, 2H, *o*-Ts) ^{13}C NMR (400 MHz, HSQC) δ 12.6 (8-CH_3), 21.5 (ArCH_3), 26.0 (C-5), 27.1 (C-4), 28.2 (CH_3), 30.4 (C-9), 37.9 (C-8), 38.4 (C-3), 51.8 (C-1), 81.3 (C), 99.4 (C-6), 126.7 (*o*-Ar), 129.6 (*m*-Ar), 138.9 (*p*-Ar), 142.9 (i*pso*-Ar), 171.3 (C-7), 174.5 (CO). HRMS calcd for $C_{21}H_{30}NO_5S$ $[M+H]^+$ 408.1839, found 408.1847.


Ts
H
N
H3C
HO
H
CO2t-Bu
1.73
2.03
1.00
1.14
1.06
0.99
1.10
2.74
17.05
f1 (ppm)

3.22

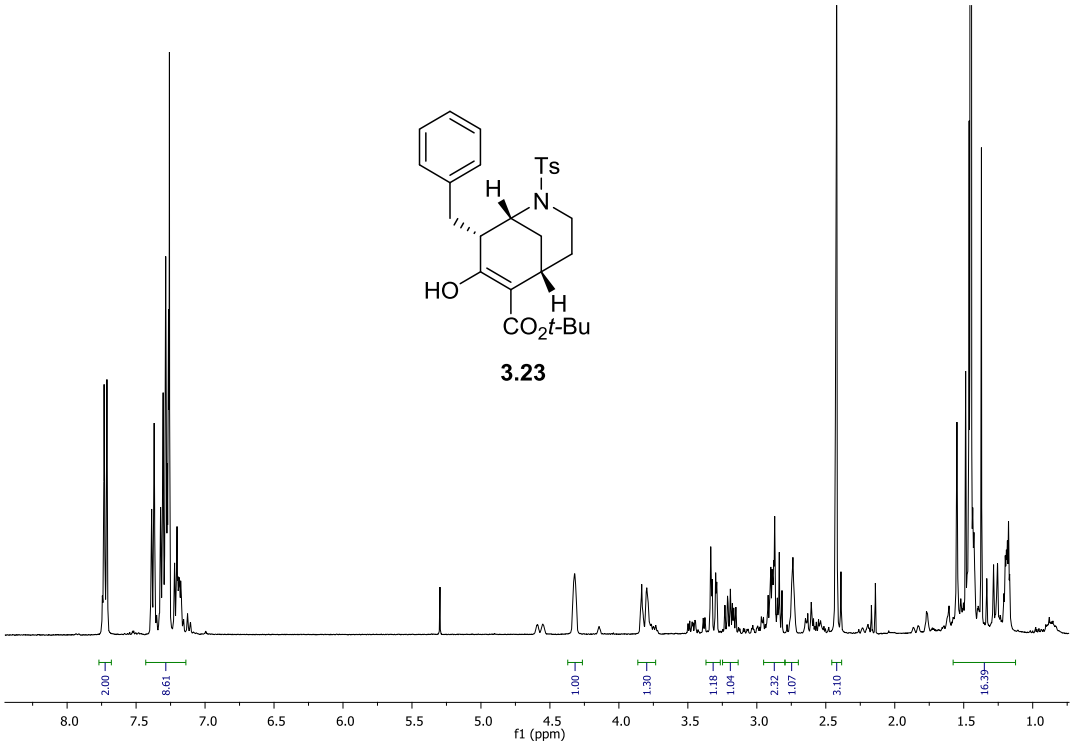

174.50
171.34
142.88
138.94
129.63
126.91
126.77
99.35
81.26
77.32
77.00
76.69
51.80
38.40
37.89
30.39
28.23
27.07
26.03
21.48
12.58
f1 (ppm)

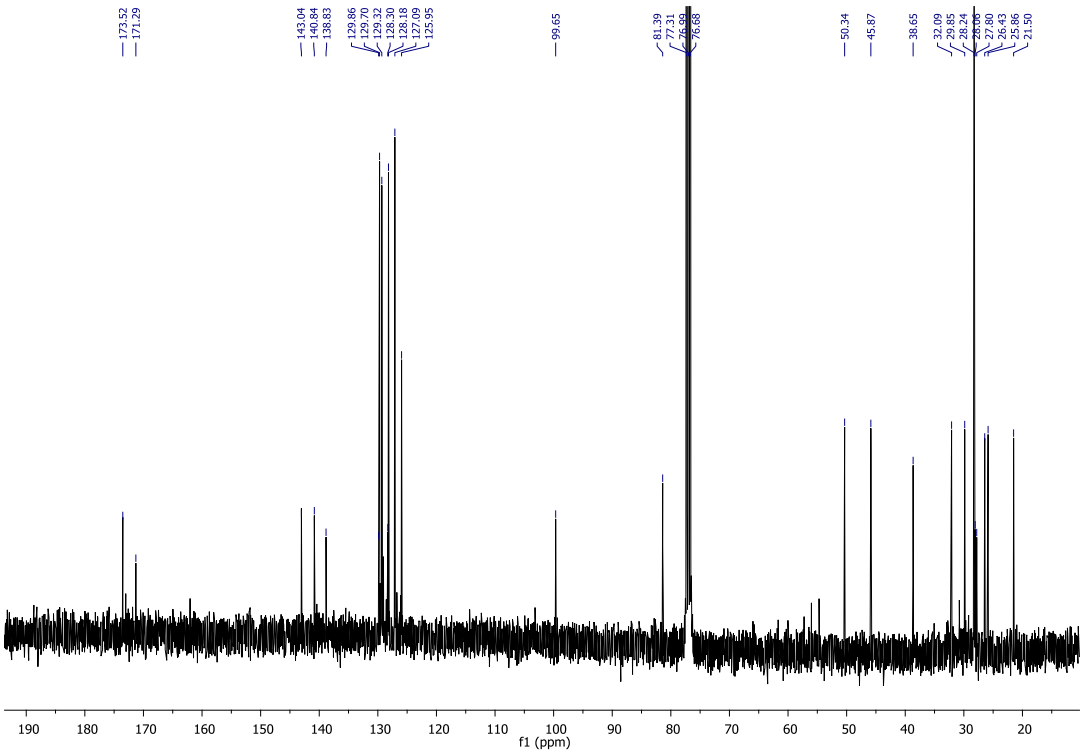
(1*R*,5*S*,8*S*)-*tert*-Butyl 8-Benzyl-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.23)



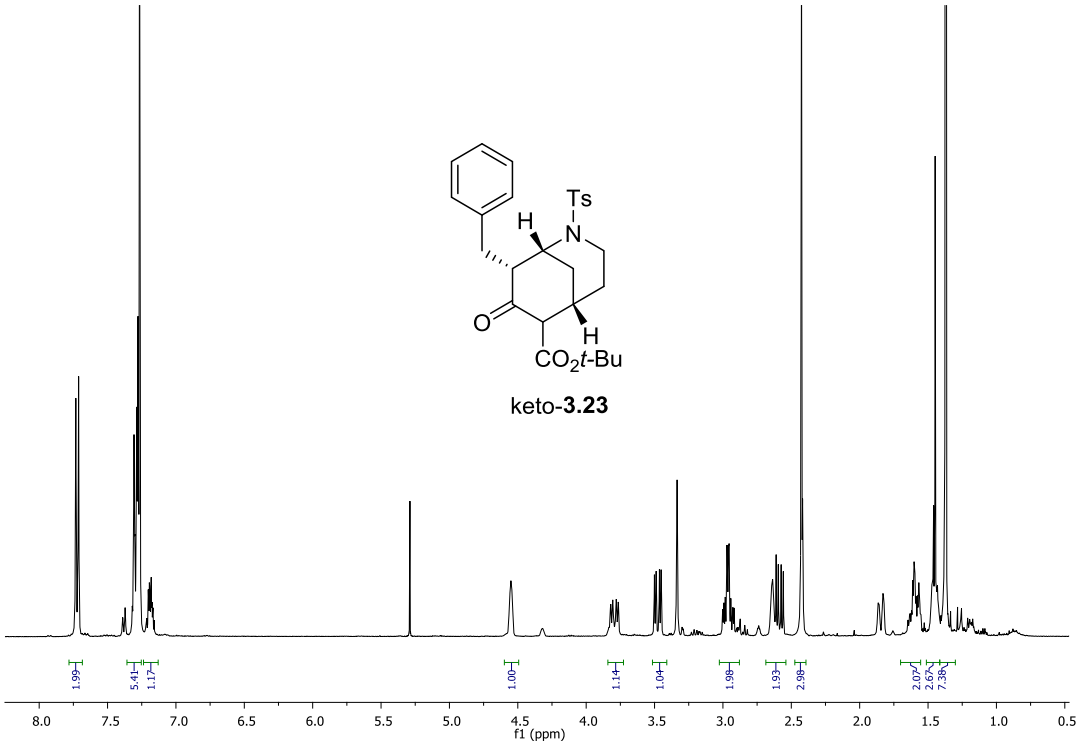
This compound was prepared according to general method **C** using β-keto ester **3.13c** (97 mg, 0.39 mmol), enal (49 mg, 0.20 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (10 mg, 0.020), LiOAc (1.3 mg, 0.02 mmol) and H_2O (35 mg, 2.0 mmol). *i*PrOH (0.8 mL) and $LiOH \cdot H_2O$ (25 mg, 0.59 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave sequentially 32 mg of **3.23** and 32 mg of its keto tautomer, as amorphous solids (68% overall yield).

***enol tautomer*:** ^{1}H NMR (400 MHz, COSY) δ 1.18 (m, 1H, H-4), 1.45 (s, 9H, CH_3), 1.40-1.48 (m, 3H, H-4 and H-9), 2.42 (s, 3H, CH_3Ar), 2.74 (br, 1H, H-5), 2.82-2.92 (m, 2H, 8-CH_2 and H-8), 3.20 (tm, *J* = 13.2 Hz, 1H, H-3ax), 3.21 (dd, *J* = 14.0, 3.8 Hz, 1H, 8-CH_2), 3.67 (dm, *J* = 14.4 Hz, 1H, H-3eq), 4.33 (*br*, 1H, H-1), 7.07 (d, *J* = 7.6 Hz, 2H, *m*-ArH), 7.26 (d, *J* = 7.2 Hz, 2H, *o*-ArH), 7.28 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.72 (d, *J* = 8.4 Hz, 2H, *o*-Ts) ^{13}C NMR (400 MHz, HSQC) δ 21.5 ($ArCH_3$), 25.9 (C-5), 26.4 (C-4), 28.2 (CH_3), 29.9 (C-9), 32.1 (CH_2Ar), 38.7 (C-3), 45.9 (C-8), 50.3 (C-1), 81.4 (C), 99.7 (C-6), 126.0 (p-Ph), 127.1 (*o*-Ts), 128.3 (*m*-PhH), 129.3 (*o*-PhH) 129.7 (*m*-Ts), 138.9 (*p*-Ts), 140.8 (*ipso*-Ph), 143.1 (i*pso*-Ts), 171.3 (C-7), 173.5 (CO). HRMS calcd for $C_{27}H_{34}NO_5S$ $[M+H]^+$ 484.2152, found 484.2153.

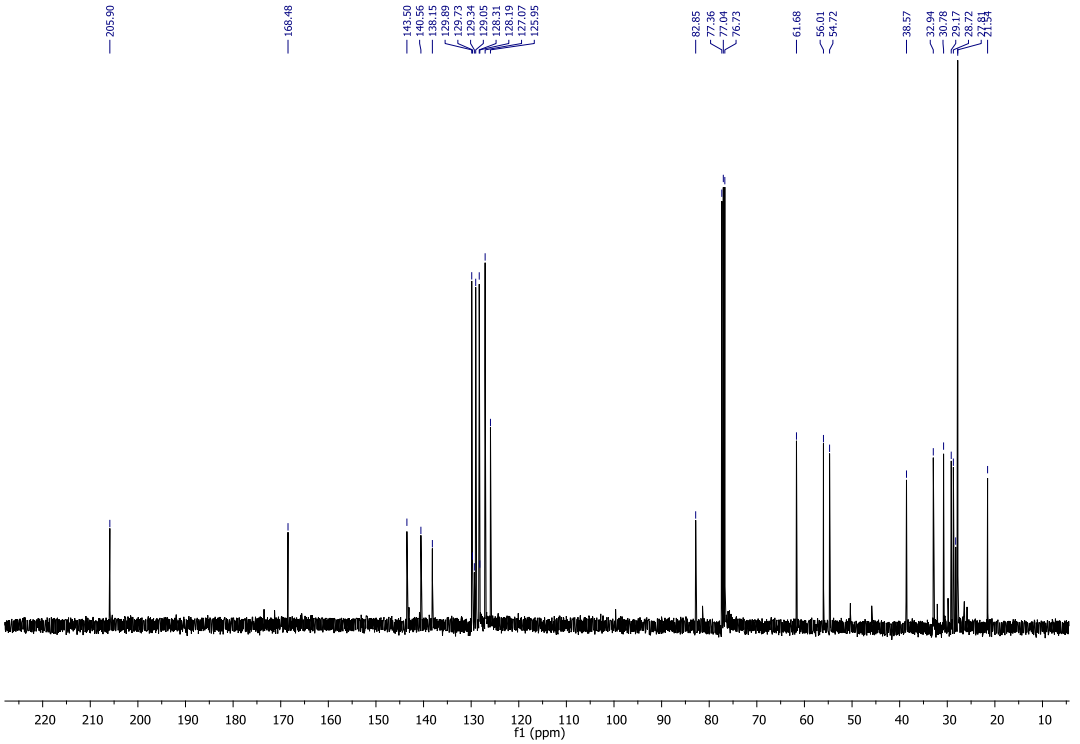

Ts
H
N
HO
H
CO2t-Bu
3.23
2.00
8.61
1.00
1.30
1.18
1.04
2.32
1.07
3.10
16.39
f1 (ppm)


173.52
171.29
143.04
140.84
138.83
129.86
129.70
128.33
128.30
128.18
127.09
125.95
99.65
81.39
77.31
76.99
76.68
50.34
45.87
38.65
32.09
29.85
28.24
28.06
27.80
26.43
25.86
21.50
f1 (ppm)

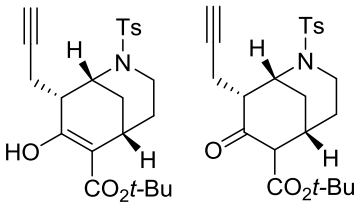
***keto tautomer*:** ^{1}H NMR (400 MHz, COSY) δ 1.38 (masked, 1H, H-4), 1.38 (s, 9H, CH_3), 1.62 (m, 2H, H-9 and H-4), 186 (d, *J* = 13.6 Hz, H-9), 2.44 (s, 3H, $ArCH_3$), 2.59 (dd, *J* = 14.6, 6.2 Hz, 1H, 8-CH_2), 2.65 (br, 1H, H-5), 2.97 (masked, 1H, H-8), 2.98 (td, *J* = 16.0, 3.6 Hz, 1H, H-3ax), 3.35 (t, *J* = 1.8 Hz, 1H, H-6), 3.49 (dd, *J* =14.4, 5.0 Hz, 1H, 8-CH_2), 3.84 (dd, *J* = 16.0, 5.8 Hz, 1H, H-3eq), 4.56 (*br* s, 1H, H-1), 7.20 (m, 1H, PhH), 7.27-7.32 (m, 4H, PhH), 7.30 (d, *J* = 7.6 Hz, 2H, *m*-Ts), 7.73 (d, *J* = 7.6 Hz, 2H, *o*-Ts); ^{13}C NMR (400 MHz, HSQC) δ 21.5 ($ArCH_3$), 27.8 (CH_3), 28.7 (C-9), 29.1 (C-4), 30.7 (8-CH_2), 32.9 (C-5), 38.5 (C-3), 54.7 (C-1), 56.0 (C-8), 61.6 (C-6), 82.8 (C), 125.9 (-Ph), 127.0 (*o*-Ts), 128.3 (-Ph), 129.0 (-Ph), 129.8 (*m*-Ts), 138.1 (*p*-Ts), 140.5 *(ipso*-Ph), 143.5 (i*pso*-Ts), 168.5 (CO), 205.9 (C-7).


Ts
H
N
O
H
CO2t-Bu
1.99
5.41
1.17
1.00
1.14
1.04
1.98
1.93
2.98
2.07
2.67
7.38
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

keto-**3.23**


205.90
168.48
143.50
140.56
138.15
129.89
129.73
129.34
129.05
128.31
128.19
127.07
125.95
82.85
77.36
77.04
76.73
61.68
56.01
54.72
38.57
32.94
30.78
29.17
28.72
21.84
21.54
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

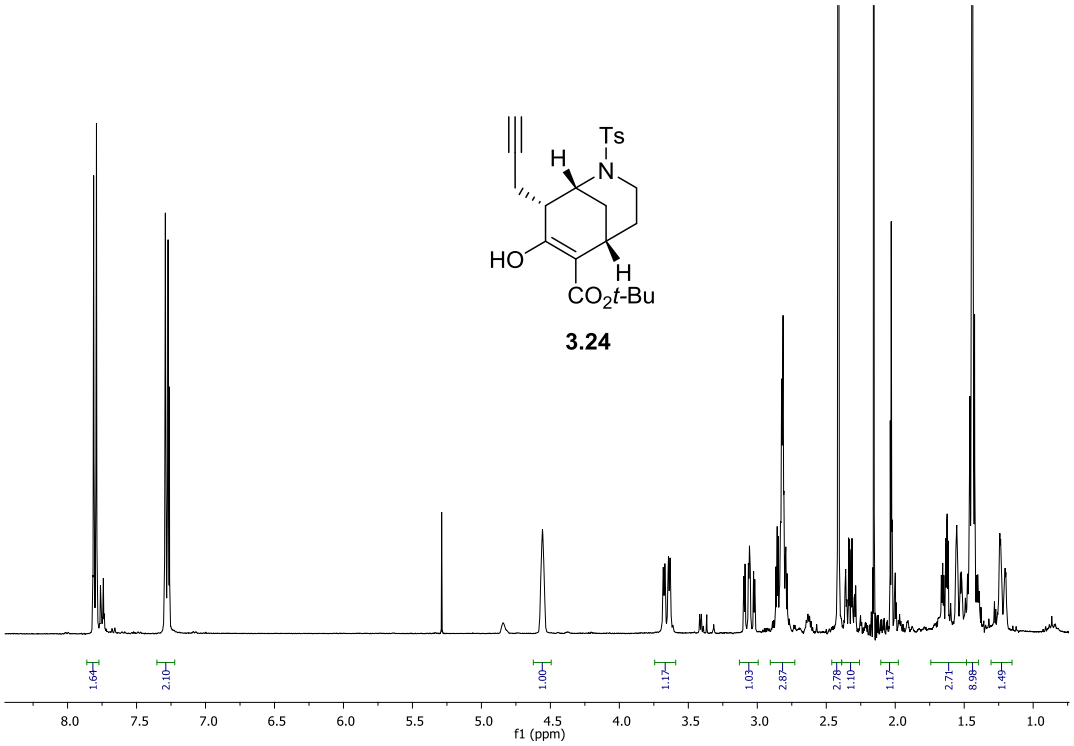
(1*R*,5*S*,8*S*)-*tert*-Butyl 7-Hydroxy-2-(4-methylphenylsulfonyl)- 8-(prop-2-yn-1-yl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.24)



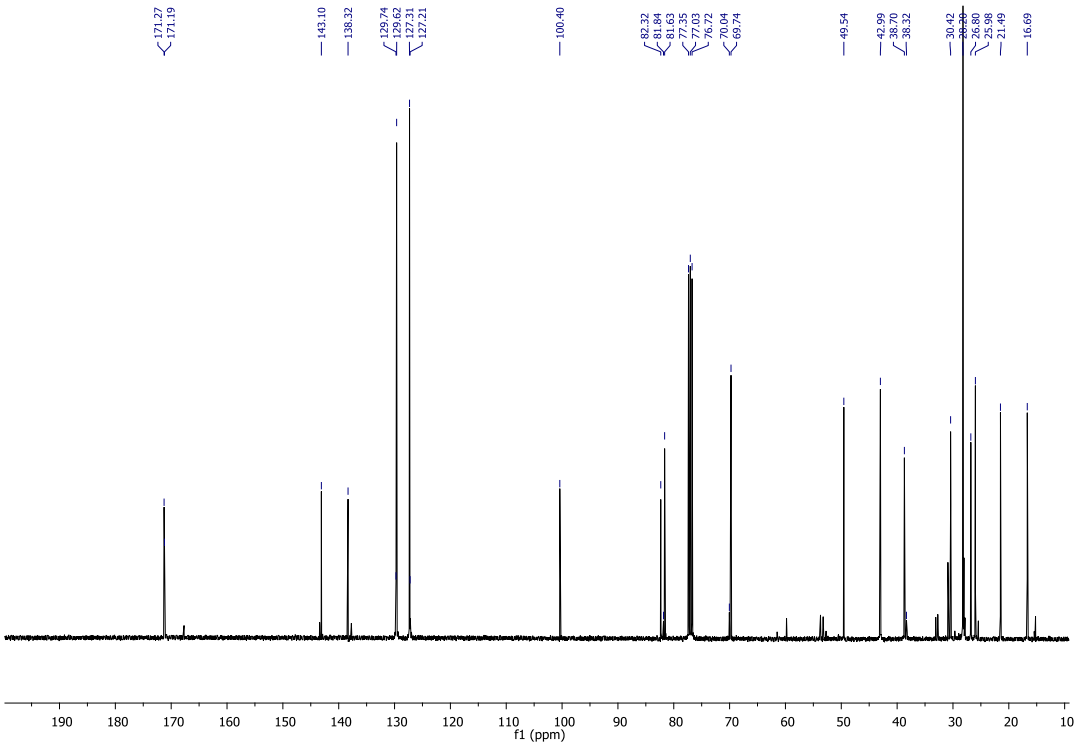
3.24 keto-**3.24**

This compound was prepared according to the above general method **C** using β-keto ester **3.13d** (98 mg, 0.50 mmol), enal (63 mg, 0.25 mmol), bis-phenyl-$OSiPh_3$-pyrrolidine organocatalyst **2.16** (13 mg, 0.025), LiOAc (1.6 mg, 0.025 mmol) and H_2O (45 mg, 2.5 mmol). *i*PrOH (1.0 mL) and $LiOH \cdot H_2O$ (31 mg, 0.747 mmol). Purification by column chromatography (0→2.5→5→10% EtOAc/hexane) gave **3.24** (41 mg, 38%) as an off-white solid.

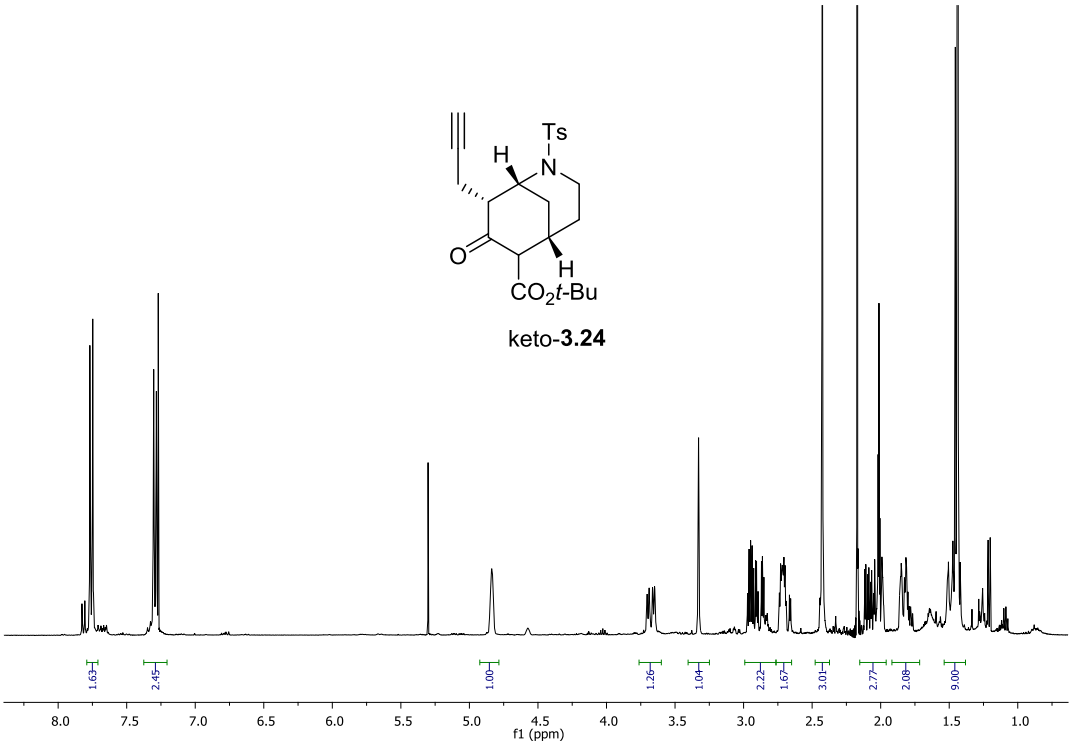
enol tautomer ^{1}H NMR (400 MHz, COSY) δ 1.20 (dm, *J* = 14.2 Hz, 1H, H-4eq), 1.44 (s, 9H, CH_3), 1.45 (masked, 1H, H-4ax), 1.53 (dm, *J* = 13.2 Hz, 1H, H-9), 1.64 (dt, *J* = 13.0, 3.6 Hz, 1H, H-9), 2.03 (t, *J* = 2.8 Hz, 1H, $C_{sp}H$), 2.33 (m, 1H, 8-CH_2), 2.41 (s, 3H, ArCH_3), 2.80 (m, 3H, H-5, H-8 and 8-CH_2), 3.06 (ddd, *J* = 15.2, 12.8, 3.2 Hz, 1H, H-3ax), 3.65 (dd, *J* = 14.2, 4.0 Hz, 1H, H-3eq), 4.56 (br s, 1H, H-1), 7.28 (d, *J* = 8.0, 2H, *m*-ArH), 7.80 (d, *J* = 8.0, 2H, *o*-ArH), ^{13}C NMR (100 MHz, HSQC) δ 16.7 (8-CH_2), 21.5 (ArCH_3), 25.9 (C-5), 26.8 (C-4), 28.2 (CH_3), 30.4 (C-9), 38.7 (C-3), 43.0 (C-8), 49.5 (C-1), 69.7 ($C_{sp}H$), 81.6 (C), 82.3 (C_{sp}), 100.4 (C-6), 127.3 (*o*-Ar), 129.6 (*m*-Ar), 138.3 (*p*-Ar), 143.0 (i*pso*-Ar), 171.2 (C-7), 171.3 (CO). HRMS calcd for $C_{23}H_{30}NO_5S$ $[M+H]^+$ 432.1839, found 432.1842.

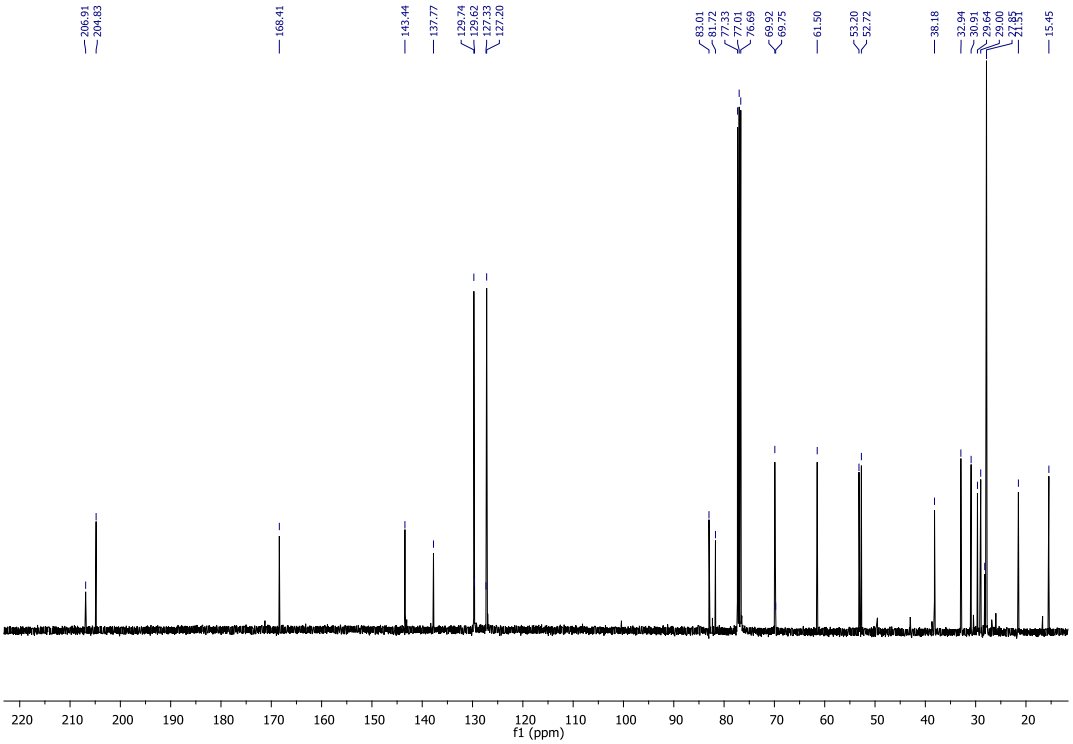

Ts
H
N
HO
H
CO2t-Bu
1.64
2.10
1.00
1.17
1.03
2.87
2.78
1.10
1.17
2.71
8.98
1.49
f1 (ppm)

3.24

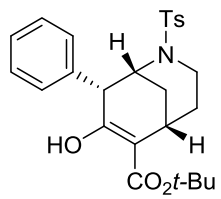

171.27
171.19
143.10
138.32
129.74
129.62
127.31
127.21
100.40
82.32
81.84
81.63
77.35
77.03
76.72
70.04
69.74
49.54
42.99
38.70
38.32
30.42
26.80
25.98
21.49
16.69
f1 (ppm)

***keto tautomer*:** ^{1}H NMR (400 MHz, COSY) δ 1.44 (s, 9H, CH_3), 1-48 (masked, 1H, H-4), 1.82 (m, 2H, H-4, H-9),1.99 (masked, 1H, H-9), 2.00 (t, *J* = 2.8 Hz, 1H, $C_{sp}H$), 2.07 (ddd, *J* = 16.0, 8.8, 2.8 Hz, 1H, 8-CH_2), 2.43 (s, 3H, ArCH_3), 2.70 (ddd, *J* = 16.8, 3.6 Hz, 1H, H-3ax), 2.71 (br s, 1H, H-5), 2.87 (ddd, *J* = 16.0, 4.4, 2.8 Hz, 1H, 8-CH_2), 2.94 (ddd, *J* = 8.8, 4.4, 4.4 Hz, 1H, H-8ax), 3.32 (t, *J* = 1.2 Hz, 1H, H-6), 3.67 (dd, *J* = 16.0, 5.8 Hz, 1H, H-3eq), 4.83 (br s, 1H, H-1), 7.28 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.75 (d, *J* = 8.0 Hz, 2H, *o*-ArH), ^{13}C NMR (100 MHz, HSQC) δ 15.5 (8-CH_2), 21.5 (ArCH_3), 27.9 (CH_3), 29.0 (C-9), 30.0 (C-4), 33.0 (C-5), 38.2 (C-3), 52.7 (C-8), 53.2 (C-1), 61.5 (C-6), 69.9 ($C_{sp}H$), 81.7 (C), 83.0 (C_{sp}), 127.2 (*o*-Ar), 129.6 (*m*-Ar), 137.8 (*p*-Ar), 143.5 (i*pso*-Ar), 168.4 (CO), 204.9 (C-7).


Ts
H
N
O
H
CO2t-Bu
keto-3.24
1.63
2.45
1.00
1.26
1.04
2.22
1.67
3.01
2.77
2.08
9.00
f1 (ppm)

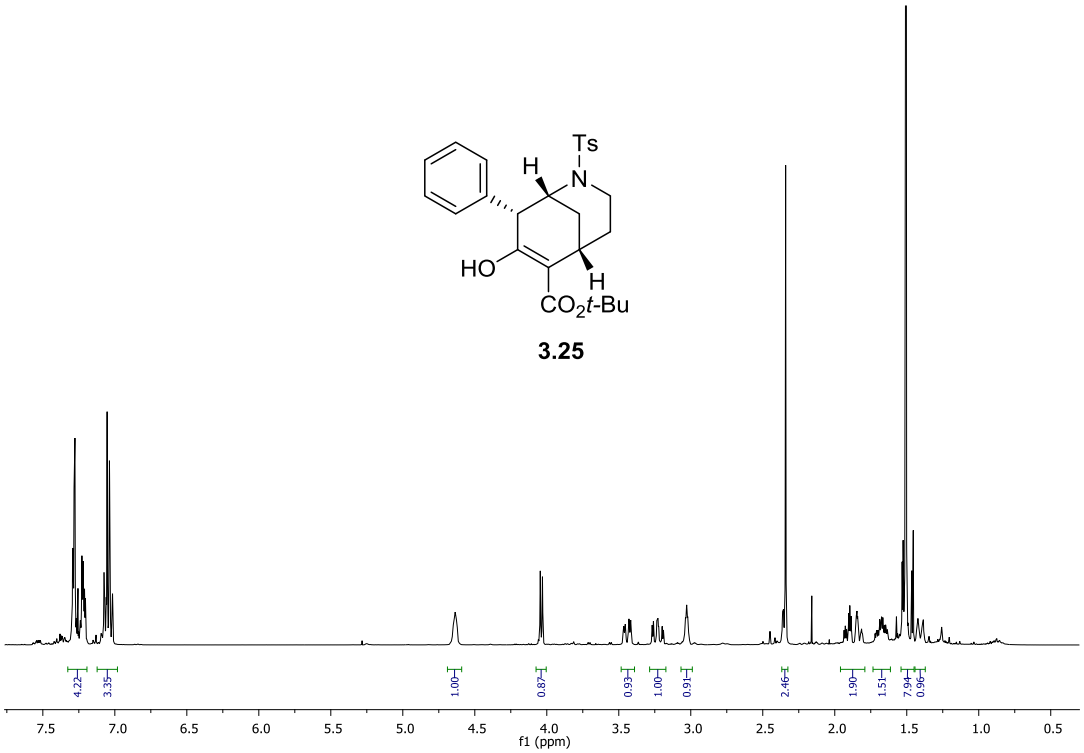

206.91
204.83
168.41
143.44
137.77
129.74
129.62
127.33
127.20
83.01
81.72
77.33
77.01
76.69
69.92
69.75
61.50
53.20
52.72
38.18
32.94
30.91
30.64
29.00
27.85
21.51
15.45
f1 (ppm)

(1*R*,5*S*,8*S*)-*tert*-Butyl 7-Hydroxy-2-(4-methylphenylsulfonyl)-8-phenyl-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.25)

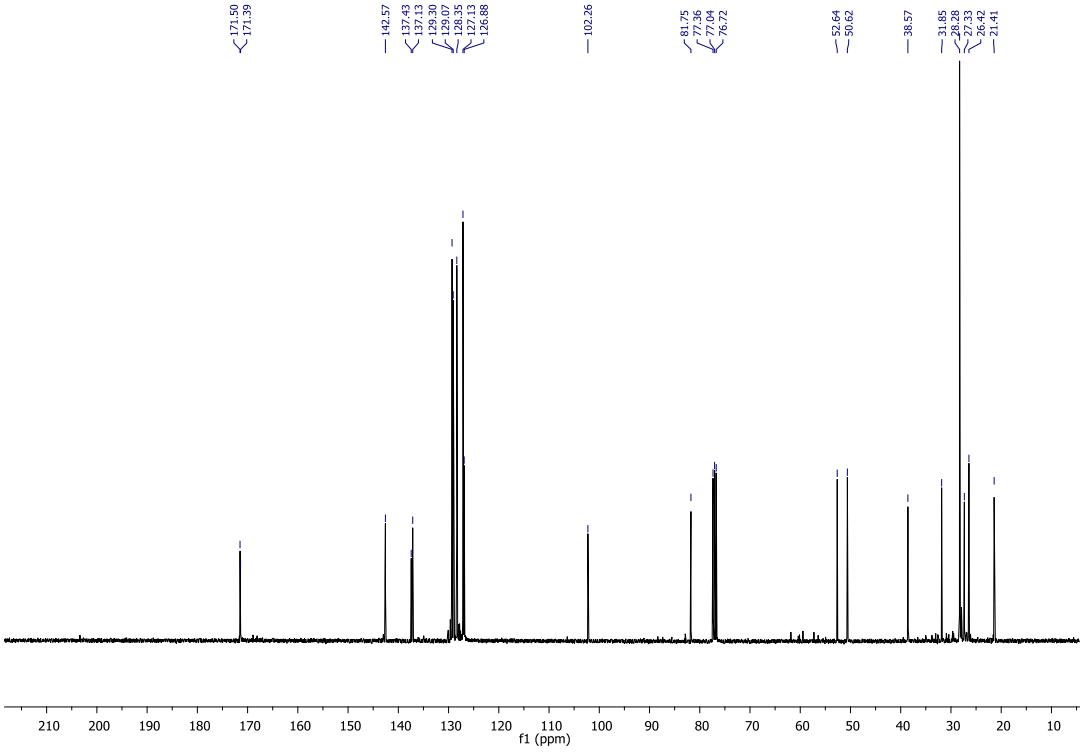


3.25

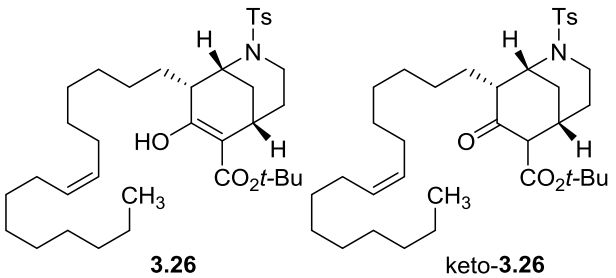
This compound was prepared according to general method **C** using β-keto ester **3.13f** (96 mg, 0.41 mmol), enal (52 mg, 0.21 mmol), bis-phenyl-OSiPh$_3$-pyrrolidine organocatalyst **2.16** (11 mg, 0.021), LiOAc (1.4 mg, 0.021 mmol) and H_2O (37 mg, 2.1 mmol). *i*PrOH (1.0 mL) and LiOH·H_2O (26 mg, 0.62 mmol). Purification by column chromatography (0→5→10→25% EtOAc/hexane) gave **3.25** as an off-white solid, (52 mg, 54%): ^{1}H NMR (400 MHz, COSY) δ 1.42 (dm, *J* = 13.2 Hz, 1H, H-4eq), 1.52 (s, 9H, CH_3), 1.69 (tdd, *J* = 12.8, 5.2, 3.2 Hz, 1H, H-4ax), 1.85 (dm, *J* = 13.2 Hz, 1H, H-9), 1.93 (dt, *J* = 13.2, 2.4 Hz, 1H, H-9), 2.36 (s, 3H, ArCH_3), 3.04 (t, *J* = 3.2 Hz, 1H, H-5), 3.25 (ddd *J* = 14.8, 13.2, 3.6 Hz, 1H, H-3ax), 3.46 (dd, *J* = 14.8, 4 Hz, 1H, H-3eq), 4.05 (d, *J* = 5.6 Hz, 1H, H-8), 4.65 (br s, 1H, H-1), 7.05 (m, 4H, ArH), 7.24 (m, 2H, ArH), 7.30 (m, 3H, ArH); ^{13}C NMR (100 MHz, HSQC) δ 21.4 (ArCH_3), 26.4 (C-5), 27.3 (C-4), 27.9 (CH_3), 31.8 (C-9), 38.5 (C-3), 50.6 (C-8), 52.6 (C-1), 81.7 (C), 102.2 (C-6), 126.8 (4-Ph), 127.0 (*o*-Ts), 127.1 and 127.2 (2,6-Ph), 129.3 (*m*-Ts), 129.0 and 129.4 (3,5-Ph), 137.1 (1-Ph), 137.4 (*p*-Ts), 142.5 (i*pso*-Ts), 171.4 (C-7), 171.5 (CO). HRMS calcd for $C_{26}H_{32}NO_5S$ $[M+H]^+$ 470.1996, found 470.2001.


Ts
H
N
HO
H
CO2t-Bu
4.22
3.35
1.00
0.87
0.93
1.00
0.91
2.46
1.90
1.51
7.94
0.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

3.25


171.50
171.39
142.57
137.43
137.13
129.30
129.07
128.35
127.13
126.88
102.26
81.75
77.36
77.04
76.72
52.64
50.62
38.57
31.85
28.28
27.33
26.42
21.41
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

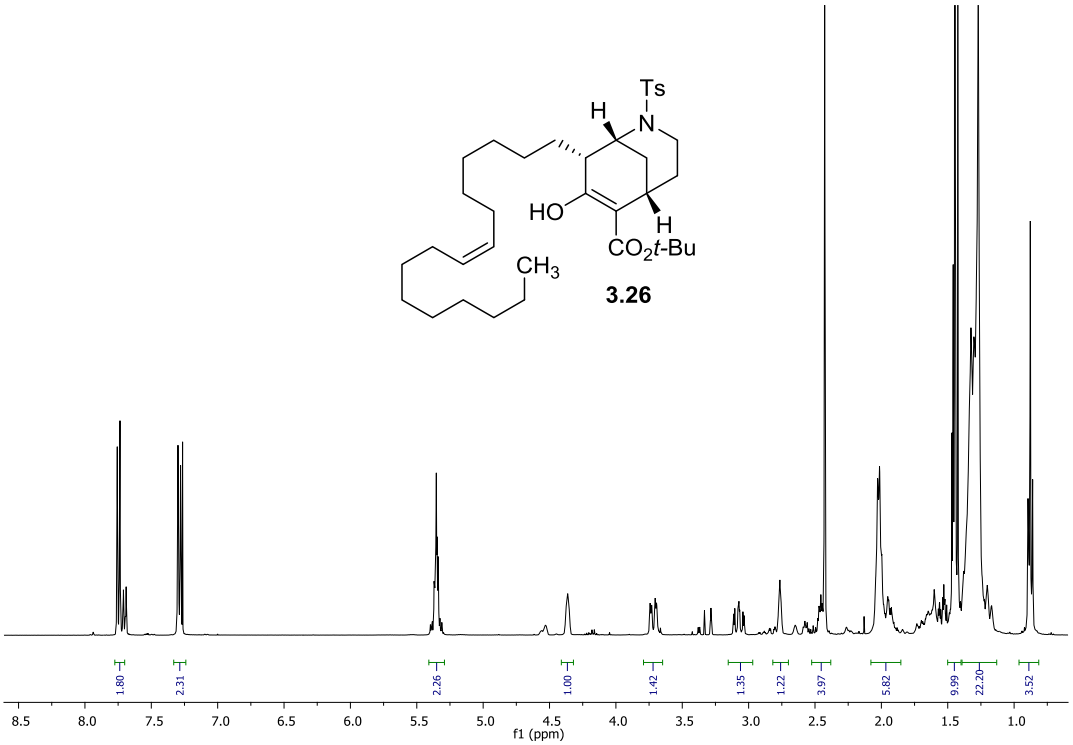
(1*R*,5*S*,8*S*)-*tert*-Butyl 8-((*Z*)-Heptadec-7-en-1-yl)-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.26)

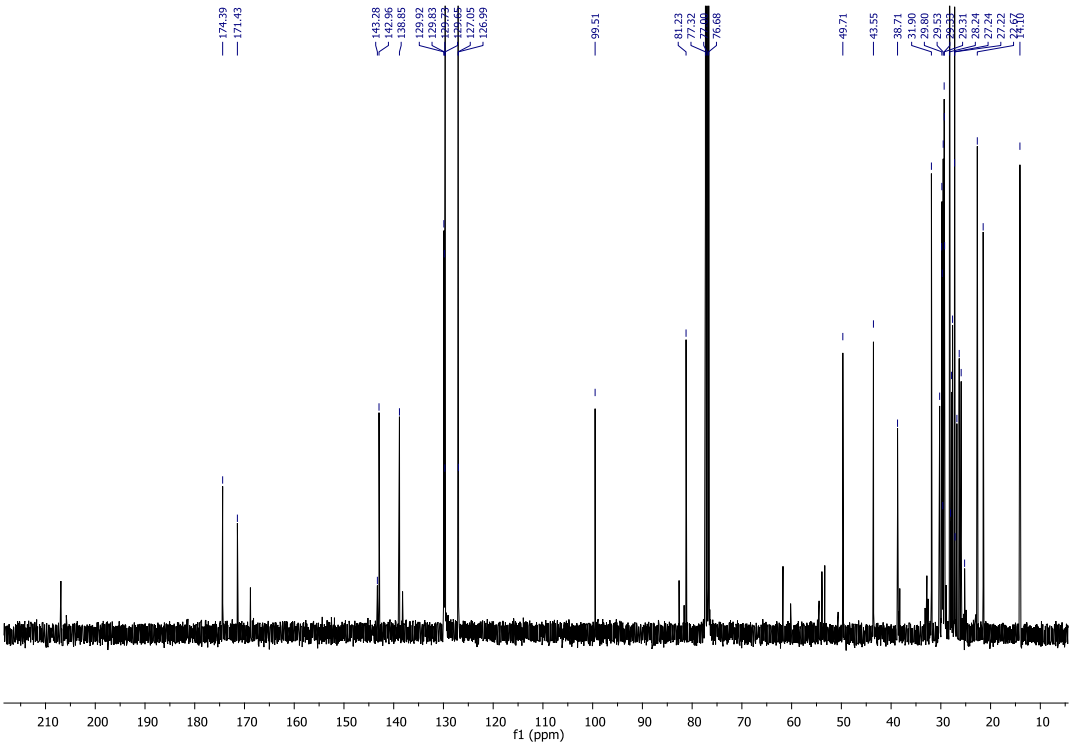


3.26 keto-**3.26**

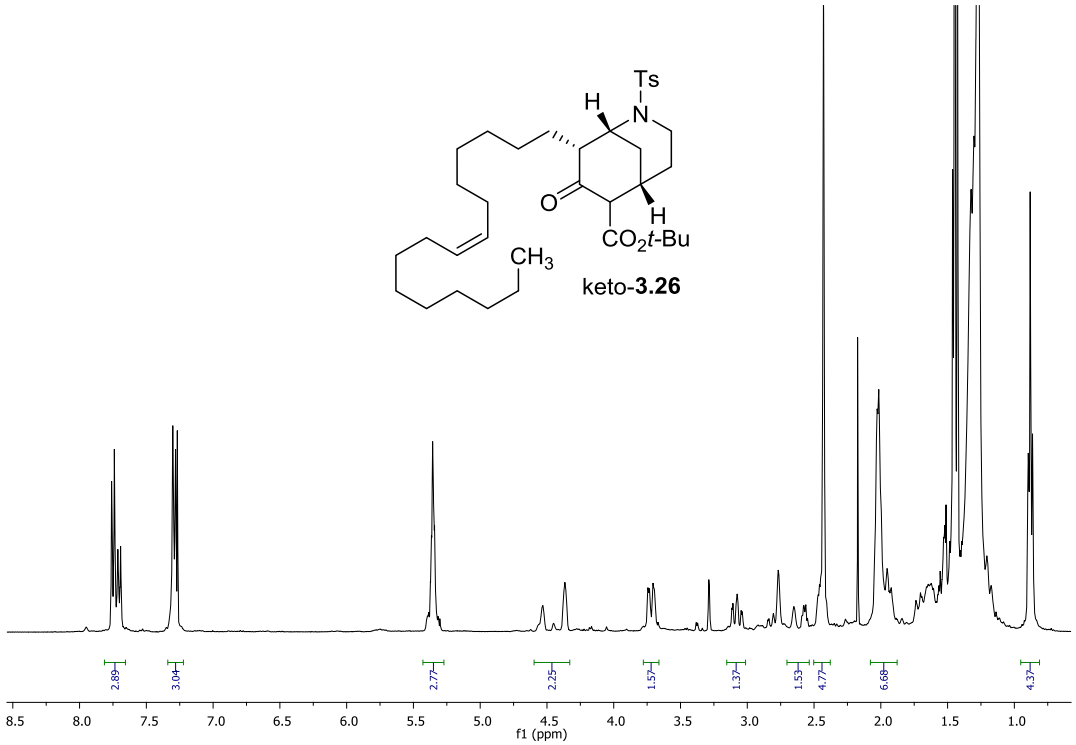
This compound was prepared according to general method **C** using β-keto ester **3.13e** (162 mg, 0.44 mmol), enal (56 mg, 0.22 mmol), bis-phenyl-OSiPh_3-pyrrolidine organocatalyst **2.16** (11 mg, 0.022), LiOAc (1.5 mg, 0.022 mmol) and H_2O (40 mg, 2.2 mmol). *i*PrOH (0.9 mL) and LiOH·H_2O (28 mg, 0.66 mmol). Purification by chromatography (0→5→10→25% EtOAc/hexane) gave **3.26** as an off-white solid (59 mg, 42%).

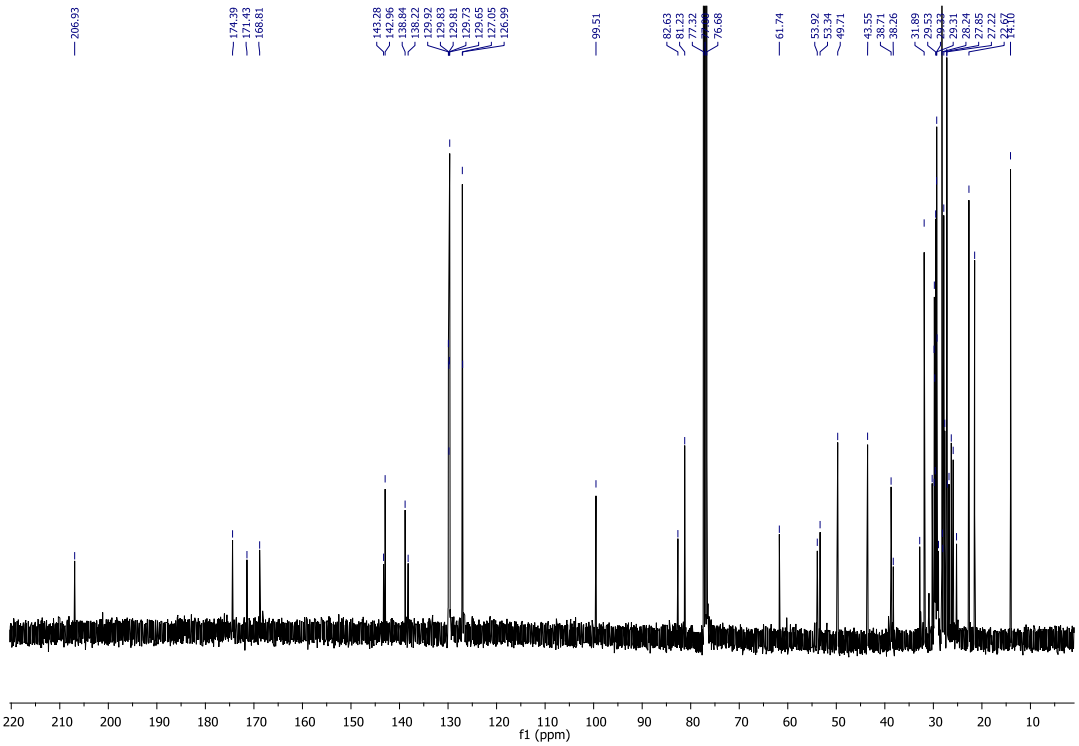
enol tautomer ^{1}H NMR (400 MHz, COSY) δ 0.87 (t, *J* = 6.4 Hz, 3H, CH_3), 1.18-1.35 (m, 23H), 1.45 (s, 9H, CH_3), 1.48 (masked, 1H, H-9), 1.54 (dt, *J* = 12.0, 3.6 Hz, 1H, H-9), 1.65 (m, 1H, H-4), 2.02 (m, 4H, C-6´and C-9), 2.42 (s, 3H, CH_3Ar), 2.45 (m, 1H, H-8), 2.76 (t, *J* = 2.8 Hz, 1H, H-5), 3.07 (ddd, *J* = 14.8, 3.6 Hz, 1H, H-3ax), 3.71 (dd, *J* = 14.8, 4.4 Hz, 1H, H-3eq), 4.36 (br s, 1H, H-1), 5.35 (m, 2H, =CH), 7.29 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.74 (d, *J* = 8.0 Hz, 2H, *o*-ArH); ^{13}C NMR (100 MHz, HSQC) δ 14.1 (CH_3), 21.5 (ArCH_3), 22.7 (CH_2), 25.9 (CH_2), 26.3 (C-5), 27.2 (2 peaks, C-6´and C-9´), 27.6 (C-4), 27.8 (CH_2), 28.3 (CH_3), 29.2, 29.3, 29.3, 29.5, 29.7, 29.8, 29.8 (all CH_2), 31.9 (C-9), 38.7 (C-3), 43.6 (C-8), 49.7 (C-1), 81.2 (C), 99.5 (C-6), 127.1 (*o*-Ar), 129.7 (*m*-Ar), 129.8 and 129.9 (=CH), 138.9 (*p*-Ar), 143.0 (i*pso*-Ar), 171.4 (C-7), 174.4 (CO). HRMS calcd for $C_{36}H_{58}NO_5S$ $[M+H]^+$ 616.403, found 616.4022.


Ts
H
N
HO
H
CO2t-Bu
CH3
3.26
1.80
2.31
2.26
1.00
1.42
1.35
1.22
3.97
5.82
9.99
22.20
3.52
f1 (ppm)

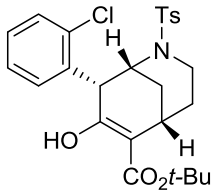

174.39
171.43
143.28
142.96
138.85
129.92
129.83
99.51
81.23
77.32
77.00
76.68
49.71
43.55
38.71
31.90
29.80
29.53
29.31
28.24
27.24
27.22
27.67
14.10
f1 (ppm)

keto tautomer ^{1}H NMR (400 MHz, COSY) δ 0.87 (t, *J* = 6.4 Hz, 3H, CH_3), 1.18-1.35 (m, 23H), 1.45 (s, 9H, CH_3), 1.48 (masked, 1H, H-9), 1.54 (dt, *J* = 12.0, 3.6 Hz, 1H, H-9), 1.65 (m, 1H, H-4), 2.02 (m, 4H, C-6´and C-9), 2.42 (s, 3H, CH_3Ar), 2.45 (m, 1H, H-8), 2.76 (t, *J* = 2.8 Hz, 1H, H-5), 3.07 (ddd, *J* = 14.8, 3.6 Hz, 1H, H-3ax), 3.71 (dd, *J* = 14.8, 4.4 Hz, 1H, H-3eq), 4.36 (br s, 1H, H-1), 5.35 (m, 2H, =CH), 7.29 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.74 (d, *J* = 8.0 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, HSQC) δ 14.1 (CH_3), 21.5 (ArCH_3), 22.7 (CH_2), 25.9 (CH_2), 26.3 (C-5), 27.2 (2 peaks, C-6´and C-9´), 27.6 (C-4), 27.8 (CH_2), 28.3 (CH_3), 29.2, 29.3, 29.3, 29.5, 29.7, 29.8, 29.8 (all CH_2), 30.2 (C-9), 31.9 (C-4), 32.8 (C-5), 38.7 (C-3), 53.3 (C-8), 53.9 (C-1), 61.7 (C-6), 81.2 (C), 127.1 (*o*-Ar), 129.7 (*m*-Ar), 129.8 and 129.9 (=CH), 138.9 (*p*-Ar), 143.0 (i*pso*-Ar), 168.8 (CO), 206.9 (C-7).


Ts
H
N
O
H
CO_2t-Bu
CH_3
keto-**3.26**
2.89
3.04
2.77
2.25
1.57
1.37
1.53
4.77
6.68
4.37
f1 (ppm)

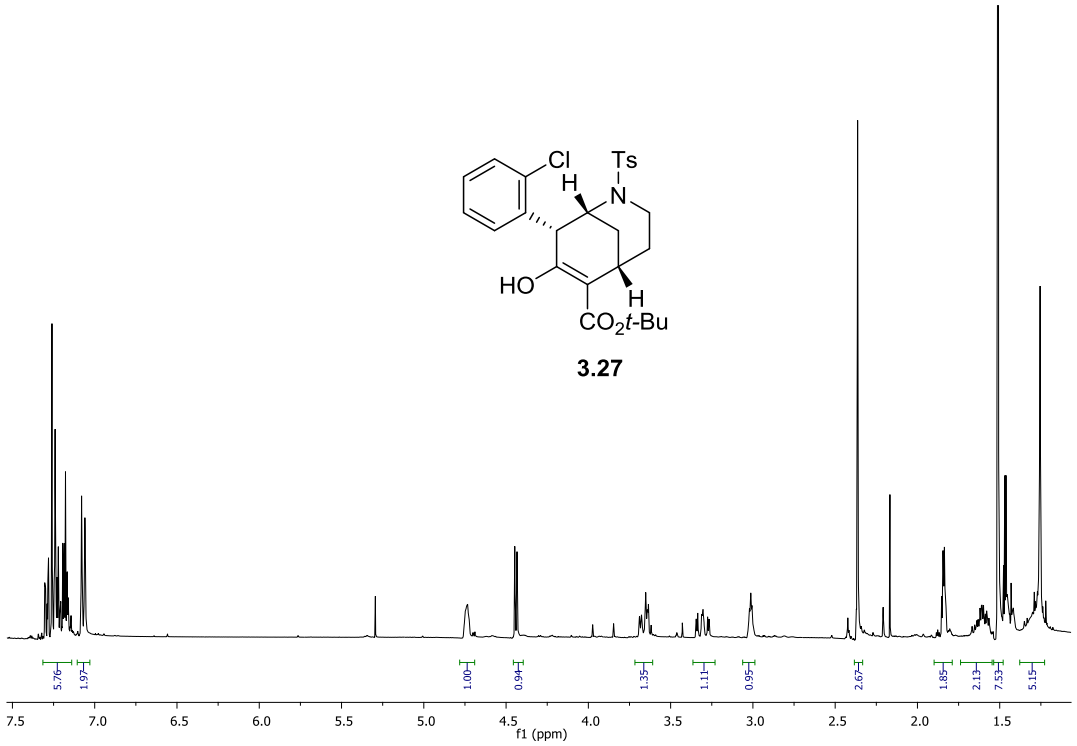

206.93
174.39
171.43
168.81
143.28
142.96
138.84
138.22
129.92
129.83
129.81
129.73
129.65
127.05
126.99
99.51
82.63
81.23
77.32
76.68
61.74
53.92
53.34
49.71
43.55
38.71
38.26
31.89
29.53
29.31
28.24
27.85
27.22
22.62
14.10
f1 (ppm)

(1*R*,5*S*,8*S*)-*tert*-Butyl 8-(2-Chlorophenyl)-7-hydroxy-2-(4-methylphenylsulfonyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.27)

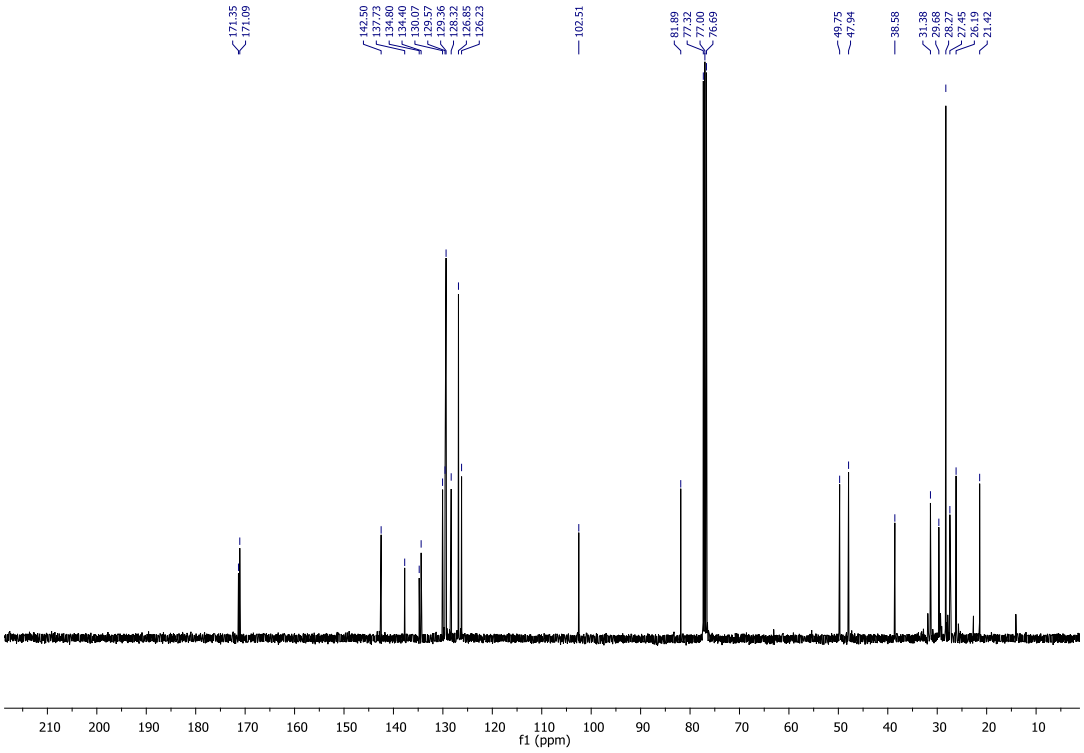


3.27

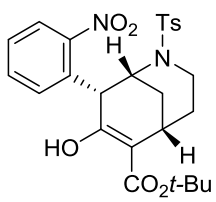
This compound was prepared according to general method **C** using β-keto ester **3.13g** (111 mg, 0.413 mmol), enal **3.4** (52 mg, 0.207 mmol), bis-phenyl-OSiPh_3-pyrrolidine organocatalyst **2.16** (11 mg, 0.0207), LiOAc (1.4 mg, 0.0207 mmol) and H_2O (37 mg, 2.07 mmol). *i*PrOH (0.8 mL) and LiOH·H_2O (26 mg, 0.621 mmol). Purification by chromatography (0→2.5→5→10% EtOAc/hexane) gave **3.27** as an off-white solid (129 mg, 62%); ^{1}H NMR (400 MHz, COSY) δ 1.42-1.45 (m, 1H, H-4), 1.52 (s, 9H, CH_3), 1.57-1.65 (m, 1H, H-4), 1.82 and 1.87 (2dt, *J* = 12.0, 3.6 Hz, 1H each, H-9), 2.37 (s, 3H, CH_3Ar), 3.02 (t, *J* = 2.8 Hz, 1H, H-5), 3.31 (td, *J* = 12.8, 3.6 Hz, 1H, H-3ax), 3.67 (dd, *J* = 14.0, 4.8 Hz, 1H, H-3eq), 4.45 (d, *J* = 6.0 Hz, 1H, H-8), 4.75 (*br*, 1H, H-1), 7.07 (d, *J* = 7.6 Hz, 2H, *m*-ArH), 7.26 (d, *J* = 7.2 Hz, 2H, *o*-ArH),7.17-7.31(m, 4H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 21.4 (ArCH_3), 26.2 (C-5), 27.4 (C-4), 28.3 (CH_3), 31.4 (C-9), 38.6 (C-3), 47.9 (C-8), 49.7 (C-1), 81.9 (C), 102.5 (C-6), 126.2 (Ph-6), 126.9 (*o*-Ts), 128.3 (Ph-5), 129.4 (*m*-Ts), 129.6 (Ph-4), 130.1 (Ph-3), 134.4 (Ph-1), 134.8 (Ph-2), 137.7 (*p*-Ts), 142.5 (i*pso*-Ts), 171.1 (C-7), 171.4 (CO). HRMS calcd for $C_{26}H_{31}ClNO_5S$ $[M+H]^+$ 504.1606, found 504.1603


Cl
Ts
H
N
HO
H
CO2t-Bu
5.76
1.97
1.00
0.94
1.35
1.11
0.95
2.67
1.85
2.13
7.53
5.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

3.27

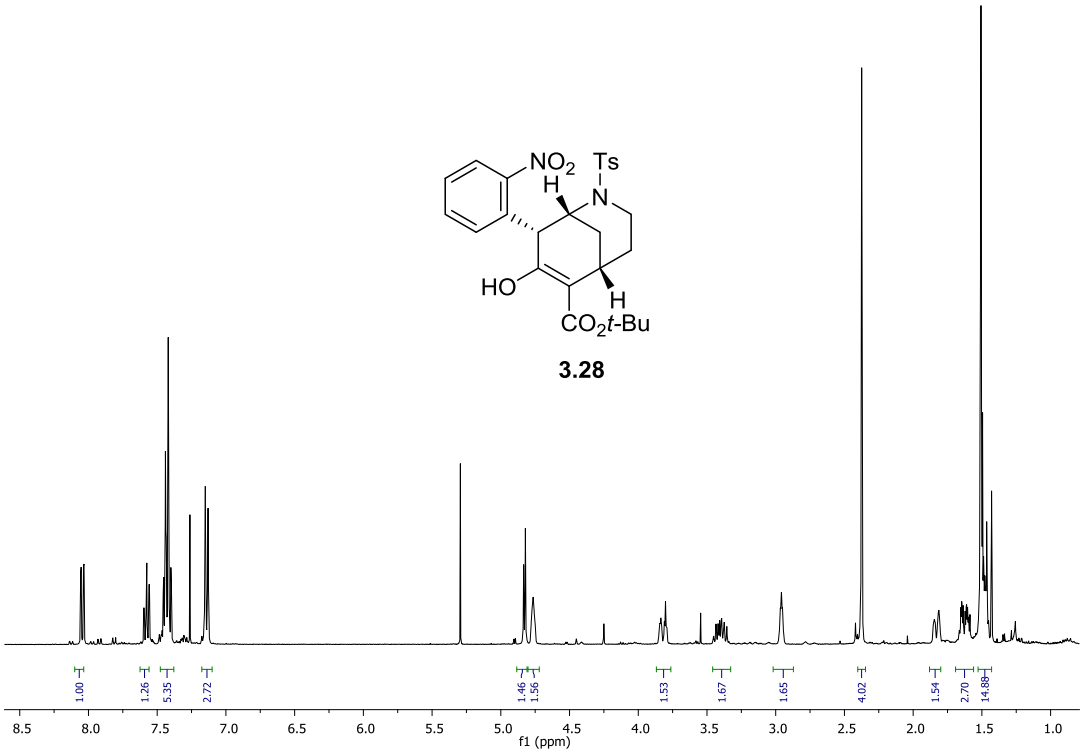

171.35
171.09
142.50
137.73
134.80
134.40
130.07
129.57
129.36
128.32
126.85
126.23
102.51
81.89
77.32
77.00
76.69
49.75
47.94
38.58
31.38
29.68
28.27
27.45
26.19
21.42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(1*R*,5*S*,8*S*)-*tert*-Butyl 7-hydroxy-2-(4-methylphenylsulfonyl)-8-(2-nitrophenyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (3.28)

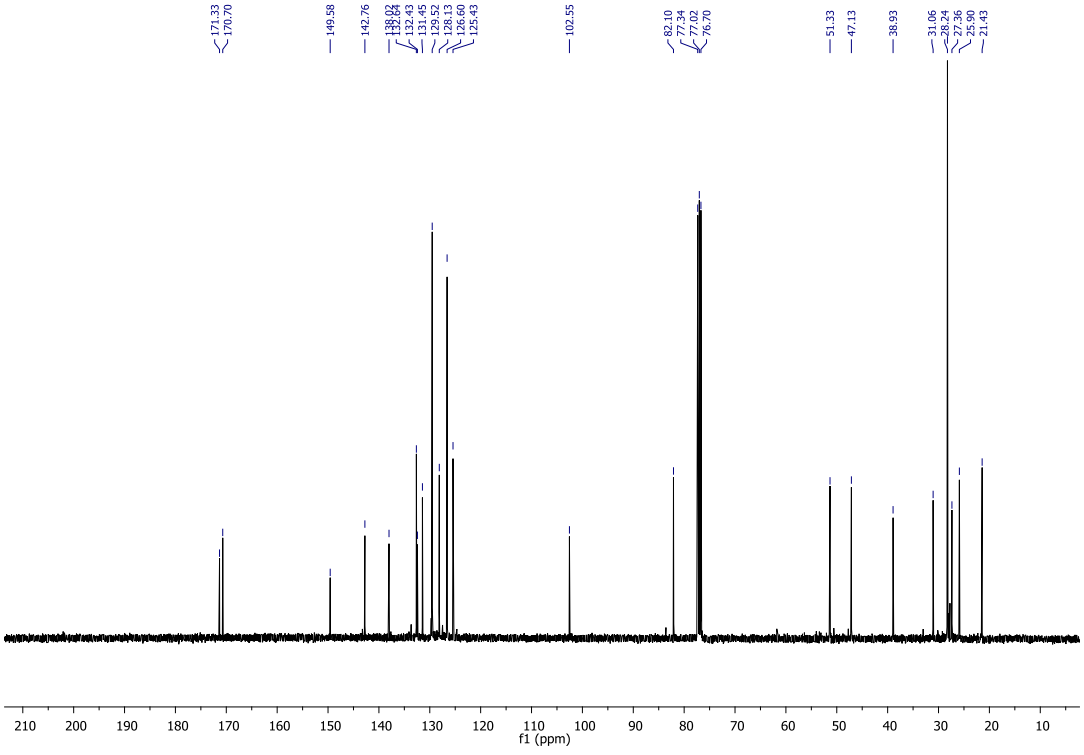


3.28

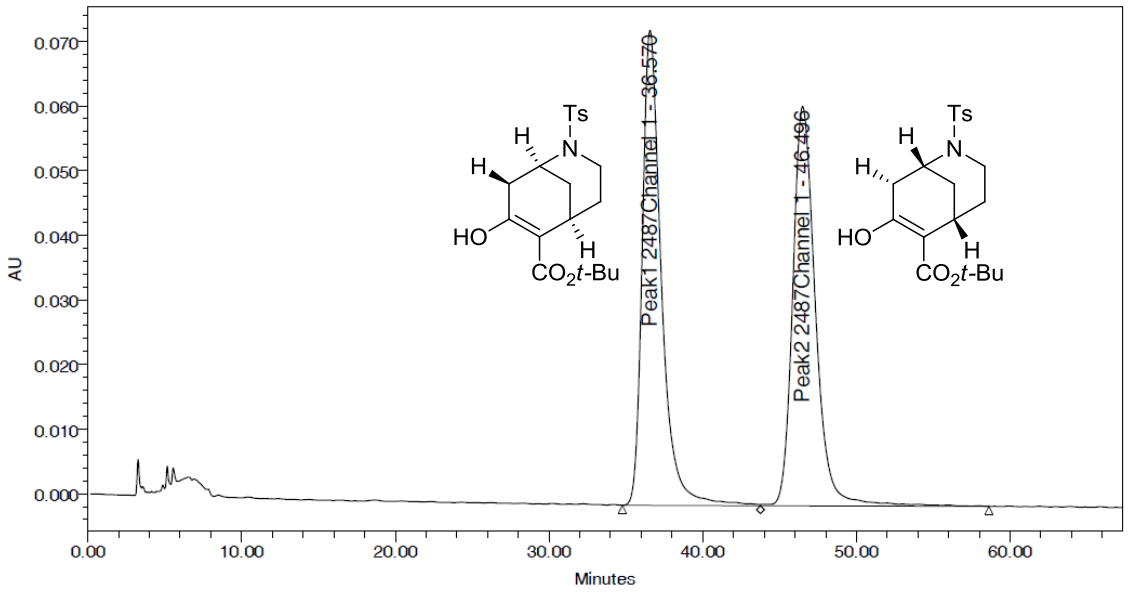
To β-keto ester (78 mg, 0.28 mmol) and enal **3.13h** (141 mg, 0.56 mmol) was added Hayashi's catalyst (18 mg, 0.056 mmol), and H_2O (50 mg, 2.78 mmol) and the mixture was stirred for 24 h at 60 ºC. *i*PrOH (1.1 mL) and $LiOH \cdot H_2O$ (35 mg, 0.836 mmol) was added, and the resulting solution was stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (15 mL/mmol) solution and the product was extracted with EtOAc (3 x 20 mL/mmol). The combined organic layers were dried and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave **3.28** (72 mg, 50%) as a brown amorphous solid. ^{1}H NMR (400 MHz, COSY) δ 1.46-1.56 (masked, 2H, H-4), 1.51 (s, 9H, CH_3), 1.63 (dq, *J* = 12.8, 2.8 Hz, 1H, H-9ax), 1.84 (dm, *J* = 12.8 Hz, 1H, H-9eq), 2.38 (s, 3H, $ArCH_3$), 2.96 (t, *J* = 2.8 Hz, 1H, H-5), 3.40 (ddd, *J* = 13.8, 12.0 5.6 Hz, 1H, 3ax), 3.83 (dt, *J* = 13.6, 3.2 Hz, 1H, 3eq), 4.77 (br, 1H, H-1), 4.83 (d, *J* = 5.2 Hz, 1H, H-8), 7.15 (d, 2H, *J* = 8.0 Hz, *m*-Ts), 7.42 (d, J = 8.0, 1.2 Hz, H-6´), 7.43 (d, *J* = 7.6 Hz, 2H, *o*-Ts), 7.45 (td, J = 8.0, 1.2 Hz, H-4´), 7.58 (td, *J* = 7.6, 1.2 Hz, 1H, H-5´), 8.05 (dd, *J* = 1.6, 8.4, 1.6 Hz, 1H, H-3´); ^{13}C NMR (100 MHz, HSQC) δ 21.4 ($ArCH_3$), 25.9 (C-5), 27.4 (C-4), 28.3 (CH_3), 31.1 (C-9), 38.9 (C-3), 47.1 (C-8), 51.3 (C-1), 82.1 (C), 102.5 (C-6), 125.5 (Ar-6´), 126.6 (*o*-Ts), 128.1 (Ar), 129.5 (*m*-Ts), 131.5 (Ar), 132.4 (Ar), 132.7 (Ar-5´), 138.0 (*p*-Ts), 142.8 (i*pso*-Ts), 149.6 (Ar-2´), 170.7 (C-7), 171.3 (CO). HRMS calcd for $C_{26}H_{31}N_2O_7S$ $[M+H]^+$ 515.1846, found 515.1843.


NO2
H
Ts
N
HO
H
CO2t-Bu
1.00
1.26
5.35
2.72
1.46
1.56
1.53
1.67
1.65
4.02
1.54
2.70
14.88
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

3.28

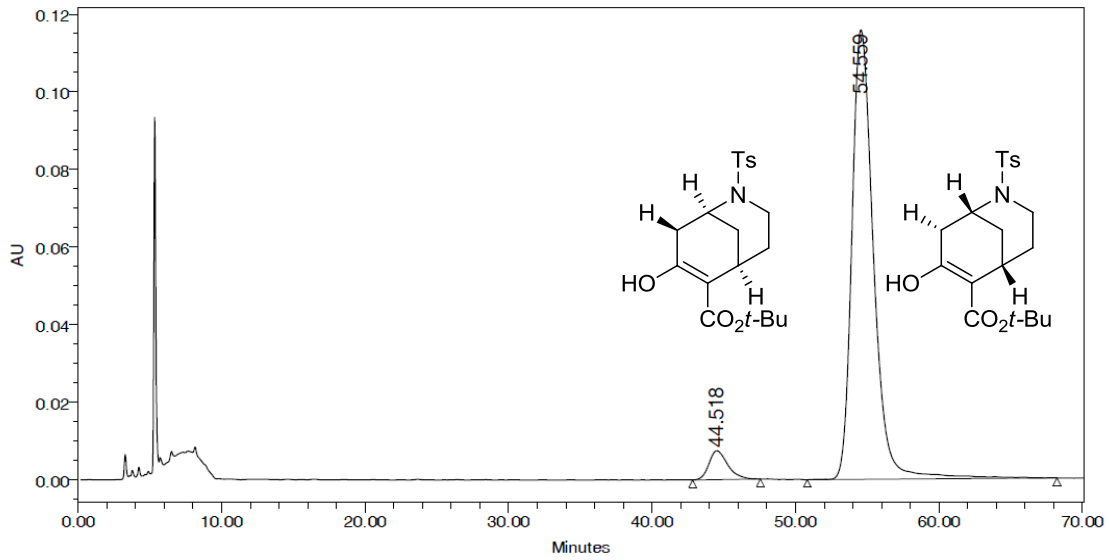

171.33
170.70
149.58
142.76
138.02
132.64
132.43
131.45
129.52
128.13
126.60
125.43
102.55
82.10
77.34
77.02
76.70
51.33
47.13
38.93
31.06
28.24
27.36
25.90
21.43
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

HPLC of Racemic reaction mixture (3.21)



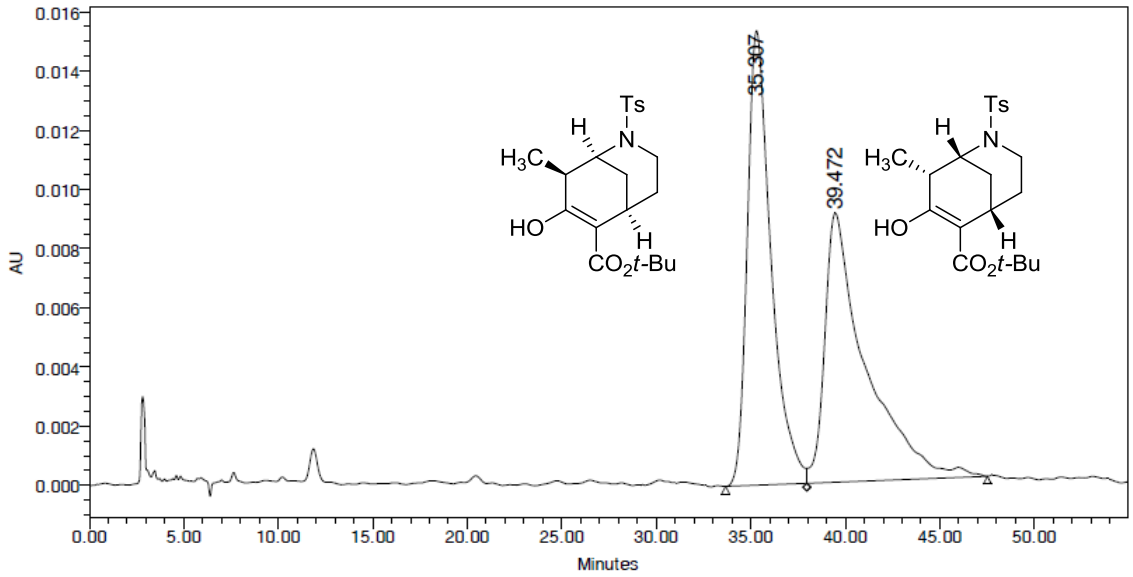
	Peak Name	RT	Area	% Area	Height
1	Peak1 2487Channel 1	36.570	6359351	49.99	73470
2	Peak2 2487Channel 1	46.496	6360808	50.01	61762

HPLC of organocatalysed reaction mixture (3.21)



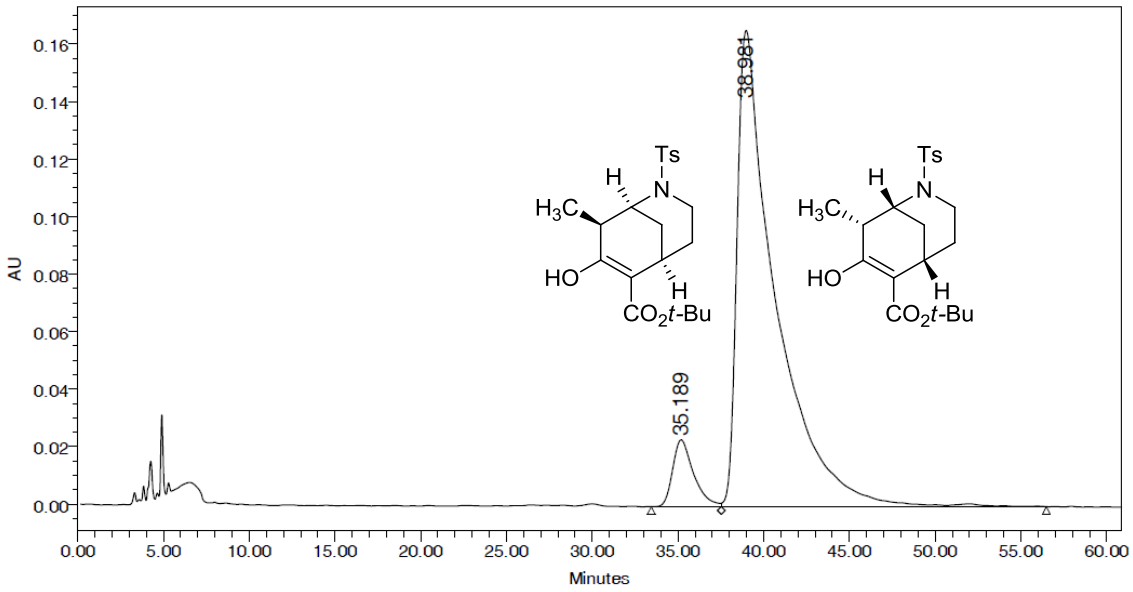
	RT	Area	% Area	Height
1	44.518	679806	5.29	7460
2	54.559	12183011	94.71	115822

HPLC of Racemic reaction mixture (3.22)



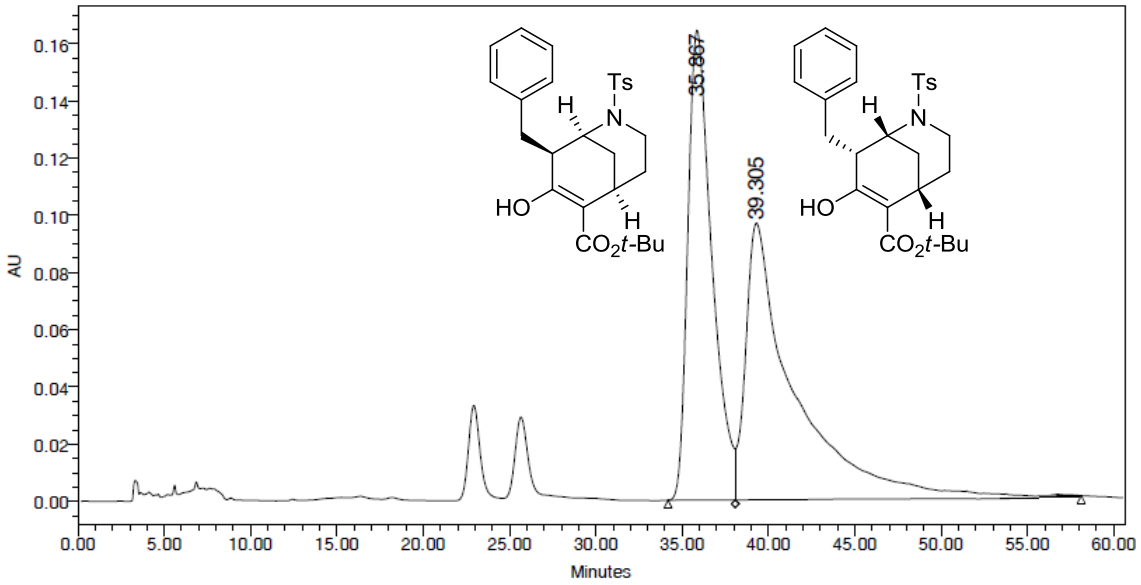
	RT	Area	% Area	Height
1	35.307	1344989	49.54	15354
2	39.472	1369755	50.46	9092

HPLC of organocatalysed reaction mixture (3.22)



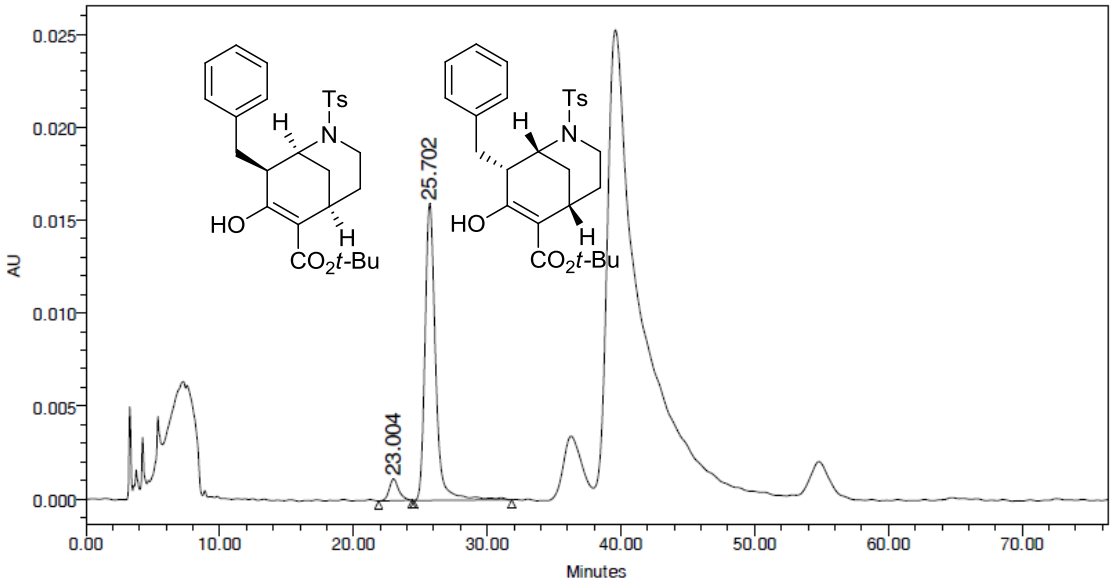
	RT	Area	% Area	Height
1	35.189	1965860	7.09	23197
2	38.981	25776921	92.91	165558

HPLC of Racemic reaction mixture (3.23)



	RT	Area	% Area	Height
1	35.867	15761408	49.30	163645
2	39.305	16209359	50.70	94758

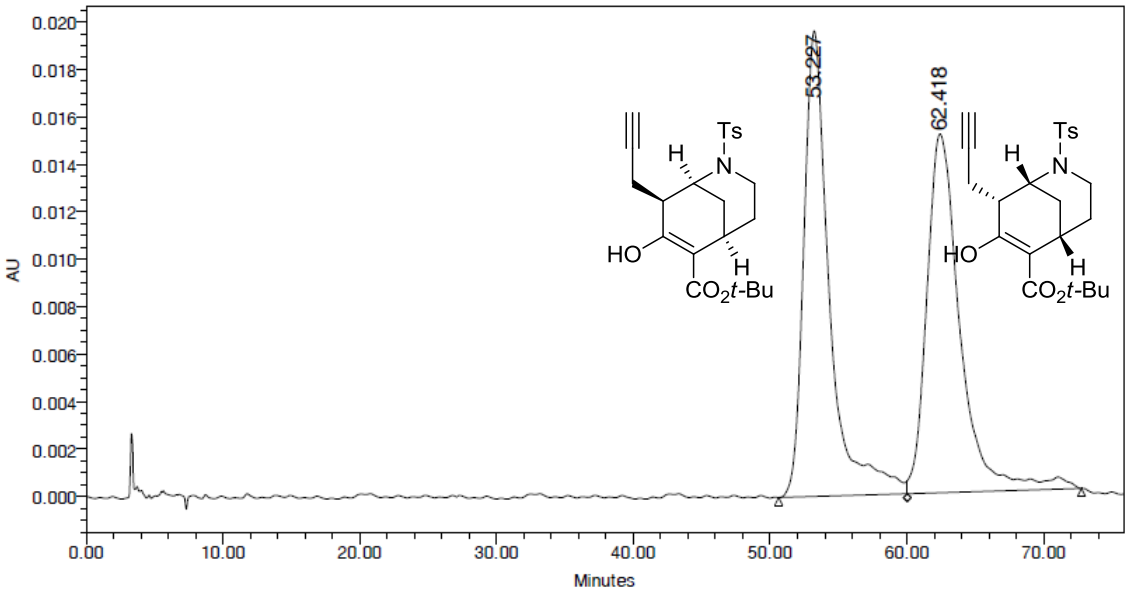
HPLC of organocatalysed reaction mixture (3.23)



	RT	Area	% Area	Height
1	23.004	58078	6.19	1172
2	25.702	879681	93.81	15971

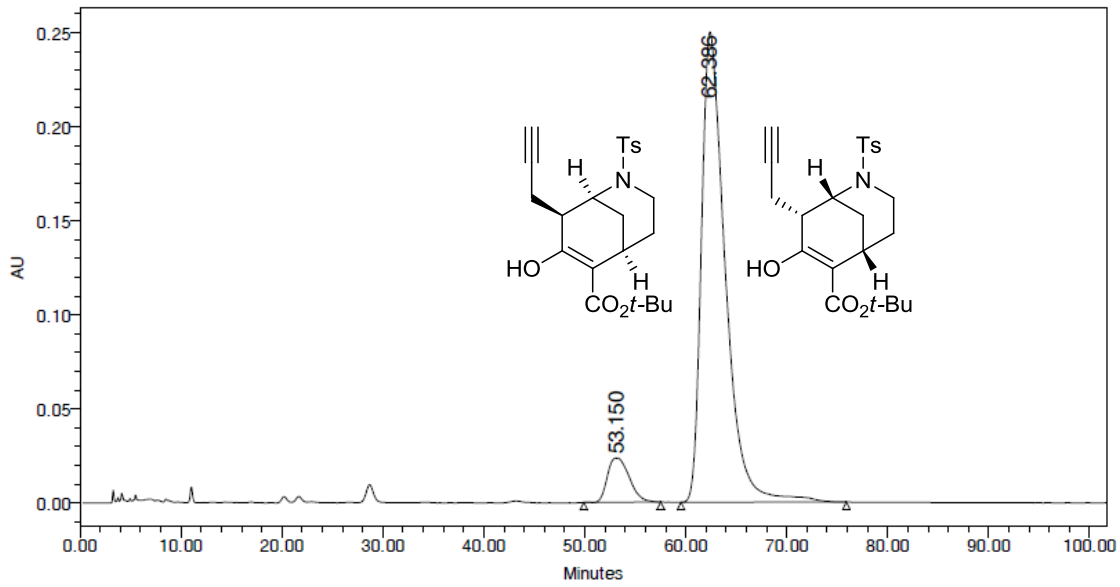
	RT	Area	% Area	Height
1	36.269	330567	6.95	3444
2	39.586	4429126	93.05	25237

HPLC of Racemic reaction mixture (3.24)



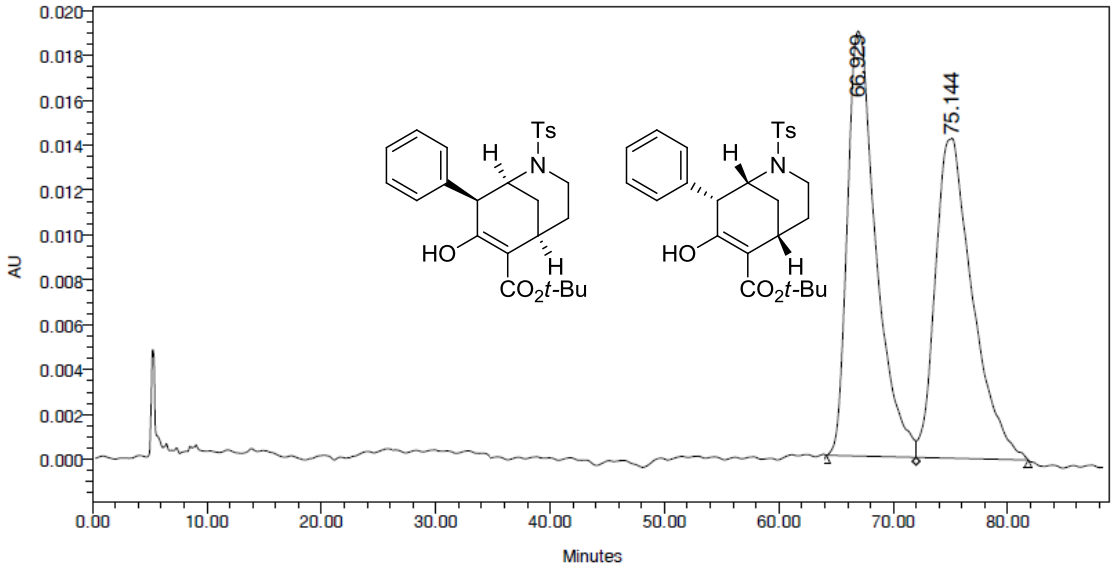
	RT	Area	% Area	Height
1	53.227	2572709	50.03	19620
2	62.418	2570016	49.97	15112

HPLC of organocatalysed reaction mixture (3.24)



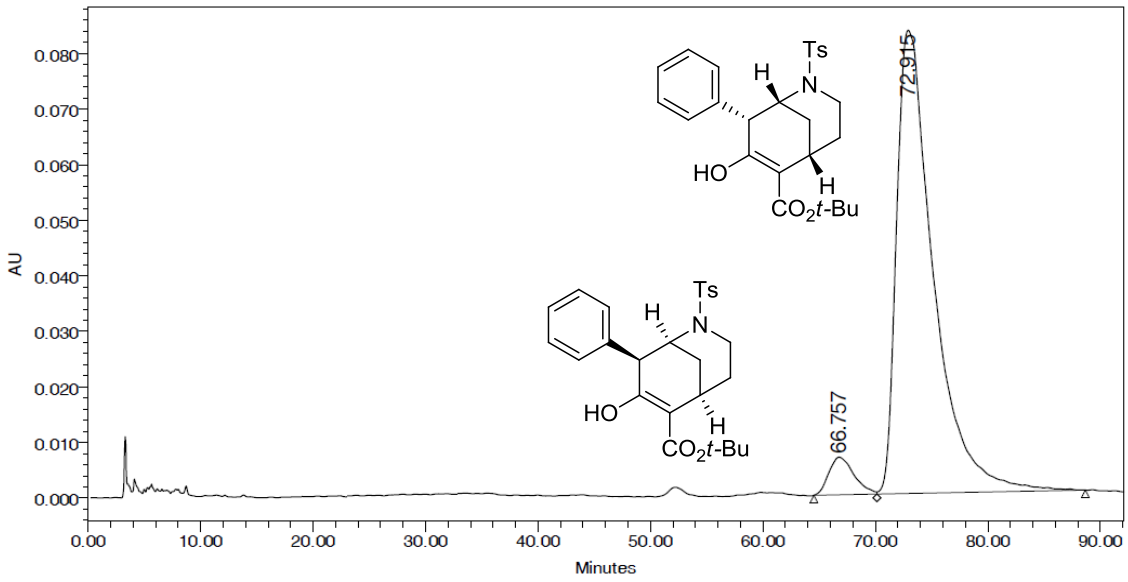
	RT	Area	% Area	Height
1	53.150	3522870	7.92	23548
2	62.386	40959813	92.08	249923

HPLC of Racemic reaction mixture (3.25)



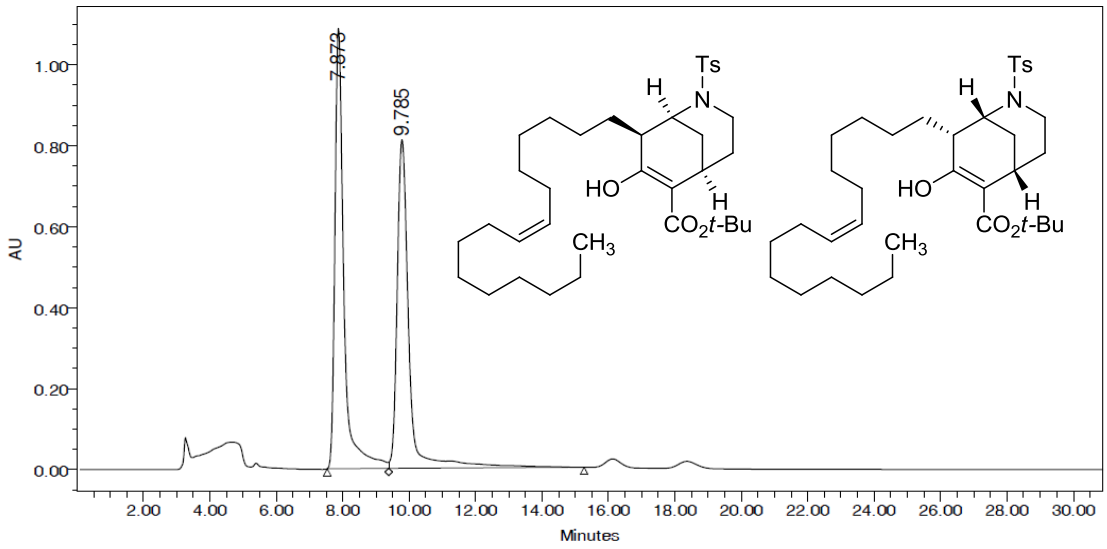
	RT	Area	% Area	Height
1	66.929	3288795	50.46	18933
2	75.144	3228349	49.54	14244

HPLC of organocatalysed reaction mixture (3.25)



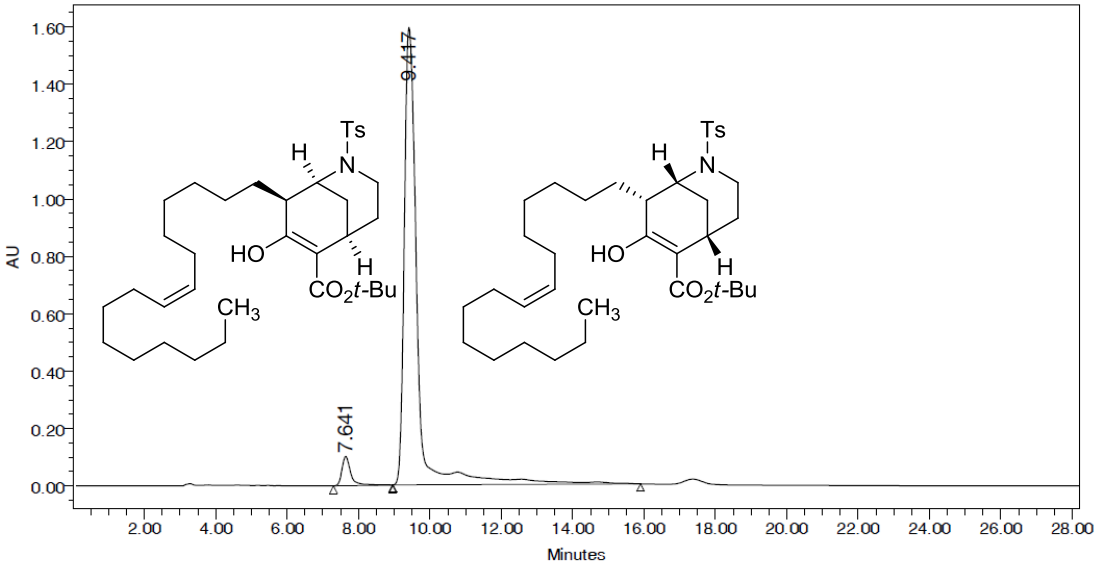
	RT	Area	% Area	Height
1	66.757	1050222	5.23	6767
2	72.915	19021505	94.77	83388

HPLC of Racemic reaction mixture (3.26)



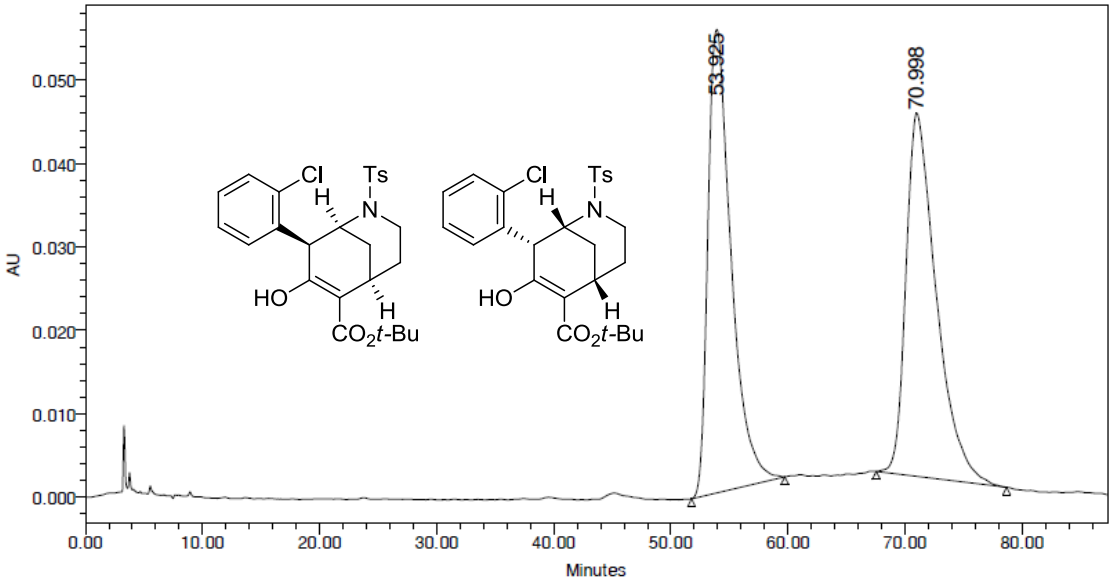
	RT	Area	% Area	Height
1	7.873	20475175	50.44	1089023
2	9.785	20119550	49.56	811460

HPLC of organocatalysed reaction mixture (3.26)



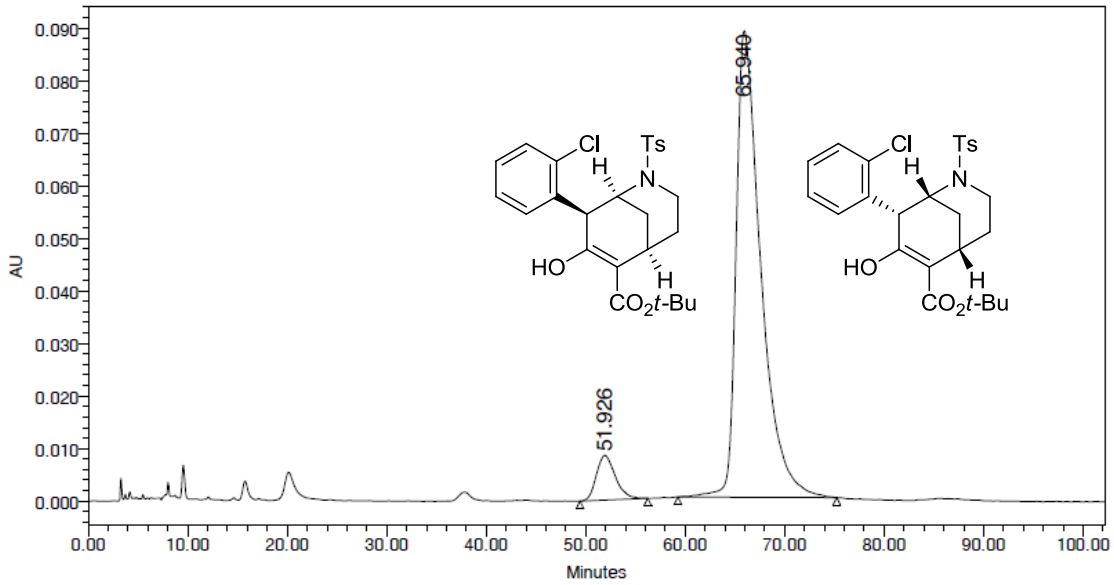
	RT	Area	% Area	Height
1	7.641	1753313	4.15	101979
2	9.417	40489786	95.85	1594758

HPLC of Racemic reaction mixture (3.27)



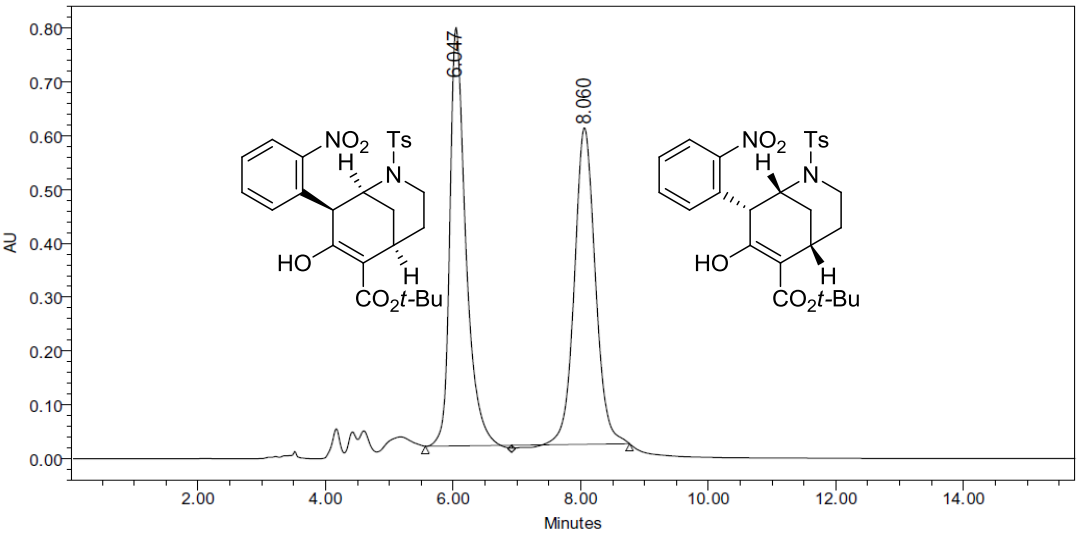
	RT	Area	% Area	Height
1	53.925	7666409	49.45	55586
2	70.998	7836036	50.55	43550

HPLC of organocatalysed reaction mixture (3.27)



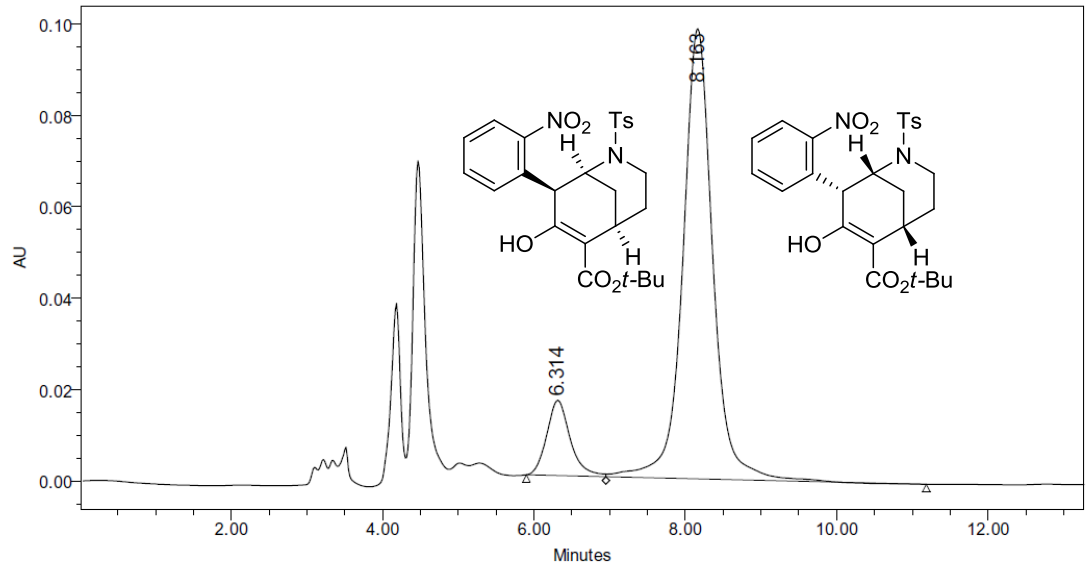
	RT	Area	% Area	Height
1	51.926	1125389	6.82	8527
2	65.940	15373722	93.18	88759

HPLC of Racemic reaction mixture (3.28)



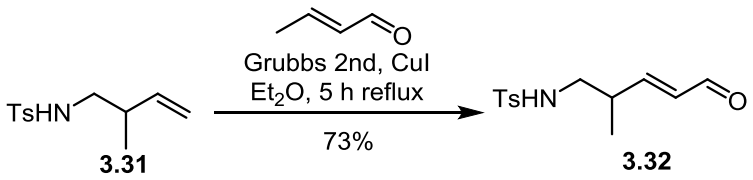
	RT	Area	% Area	Height
1	6.047	13571380	50.00	776923
2	8.060	13570214	50.00	587806

HPLC of organocatalysed reaction mixture (3.28)

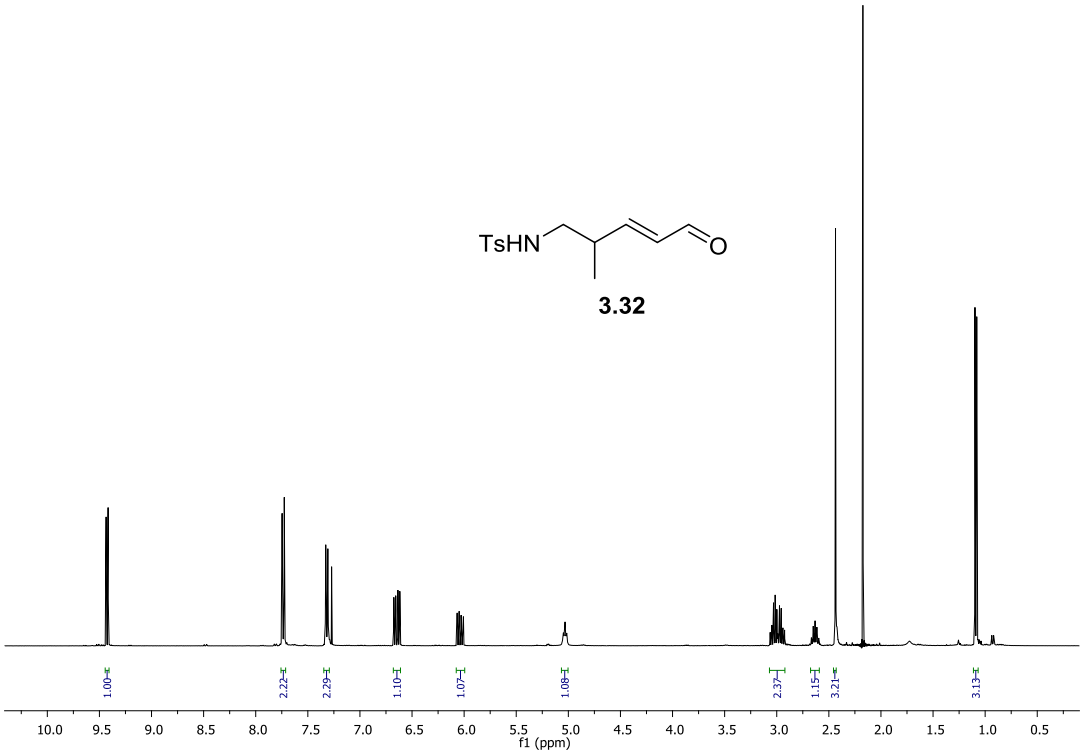


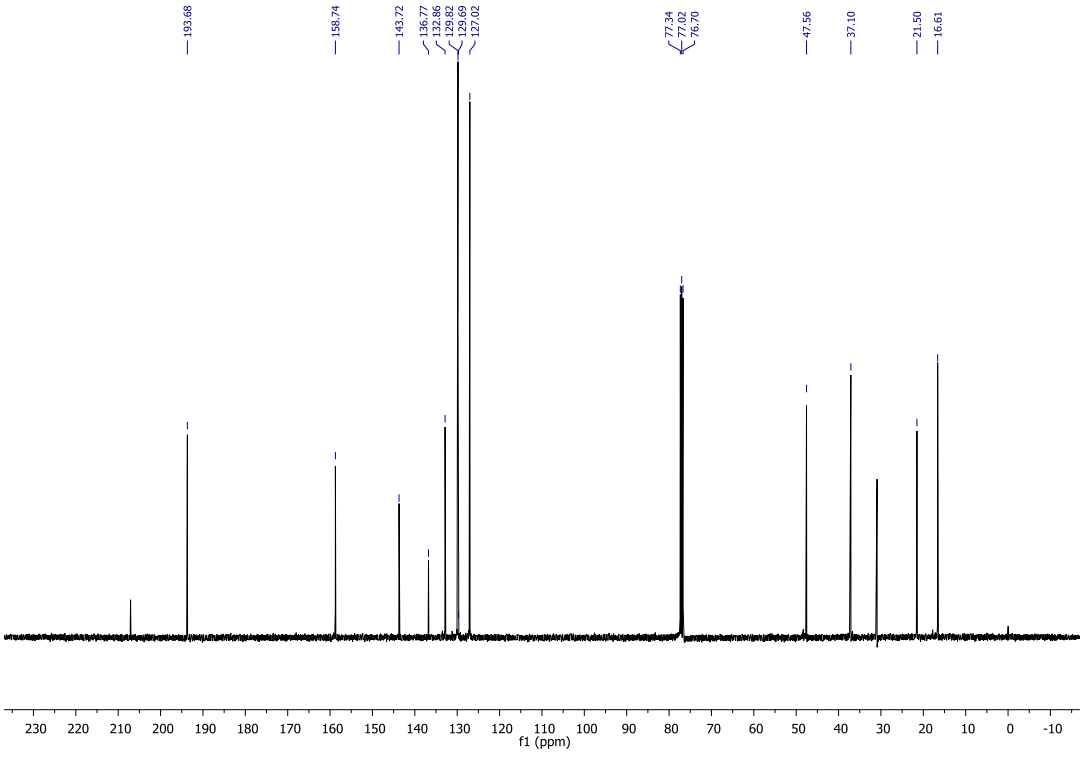
	RT	Area	% Area	Height
1	6.314	355376	11.52	16458
2	8.163	2728757	88.48	98484

(*E*)-4-Methyl-*N*-(2-methyl-5-oxopent-3-en-1-yl) benzenesulfonamide. (3.32)

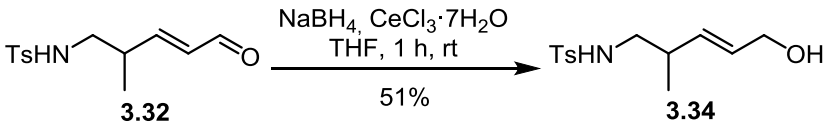


To alkene **3.31** (135 mg, 0.564 mmol), crotonaldehyde (118 mg, 1.69 mmol), Grubbs-2 catalyst (5.0 mg, 5.6 μmol), and CuI (2.0 mg, 8.5 μmol) under an Ar atmosphere was added diethyl ether (6.0 mL) and the resulting mixture heated to reflux for 5 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the crude oil was purified by column chromatography (0→10→25→50% EtOAc/hexane) to give **3.32** (110 g, 73%) as a brown oil. ^{1}H NMR (400 MHz, COSY) δ 1.09 (d, *J* = 6.8 Hz, 3H, CH_3), 2.44 (s, 3H, $ArCH_3$), 2.63 (dt, *J* = 13.7, 6.9 Hz, 1H, H-4), 2.92-3.07 (m, 2H, H-5), 5.03 (br, 1H, NH), 6.04 (ddd, *J* = 15.8, 7.7 1.2 Hz, 1H, H-2), 6.65 (dd, *J* = 15.8, 7.3 Hz, 1H, H-3), 7.32 (d, *J* = 7.9 Hz, *m*-Ts), 7.74 (d, *J* = 8.3 Hz, 2H, *o*-Ts) 9.43 (d, *J* = 7.7, Hz, 1H, CHO), ^{13}C NMR (400 MHz, HSQC) δ 16.6 (CH_3), 21.5 (CH_3), 37.1 (C-4), 47.6 (C-5), 127.0 (*o*-Ts), 129.7 (*m*-Ts), 132.9 (C-2), 136.8 (*p*-Ts), 143.7 (*ipso*-Ts), 158.7 (C-3), 193.7 (C-1). HRMS calcd for $C_{13}H_{18}NO_3S$ $[M+H]^+$ 268.1004, found 268.1002.

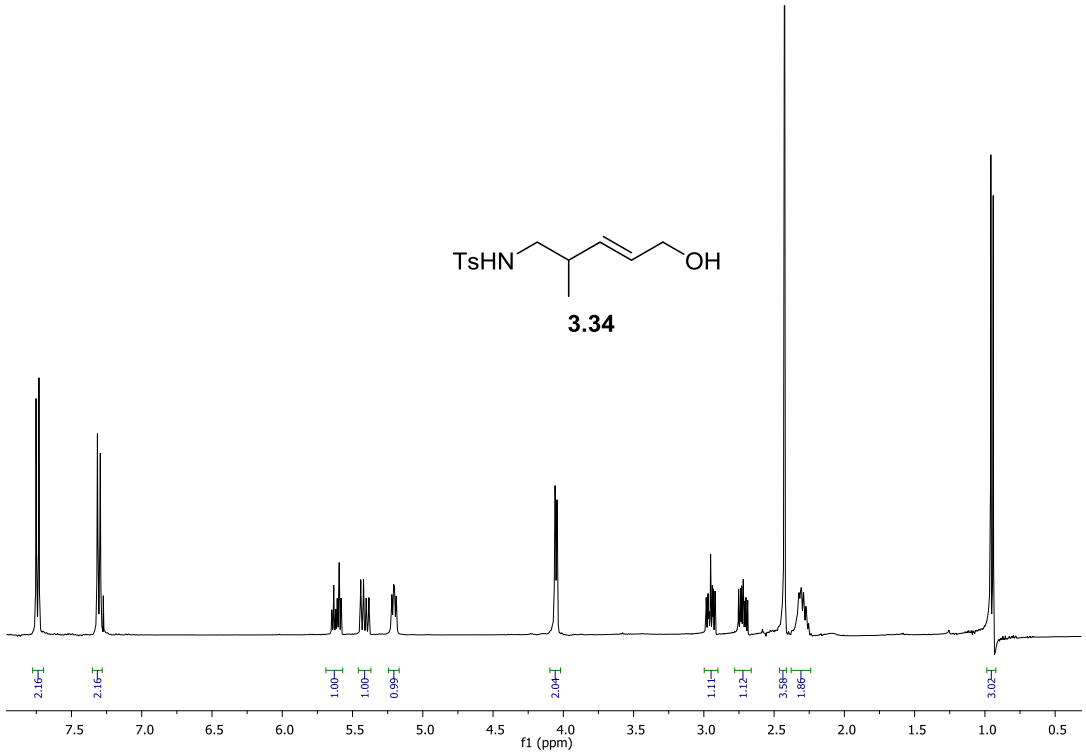

TsHN
O
3.32
1.00
2.22
2.29
1.10
1.07
1.08
2.37
1.15
3.21
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


193.68
158.74
143.72
136.77
132.86
129.82
129.69
127.02
77.34
77.02
76.70
47.56
37.10
21.50
16.61
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

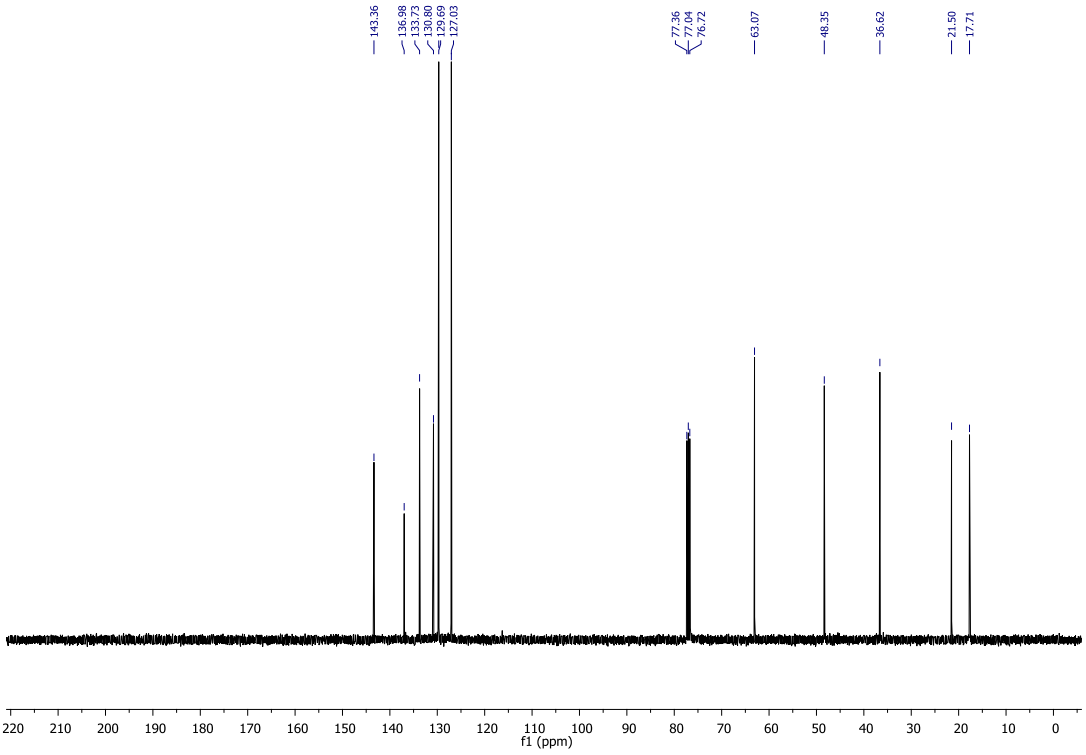
(*E*)-*N*-(5-Hydroxy-2-methylpent-3-en-1-yl)-4-methylbenzenesulfonamide. (3.34)



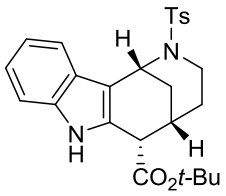
Sodium borohydride (14 mg, 0.374 mmol) was added in small portions to a cooled solution of enal (100 mg, 0.374 mmol) and cerium trichloride heptahydrate (139 mg, 0.374 mmol) in dry THF (6.4 mL). The resulting solution was allowed to warm to room temperature and stirred for 1 h under nitrogen. The reaction mixture was diluted with water (9 mL, dropwise at first) and then extracted into Et_2O (3 x 5 mL). The organic layers were combined, washed with water (5 mL), brine (5 mL), dried (Na_2SO_4). concentrated *in vacuo* and purified by column chromatography (0→10→25→50% EtOAc/hexane) to give **3.34** (51 mg, 51%) as a brown. ^{1}H NMR (400 MHz, COSY) δ 0.95 (d, *J* = 6.8 Hz, 3H, CH_3), 2.24-2.38 (m, 2H, H-2), 2.43 (s, 3H,ArCH_3), 2.66-2.78 (m, 1H, H-5), 2.95 (ddd, *J* = 12.6, 7.5, 5.2 Hz, 1H, H-5), 4.05 (d, *J* = 5.5 Hz, 2H, H-1), 5.20 (2d, *J* = 7.3, Hz, 1H, OH), 5.41 (dd, *J* = 15.5, 7.9 Hz, 1H, H-3), 5.61 (dt, *J* = 15.5, 5.5 Hz, 1H, H-4), 7.31 (d, *J* = 8.2 Hz, *m*-Ts), 7.74 (d, *J* = 8.2 Hz, 2H, *o*-Ts) ^{13}C NMR (400 MHz, HSQC) δ 17.7 (CH_3), 21.5 (CH_3), 36.6 (C-2), 48.3 (C-1), 63.1 (C-5), 127.0 (*o*-Ts), 129.7 (*m*-Ts), 130.8 (C-3), 133.7 (C-4), 137.0 (*p*-Ts), 143.4 (*ipso*-Ts). HRMS calcd for $C_{13}H_{20}NO_3S$ $[M+H]^+$ 270.1169, found 270.1158.


TsHN
OH
2.16
2.16
1.00
1.00
0.99
2.04
1.11
1.12
3.58
1.86
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

3.34

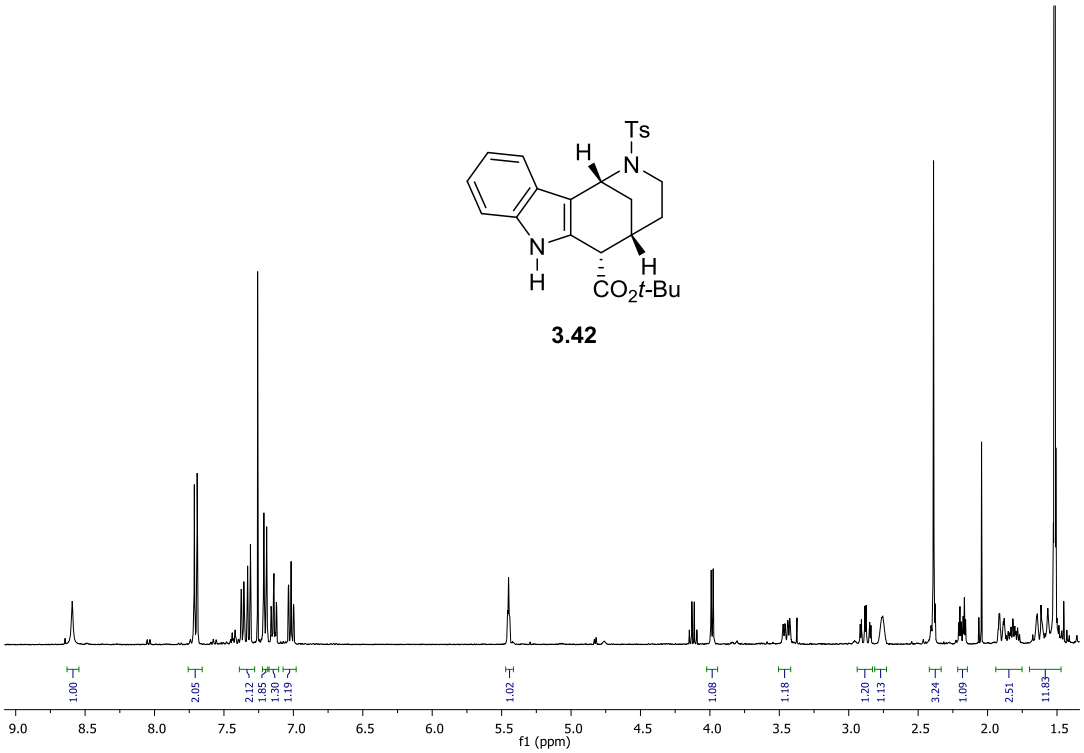

143.36
136.98
133.73
130.80
129.69
127.03
77.36
77.04
76.72
63.07
48.35
36.62
21.50
17.71
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(1*R*,5*S*,6*S*)-*tert*-Butyl 2-(4-Methylphenylsulfonyl)-2,3,4,5,6,7-hexahydro-1*H*-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate (3.42)

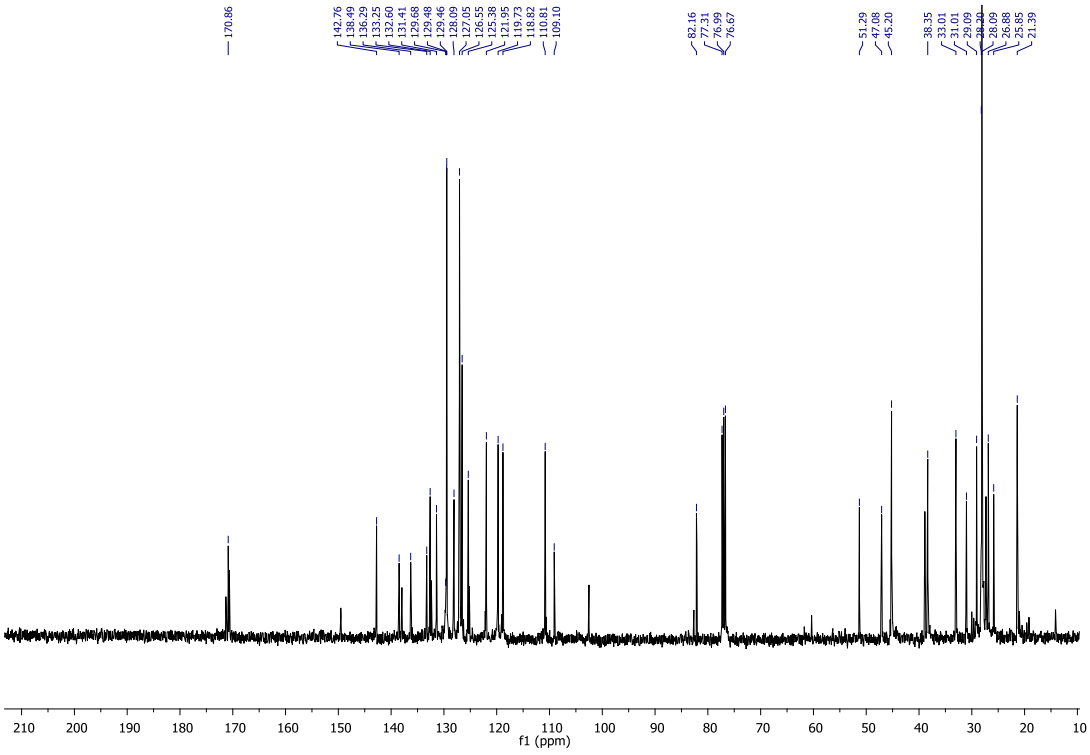


3.42

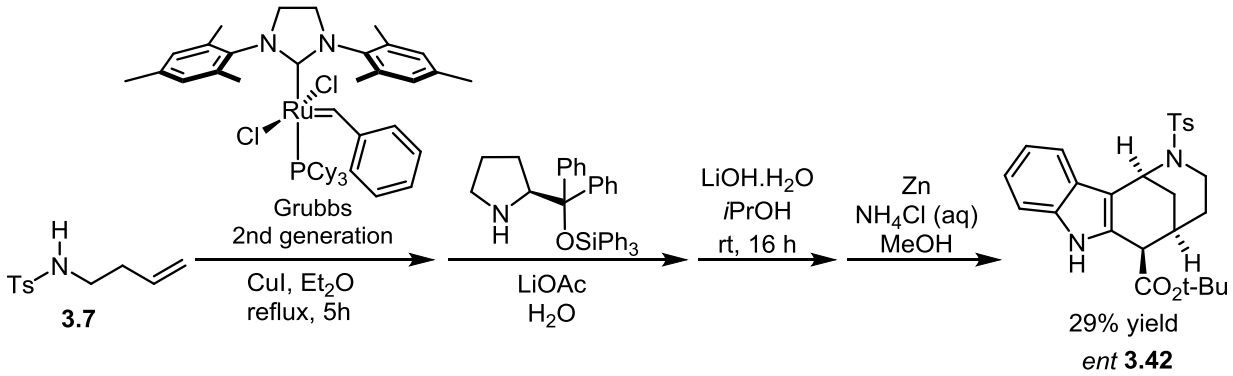
To a solution of **3.28** (33 mg, 0.064 mmol) in MeOH (1.9 mL) were added sequentially sat. aq. NH_4Cl (0.6 mL), Zn dust (419 mg, 6.4 mmol) and the mixture was stirred at rt for 5 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, filtered through Celite and washed with EtOAc. The combined organic layers were washed with $NaHCO_3$ aq, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave indole **3.42** (21 mg, 70%) as a light yellow solid: ^{1}H NMR (400 MHz, COSY) δ 1.52 (s, 9H, CH_3), 1.63 (dm, *J* = 12.4 Hz, 1H, H-4eq), 1.82 (m, *J* = 13.6, 12.4, 5.2, 2.4 Hz, 1H, H-4ax), 1.90 (dq, *J* = 12.8, 2.6 Hz, 1H, H-9), 2.19 (dt, *J* =12.4, 3.6 Hz, 1H, H-9) 2.39 (s, 3H, $ArCH_3$), 2.76 (br, 1H, H-5), 2.88 (td, *J* = 13.6, 3.6 Hz, 1H, H-3ax), 3.45 (dd, *J* = 13.2, 5.2 Hz, 1H, H-3eq), 3.99 (d, *J* = 5.2 Hz, 1H, H-6ax), 5.45 (t, *J* = 2.8 Hz, 1H, H-1), 7.02 (td, *J* = 7.8, 1.2 Hz, 1H, H-10), 7.14 (td, *J* = 8.4, 1.2, 1H, H-11), 7.20 (d, *J* = 8.4 Hz, 2H, m-Ts), 7.32 (dd, *J* = 8.0, 0.8 Hz, 1H, H-12), 7.37 (d, *J* = 7.2 Hz, 1H, H-9), 7.71 (dt, *J* = 8.4, 2.0 Hz, 2H, *o*-Ts), 8.60 (br, 1H, NH); ^{13}C NMR (100 MHz, HSQC) δ 21.4 ($ArCH_3$), 26.9 (C-4), 28.1 (CH_3), 29.1 (C-5), 33.0 (C-12), 38.4 (C-3), 45.2 (C-1), 45.3 (C-6), 82.1 (C), 109.2 (C-11b), 110.8 (C-8), 118.8 (C-11), 119.7 (C-10), 122.0 (C-9), 125.2 (*o*-Ts), 127.1 (C-11a), 129.5 (*m*-Ts), 133.3 (C-6a), 136.3 (C-7a), 138.5 (*p*-Ts), 142.8 (i*pso*-Ts), 170.9 (CO). HRMS calcd for $C_{26}H_{31}N_2O_4S$ $[M+H]^+$ 467.1998, found 467.1995.


Ts
H
N
N
H
H
CO2t-Bu
1.00
2.05
2.12
1.85
1.30
1.19
1.02
1.08
1.18
1.20
1.13
3.24
1.09
2.51
11.83
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

3.42

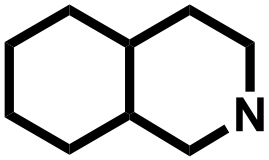

170.86
142.76
138.49
136.29
133.25
132.60
131.41
129.68
129.48
129.46
128.09
127.05
126.55
125.38
121.95
119.73
118.82
110.81
109.10
82.16
77.31
76.99
76.67
51.29
47.08
45.20
38.35
33.01
31.01
29.09
28.30
28.09
26.88
25.85
21.39
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(1*S*,5*R*,6*R*)-*tert*-Butyl 2-(4-Methylphenylsulfonyl)-2,3,4,5,6,7-hexahydro-1*H*-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate. (ent-3.42)

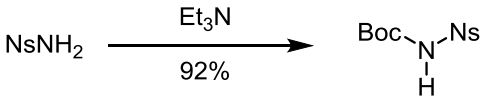


To alkene **3.7** (100 mg, 0.444 mmol), crotonaldehyde (93 mg, 1.33 mmol), Grubbs-2 catalyst (4.0 mg, 4.4 μmol), and CuI (1.3 mg, 6.7 μmol) under an Ar atmosphere was added diethyl ether (4.0 mL) and the solution was heated at reflux for 5 h. After cooling to room temperature the reaction mixture was concentrated *in vacuo*. β-keto ester **3i** (62 mg, 0.222 mmol), H_2O (80 mg, 4.44 mmol) and LiOAc (3.0 mg, 0.044 mmol) and by bis-phenyl-$OSiPh_3$-pyrrolidine ent-**2.16** (23 mg, 0.044) were added and the resulting mixture was stirred at room temperature for 24 h. The residue was dissolved in *i*PrOH (2 mL), and $LiOH{\cdot}H_2O$ (56 mg, 1.33 mmol) was added and the resulting solution was stirred for 16 h. MeOH (13 mL) was added followed by sat. aq. NH_4Cl (4.4 mL), Zn dust (2.9 g, 44.4 mmol) and the mixture was stirred at rt for 5 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, filtered through Celite and washed with EtOAc. The combined organic layers were washed with $NaHCO_3$ aq, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave indole **3.42** (60 mg, 29%) as a light yellow solid. Spectra data was identical to that previously reported.

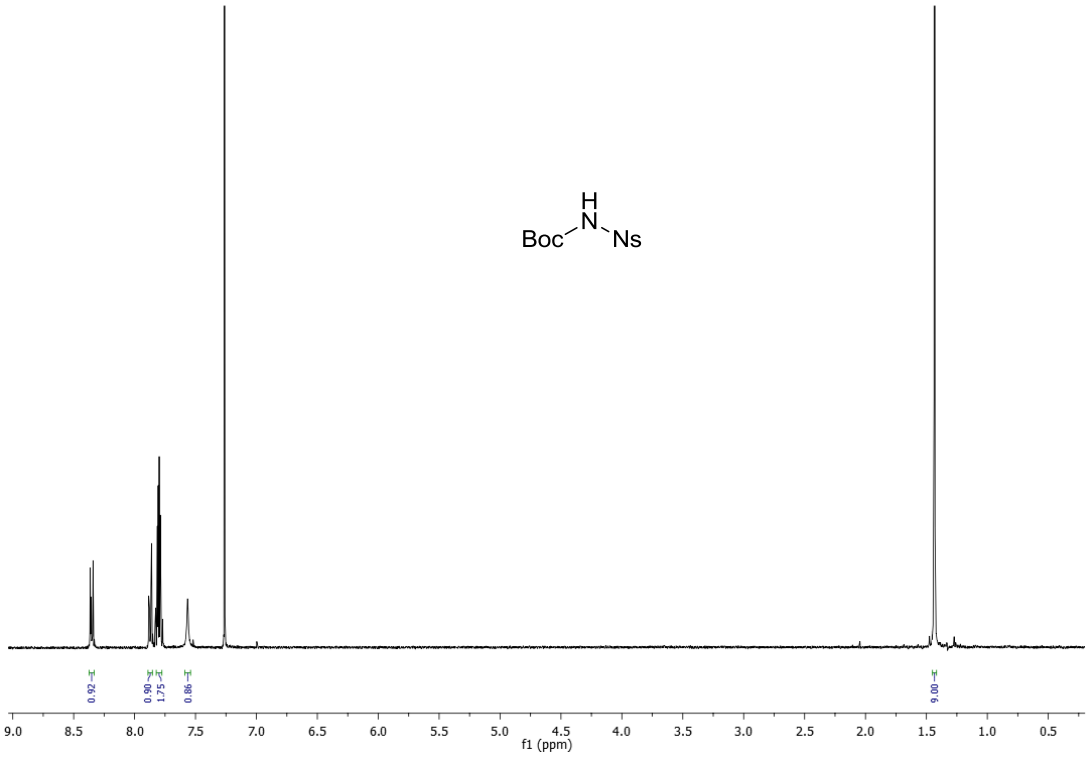
HYDROISOQUINOLINES



***N*-Boc-*o*-Nitrobenzenesulfonamide**

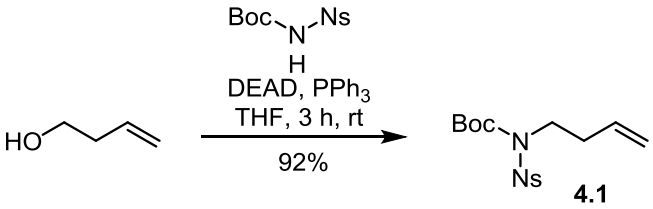


This product was prepared according to the literature procedure[159] (2.87 g, 96%); ^{1}H NMR (400 MHz, COSY) 1.43 (s, 9H, CH_3), 7.57 (br, 1H, NH), 7.82-7.78 (m, 2H), 7.85-7.89 (m, 1H), 8.33-8.37 (m, 1H).

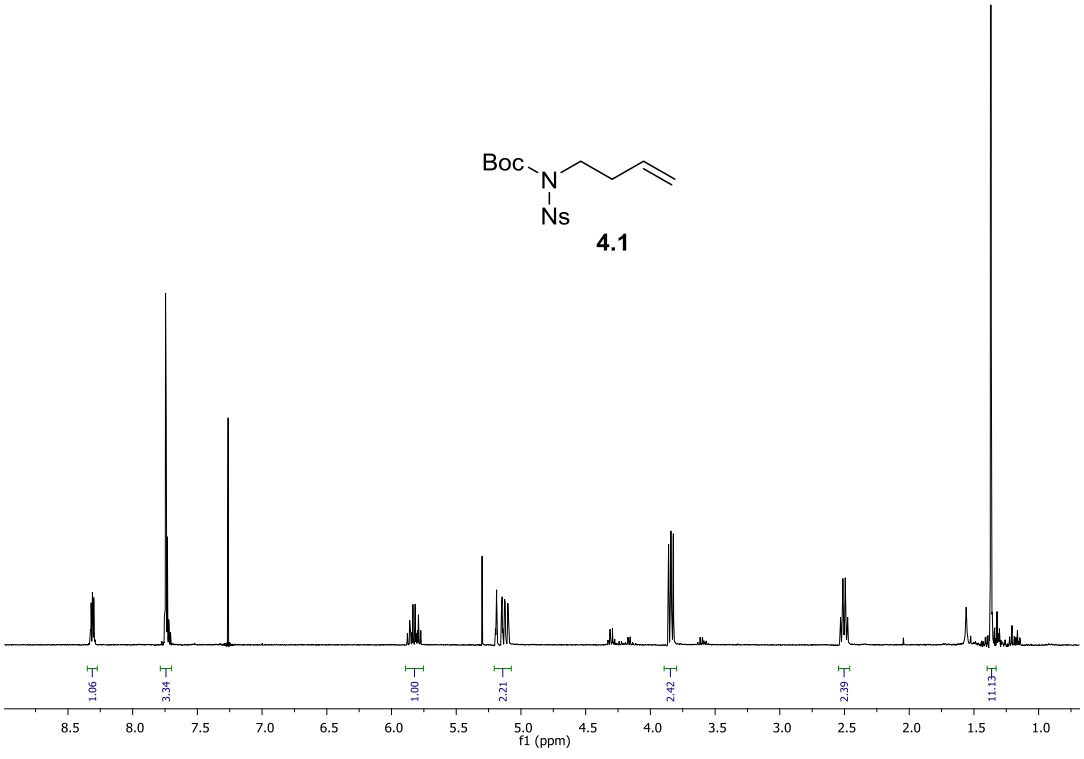


[159] Fukuyama, T.; Cheung, M.; Kan, T. *Synlett*, **1999**, *8*, 1301-1303.

tert-Butyl But-3-en-1-ylcarbamate. (4.1)

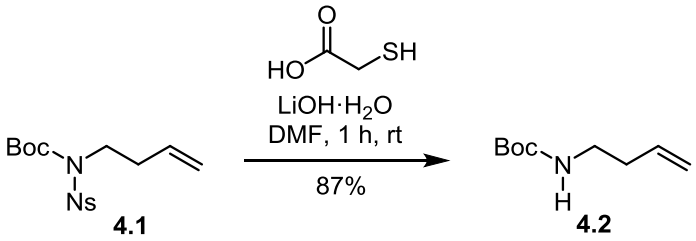


This product was prepared according to the known literature procedure[160] using *N*-Boc-*o*-nitrobenzenesulfonamide (3.00 g, 9.92 mmol), 3-buten-1-ol (0.715 g, 9.95 mmol), tryphenylphosphine (7.81 g, 29.76 mmol) DEAD (4.5 mL, 24.81 mmol), in THF (17 mL). Purification by column chromatography (0→25→50→100% EtOAc/hexane) gave **4.1** (3.26 g, 92%); ^{1}H NMR (400 MHz, COSY) δ 1.37 (s, 9H, CH_3), 2.50 (q, *J* = 6.9 Hz, 2H, H-2), 3.84 (t, *J* = 9.2 Hz, 2H, H-1), 5.08-5.22 (m, 2H, H-4), 5.75-5.90 (m, 1H, H-3), 7.73-7.77 (m, 3H, Ph), 8.29-8.34 (m, 1H, Ph).

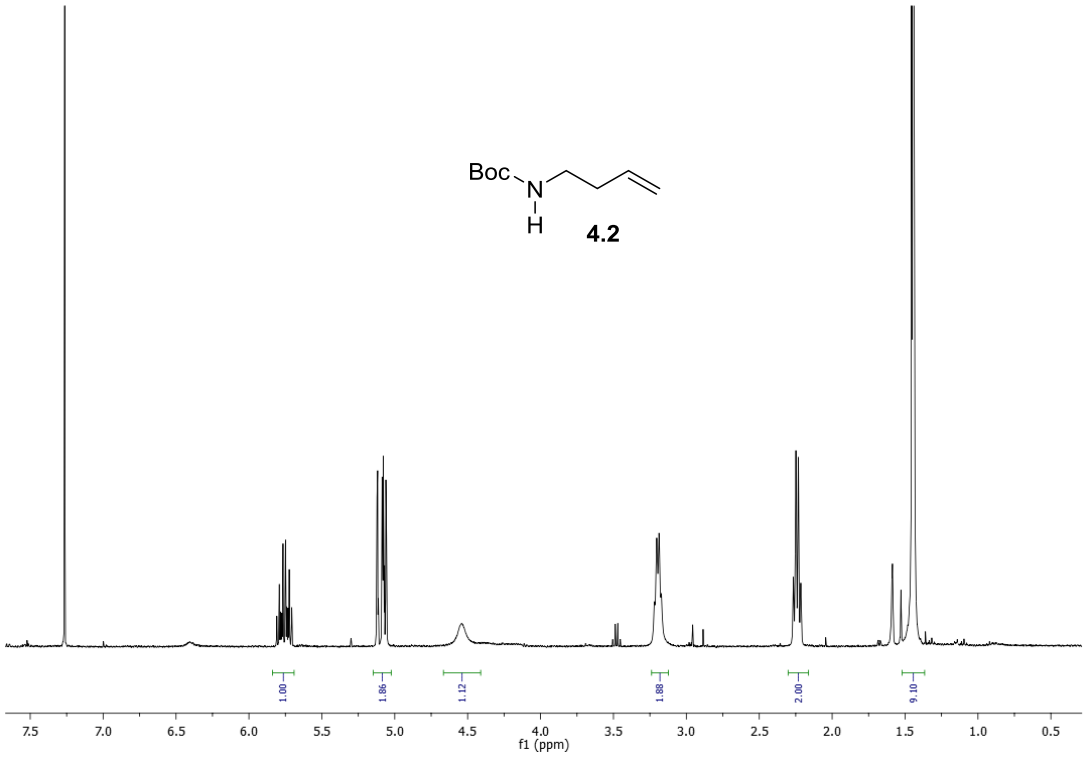


[160] Kan, T.; Cheung, M.; Fukuyama, T. *Synlett*, **1999**, *8*, 1301-1303.

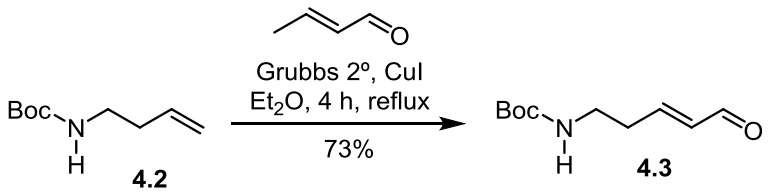
tert-Butyl But-3-en-1-ylcarbamate (4.2)



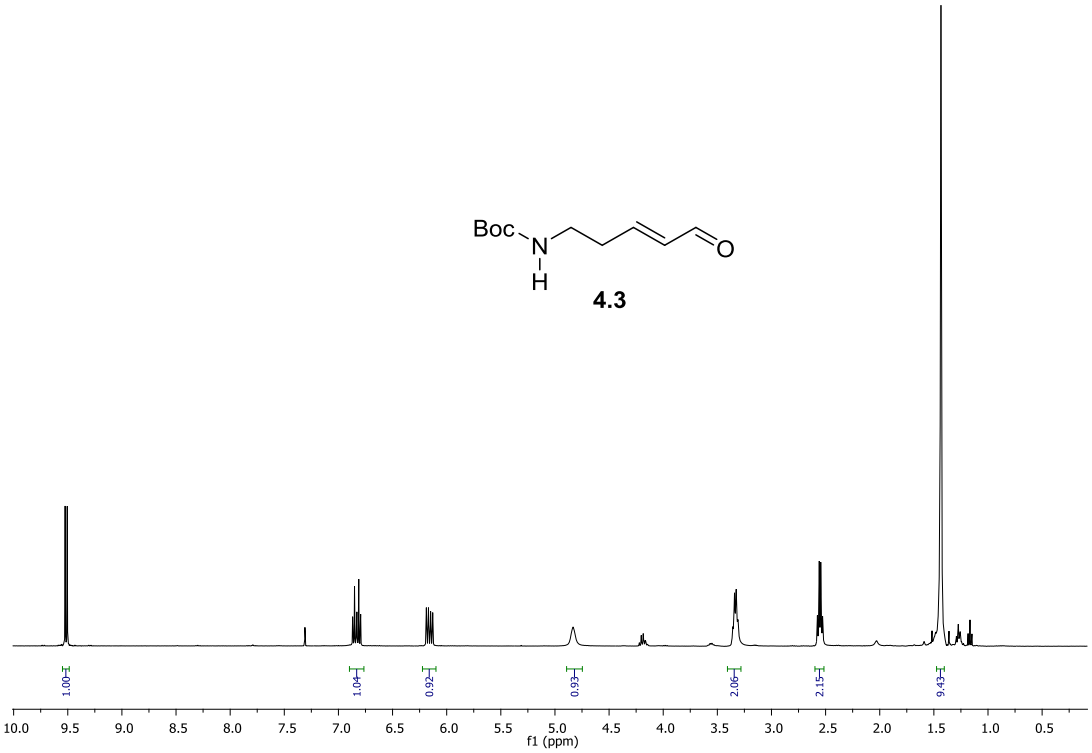
This product was prepared according to a literature procedure[160] using *tert*-butyl but-3-en-1-ylcarbamate (670 mg, 1.72 mmol) in DMF (13 mL), added $LiOH·H_2O$ (505 mg, 12.03 mmol), and mercaptoacetic acid (475 mg, 5.16 mmol). After standard workup purification by column chromatography (5→10→25→50% EtOAc/hexane) gave **4.2** (306 mg, 87%); ^1H NMR (400 MHz, COSY) δ 1.44 (s, 3H, CH_3), 2.24 (q, *J* = 13.6, 6.8 Hz, 2H, H-2), 3.20 (dd, *J* = 12.8, 6.4 Hz, 2H, H-1), 4.54 (br, 1H, NH), 5.05-5.13 (m, 2H, H-4), 5.76 (ddt, *J* = 17.1, 10.2, 6.8, 1H, H-3).



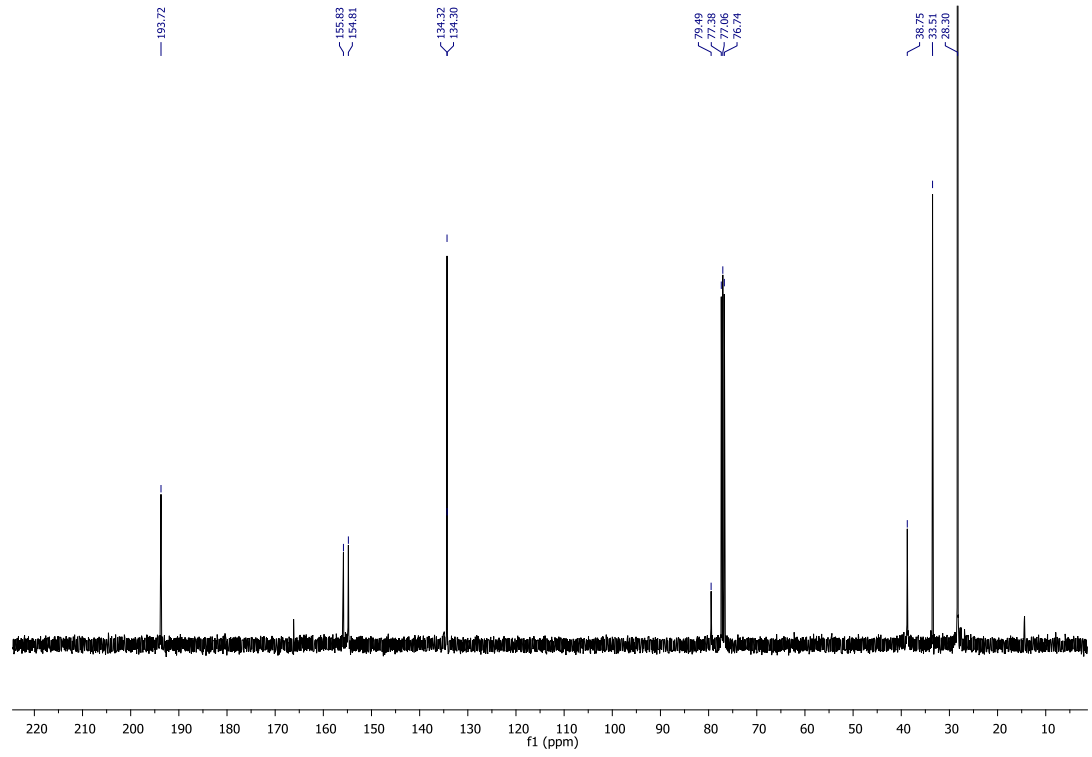
(*E*)-*tert*-Butyl-(5-Oxopent-3-en-1-yl)carbamate. (4.3)



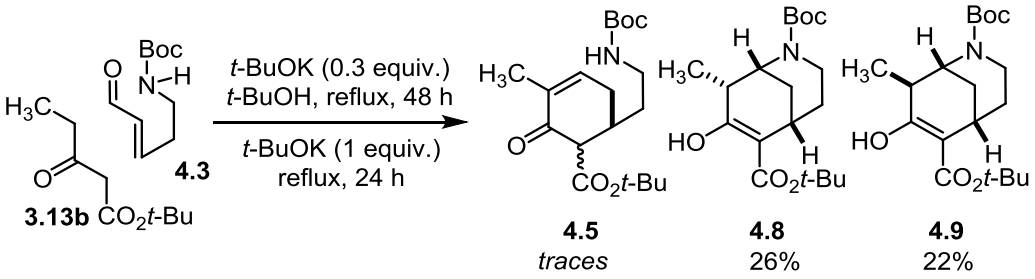
To alkene **4.2** (100 mg, 0.584 mmol) and crotonaldehyde (205 mg, 2.92) in diethyl ether (7 mL), was added Grubbs-2 catalyst (6 mg, 0.007 mmol), and CuI (2 mg, 0.011 mmol) under an Ar atmosphere. The solution was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (0→25→50→100% EtOAc/hexane) gave **4.3** (85 mg, 73%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.44 (s, 9H, CH_3); 2.55 (qd, *J* = 10.8, 9.2, 2.0 Hz, 2H, H-2), 3.34 (dd, *J* = 8.4 Hz, 2H, H-1), 4.58 (br, 1H, NH), 6.16 (ddt, *J* = 14.4, 7.7, 1.6 Hz,1H, H-3), 6.82 (dt, J = 15.6, 6.9 Hz, 1H, H-3), 9.52 (d, *J* = 10.4 Hz, 1H, H-5). ^{13}C NMR (100 MHz, HSQC) δ 28.3, 33.5, 38.8, 79.5, 134.3, 154.8, 155.8, 193.7.


Boc
N
H
O
1.00
1.04
0.92
0.93
2.06
2.15
9.43
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

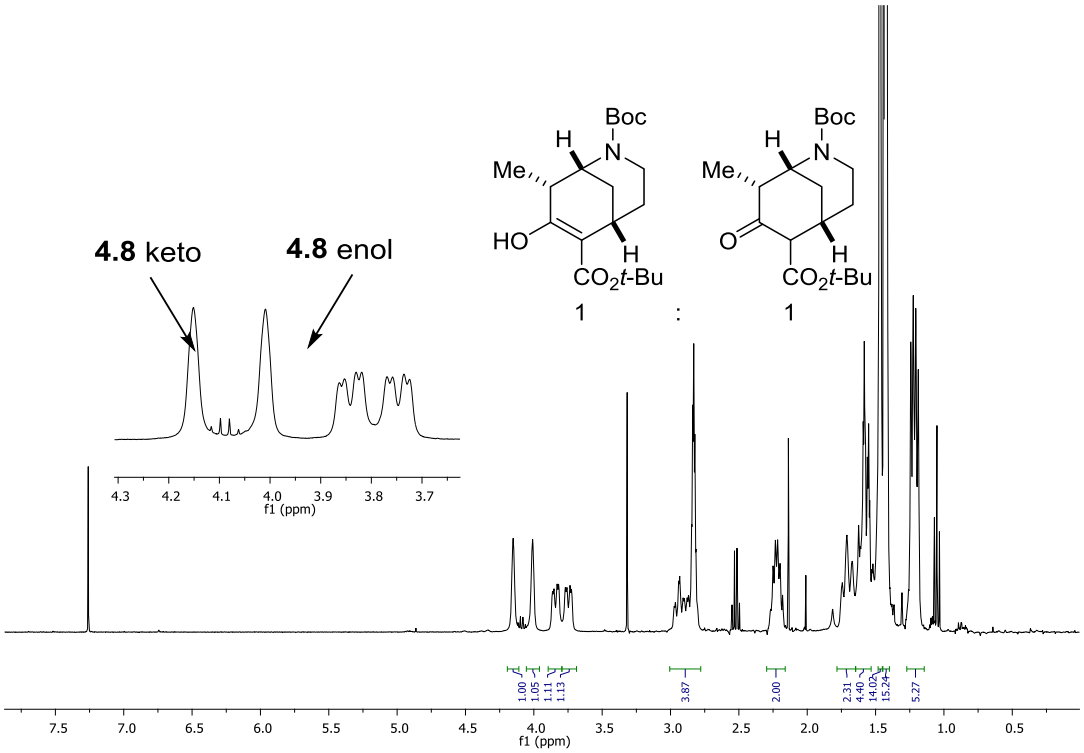
4.3

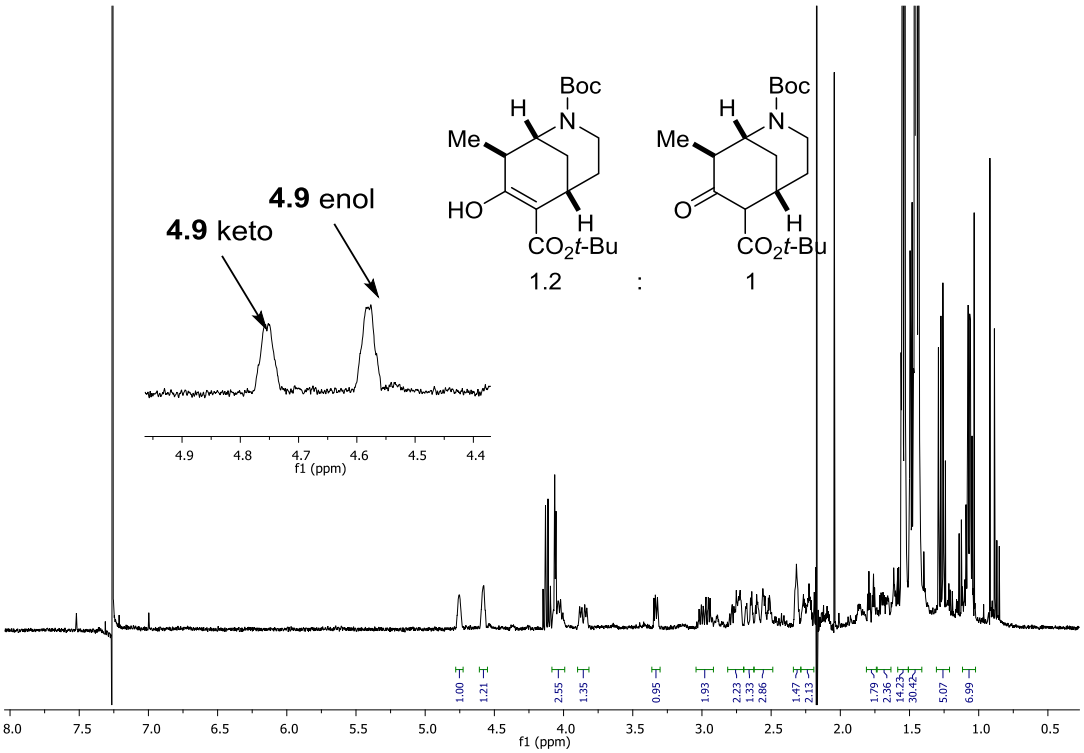

193.72
155.83
154.81
134.32
134.30
79.49
77.38
77.06
76.74
38.75
33.51
28.30
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

Aza-Michael cyclisation to the thermodynamic morphan ring structure.

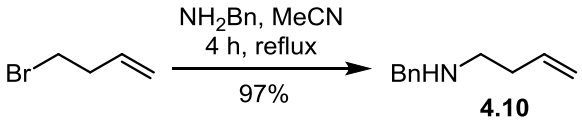


A solution of enal **4.3** (350 mg, 1.76 mmol) and β-keto ester **3.13b** (311 mg, 1.76 mmol) in *t*-BuOH (47 mL/mmol) was added *t*-BuOK (64.5 mg, 0.528 mmol) and stirred at reflux for 48 h. After this time a further equivalent of *t*-BuOK was added (198 mg, 1.76 mmol) and the mixture was refluxed for a further 24 h. After evaporation of the solvent the residue was directly submitted to flash chromatography (0→25→50→100% EtOAc/hexane) to give **4.8** and **4.9** as a brown oil (347 mg, 48%). **Data for 4.8:** ^{1}H NMR (400 MHz, COSY) δ 1.20/1.23 (2d, *J* = 7.2/6.8 Hz, 6H, CH_3), 1.43/1.47 (2s, 36H, CH_3), 1.57 (dt, 4H, H-9), 1.71 (t, *J* = 14 Hz, 2H, H-4), 2.18-2.27 (m, 2H, H-8), 2.85-2.91 (m, 2H, H-5), 2.97 (2td, *J* = 12.8, 3.6 Hz, 2H, H-3), 3.78 (dd, *J* = 13.2, 4.4 Hz, 1H, H-3), 3.87 (dd, *J* = 13.2, 4.0 Hz, 1H, H-3), 4.04 (br, 1H, H-1), 4.18 (br, 1H, H-1); **Data for 4.9:** ^{1}H NMR (400 MHz, COSY) δ 1.25/1.28 (2d, *J* = 7.2/6.8 Hz, 6H, CH_3), 1.54/1.55 (2s, 36H, CH_3), 1.65-1.72 (m, 4H, H-9), 1.76 (2t, *J* = 3.6 Hz, 1H, H-4) 1.79 (t, *J* = 3.6 Hz, 2H, H-4), 2.21-2.27 (m, 2H, H-8), 2.50-2.79 (m, 5H), 3.04-2.94 (m, 2H, H-3, H-5), 3.35-3.32 (m, 1H, H-3), 3.86 (dd, *J* = 14.8, 6.4 Hz, 1H, H-3), 4.07-4.01 (m, 1H, H-3), 4.58 (br, 1H, H-1), 4.75 (br, 1H, H-1).


4.8 keto
4.8 enol
Boc
H
N
Me
HO
H
CO2t-Bu
1 : 1
f1 (ppm)

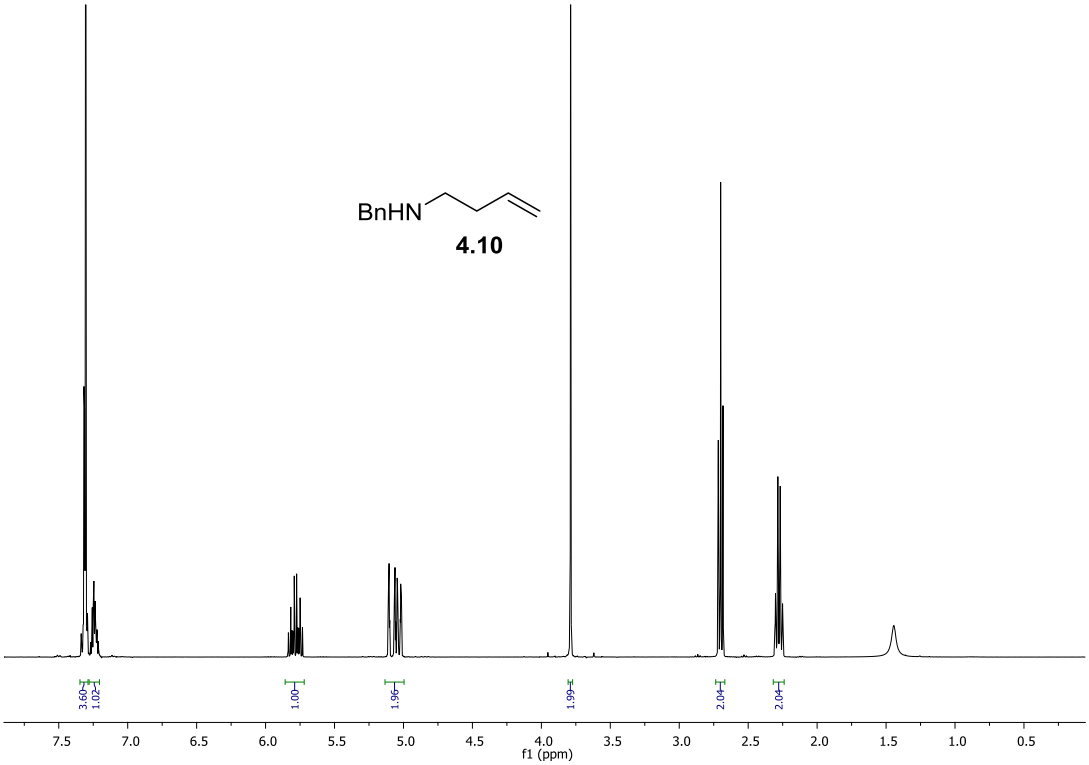

4.9 keto
4.9 enol
Boc
H
N
Me
HO
H
CO2t-Bu
1.2 : 1
f1 (ppm)

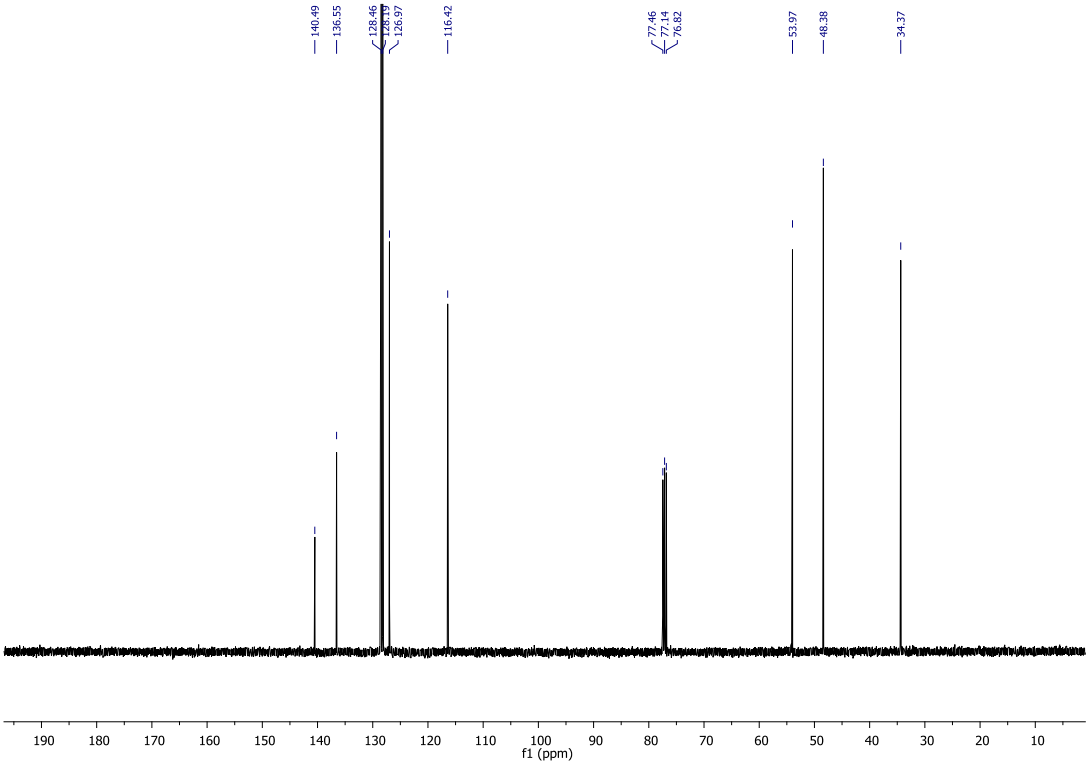
N-Benzylbut-3-en-1-amine. (4.10)[161]



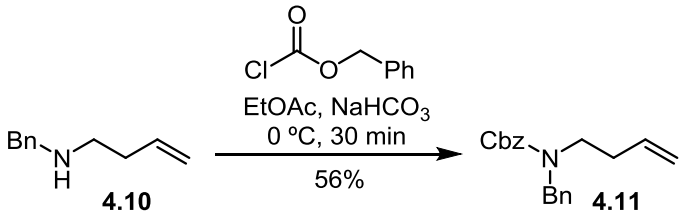
To a solution of 4-bromobutene (0.8 mL, 7.4 mmol, 1 equiv.) in acetonitrile (15 mL) was added benzylamine (2.4 mL, 22.2 mmol, 3 equiv.). The mixture was heated at reflux for 4h. After cooling to room temperature, a saturated $NaHCO_3$ solution (15 mL) was added and the organic layer was extracted with diethyl ether (3 x 15 mL). The combined extracts were dried (Na_2SO_4) concentrated *in vacuo* and purified by column chromatography (0→10→25→50% EtOAc/hexane) to give **4.10** as a yellow oil in 97% yield (1.16 g); ^{1}H NMR (400 MHz, COSY) δ 2.28 (qt, *J* = 8.0, 6.8, 2.4, 1.2 Hz, 2H, H-2), 2.70 (t, *J* = 6.8 Hz, 2H, H-1), 3.79 (s, 2H, CH_2Ph), 5.03 (dq, *J* = 4.0, 2.8, 2.0, 1.2 Hz, 1H, H-4), 5.08 (dq, *J* = 4.8, 3.2, 1.6 Hz, 1H, H-4) 5.78 (ddt, *J*= 14.0, 10.4, 6.8 Hz, 1H, H-3) 7.24 (m, 1H, Ph), 7.31 (m, 4H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 34.4 (C-2), 48.4 (C-1), 54.0 (CH_2Ph), 116.4 (C-4), 127.0 (Ph), 128.2 (Ph), 128.5 (Ph), 136.6 (C-3), 140.5 (Ph) HRMS calcd for $C_{11}H_{16}N$ $[M+H]^+$ 162.1277, found 162.1278.

[161] Bantreil, X.; Prestat, G.; Moreno, A.; Madec, D.; Fristrup, P.; Norrby, P.; Pregosin, P. S.; Poli, G.; *Chem. A Eur. J.* **2011**, *10*, 2885–2896.

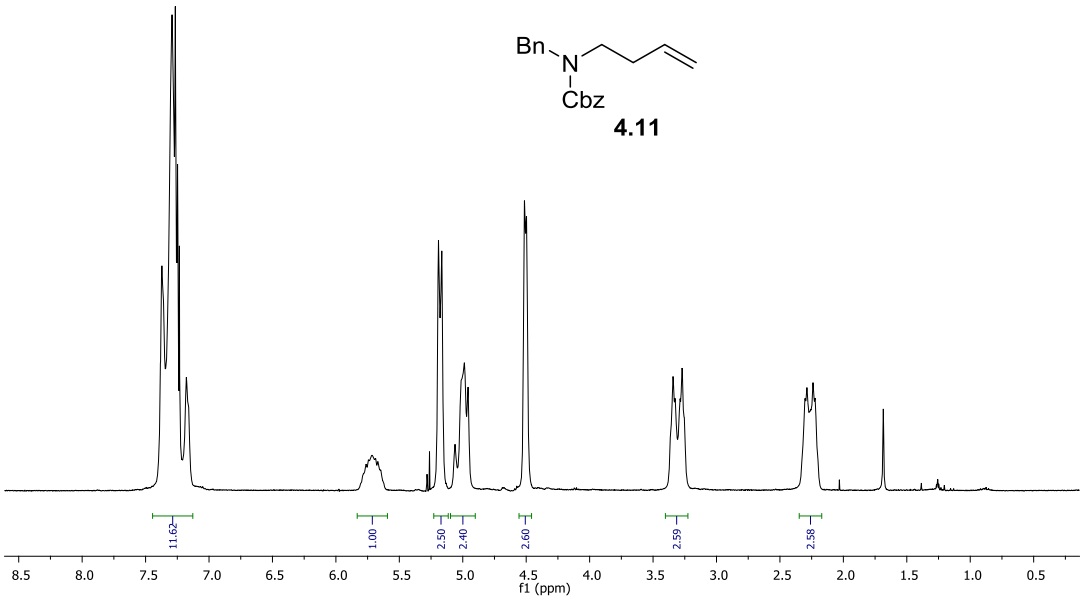

BnHN
4.10
3.60
1.02
1.00
1.96
1.99
2.04
2.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

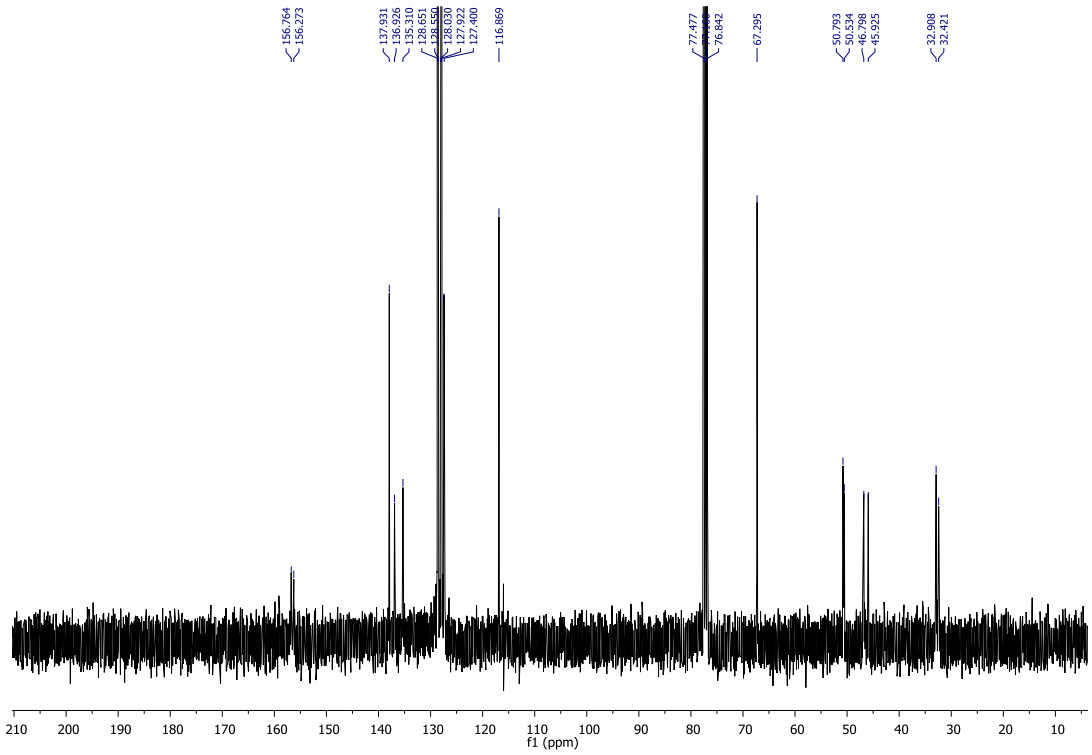

140.49
136.55
128.46
128.19
126.97
116.42
77.46
77.14
76.82
53.97
48.38
34.37
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Benzyl benzyl(but-3-en-1-yl)carbamate. (4.11)

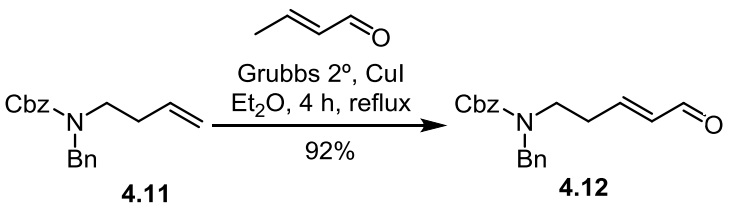


To a vigorously stirred biphasic mixture of *N*-benzylbut-3-en-1-amine (100 mg, 0.620 mmol) in 1.5 mL EtOAc and 1.0 mL saturated aqueous $NaHCO_3$ at 0 °C was added benzyl chloroformate (0.1 mL, 0.806 mmol) dropwise. After stirring for 40 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed with 1N HCl, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (0→10→25→50% EtOAc/hexane) gave **4.11** (102 mg, 56%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 2.22-2.30 (m, 2H, H-2), 3.27-3.34 (m, 2H, H-1), 4.51 (bs, 2H, CH_2), 4.96-5.19 (m, 2H, H-4), 5.18 (bs, 2H, CH_2), 5.67-5.76 (m, 1H, H-3), 7.18-7.37 (m, 10H, 2Ph); ^{13}C NMR (100 MHz, HSQC) δ 32.3 (C-2), 46.7 (C-1), 50.7 (CH_2Ph), 67.2 (CH_2Ph), 116.8 (C-4), 127.8 (C-Ph), 127.9 (Ph), 128.4 (Ph), 128.5 (Ph), 135.2, 136.8 (C-3), 137.8 (C-Ph), 156.7 (CO); HRMS calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$ 254.0845, found 254.0848.


Bn
N
Cbz
4.11
11.62
1.00
2.50
2.40
2.60
2.59
2.58
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

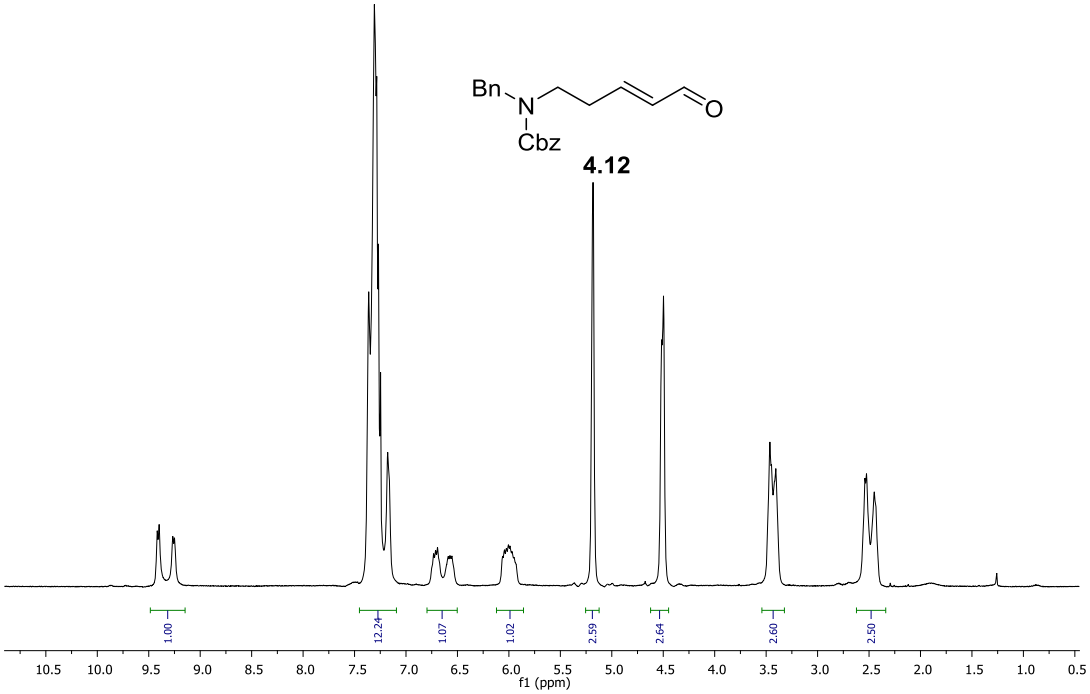

156.764
156.273
137.931
136.926
135.310
128.651
128.550
128.030
127.922
127.400
116.869
77.477
76.842
67.295
50.793
50.534
46.798
45.925
32.908
32.421
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

_N_-Benzyl-_N_-(Benzyloxycarbonyl)-5-Oxopent-3-en-1-yl. (4.12)



4.11 **4.12**

To alkene **4.11** (110 mg, 0.372 mmol) and crotonaldehyde (78 mg, 1.12 mmol) in diethyl ether (4 mL), was added Grubbs-2 catalyst (8 mg, 9.3 μmol), and CuI (3 mg, 14.8 μmol) under an Ar atmosphere. The solution was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (0→25→50→100% EtOAc/hexane) to give **4.12** (110 mg, 92%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 2.49 (dd, *J* = 6.4 Hz, 2H, H-4), 3.41-3.46 (m, 2H, H-5), 4.50 (bs, 2H, CH_2), 5.18 (bs, 2H, CH_2), 5.97-6.06 (m, 1H, H-3), 6.64 (dt, *J* = 15.2, 7.6 Hz, 1H, H-2), 7.18-7.36 (m, 10H, 2Ph); 9.33 (dd, *J* = 7.6 Hz, 1H, CHO); ^{13}C NMR (100 MHz, HSQC) δ 31.8 (C-4), 45.8 (C-5), 51.0 (CH_2Ph), 67.5 (CH_2Ph), 127.4 (C-Ph), 127.7 (C-Ph), 128.0 (C-Ph), 128.1 (C-Ph), 128.5 (C-Ph), 128.7 (C-Ph), 134.3 (C-Ph), 136.5 (C-2), 137.4 (C-Ph), 154.6 (C-3), 193.7 (CO); HRMS calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$ 254.0845, found 254.0848.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O
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1.07
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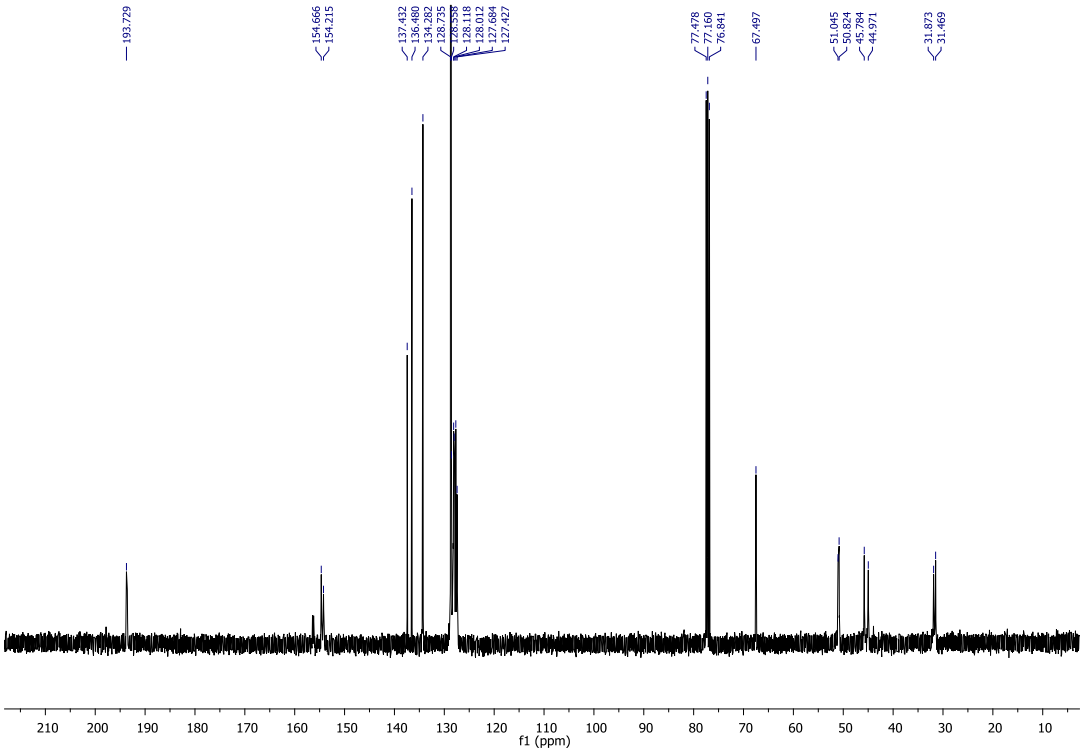
2.60
2.50
f1 (ppm)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154.215
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134.282
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128.558
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127.427
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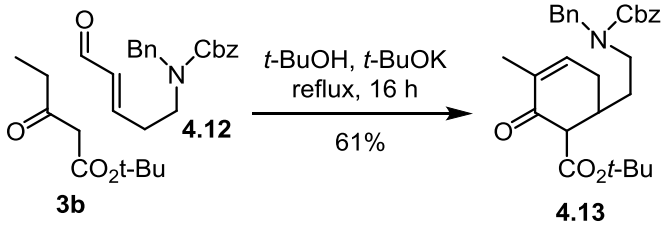
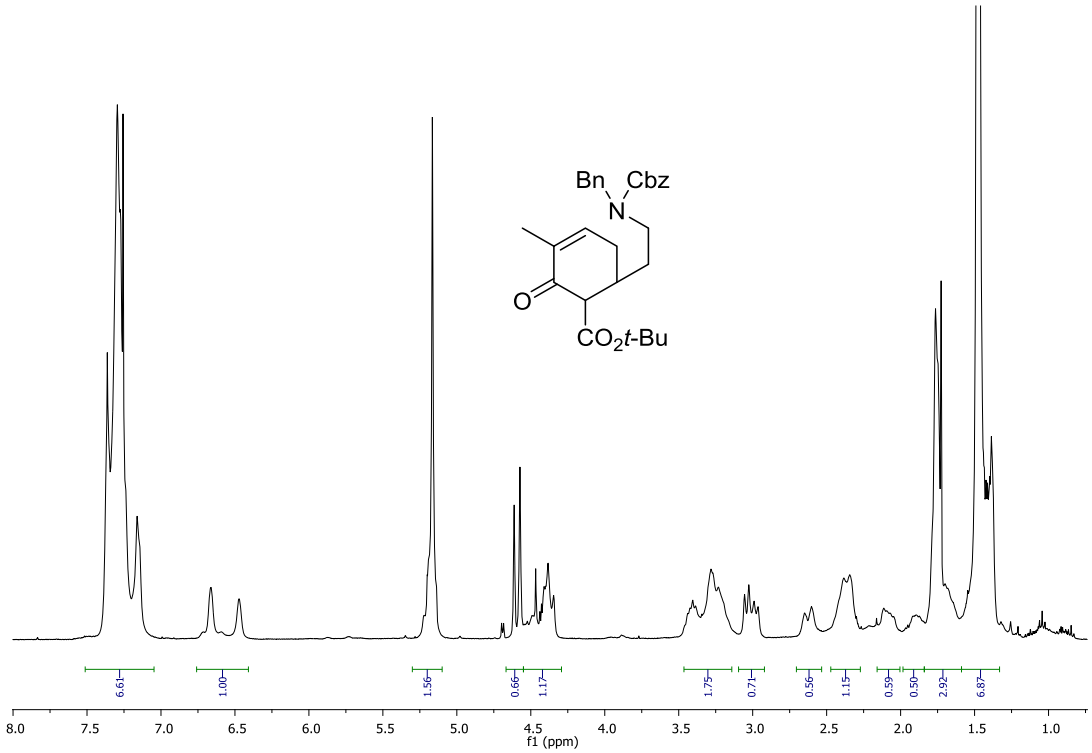
77.160
76.841
67.497
51.045
50.824
45.784
44.971
31.873
31.469
f1 (ppm)

tert-Butyl-6-(2-(Benzyl((benzyloxy)carbonyl)amino)ethyl)-3-methyl-2-oxocyclohex-3-ene-1-carboxylate. (4.13)



To a solution of β-keto ester **3b** (53 mg, 0.309 mmol) in *tert*-butanol (15 mL) was added enal **4.12** (100 mg, 0.309 mmol). After stirring for 5 min at room temperature the solution was cooled to 0 ºC and potassium *tert*-butoxide (2 mg, 0.019 mmol) was added. The reaction mixture was stirred for 30 min at room temperature and a further portion of potassium *tert*-butoxide (8 mg, 0.074 mmol) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature and quenched by the addition of sat NH_4Cl (aq) (1.5 mL/mmol), diluted with Et_2O (8.6 mL/mmol) and the phases separated, brine (2 x 3 mL/mmol), dried and concentrated *in vacuo*. Purificacion by column chromatography (10→25→50% EtOAc/hexane) gave **4.13** (90 mg, 61%); ^{1}H NMR (400 MHz, COSY) δ 1.39-1.55 (m, 1H, H-1'), 1.48 (s, 9H, CH_3), 1.72-1.74 (m, 1H, H-1'), 1.76 (s, 3H, CH_3), 1.87-1.93 (m, 1H, H-4), 2.05-2.11 (m, 1H, H-4), 2.30-2.38 (m, 1H, H-4), 2.60-2.65 (m, 1H, H-4), 3.01 (dd, J = 11.6 Hz, 1H, H-6), 3.23-3.46 (m, 2H, H-2'), 4.35-4.47 (m, 1H, CH_2), 4.59 (d, *J* = 15.6 Hz, 1H, CH_2), 5.17 (s, 2H, CH_2), 6.47 (br, 1H, H-3), 6.66 (br, 1H, H-3), 7.16-7.36 (m, 10H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 15.8 (CH_3), 28.0 (CH_3), 30.0 (C-4), 31.5 (C-1'), 35.3 (C-5), 43.4 (C-2'), 49.5 (CH_2), 60.9 (C-6), 67.3 (CH_2), 81.6 (C), 127.3, 127.4, 127.8, 127.9, 128.1, 128.5, 128.6, 134.9, 136.6, 137.4, 144.2 (C-3), 156.4 (CO), 169.4 (CO), 195.2 (C-1). HRMS calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$ 254.0845, found 254.0848.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O
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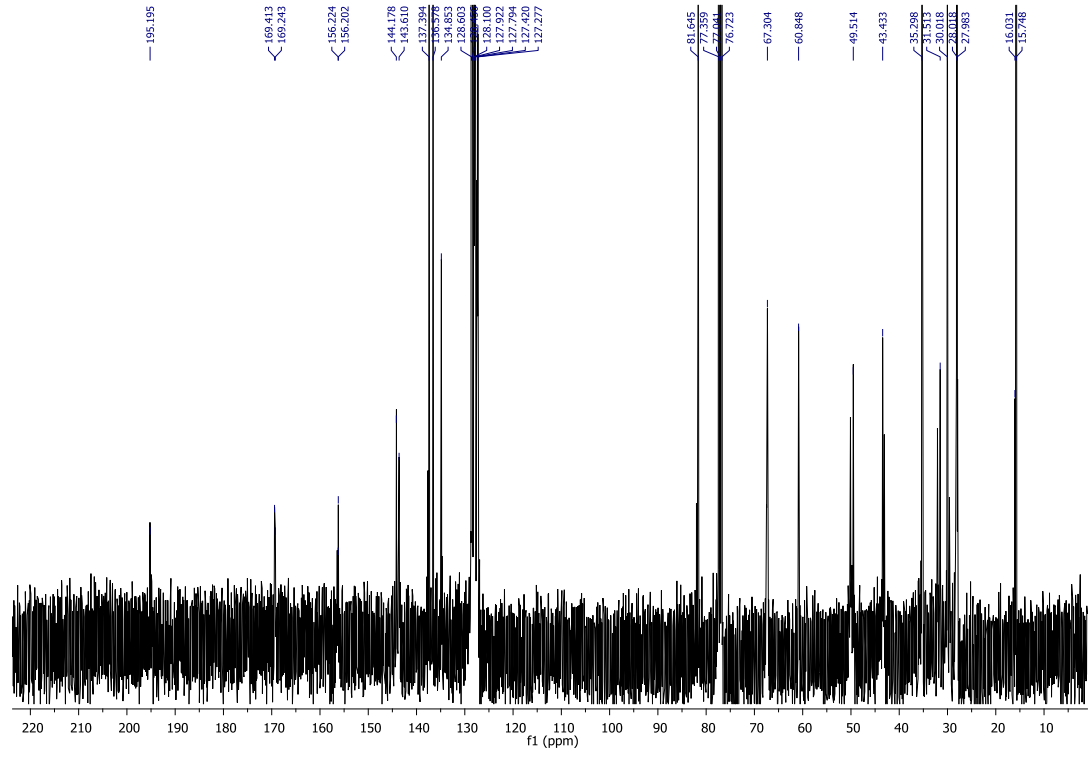
0.56
1.15
0.59
0.50
2.92
6.87
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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156.202
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136.378
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128.100
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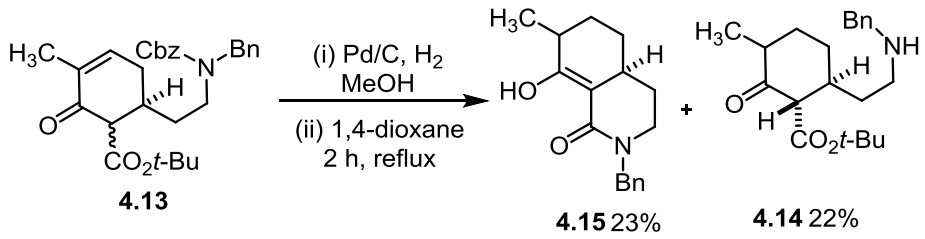
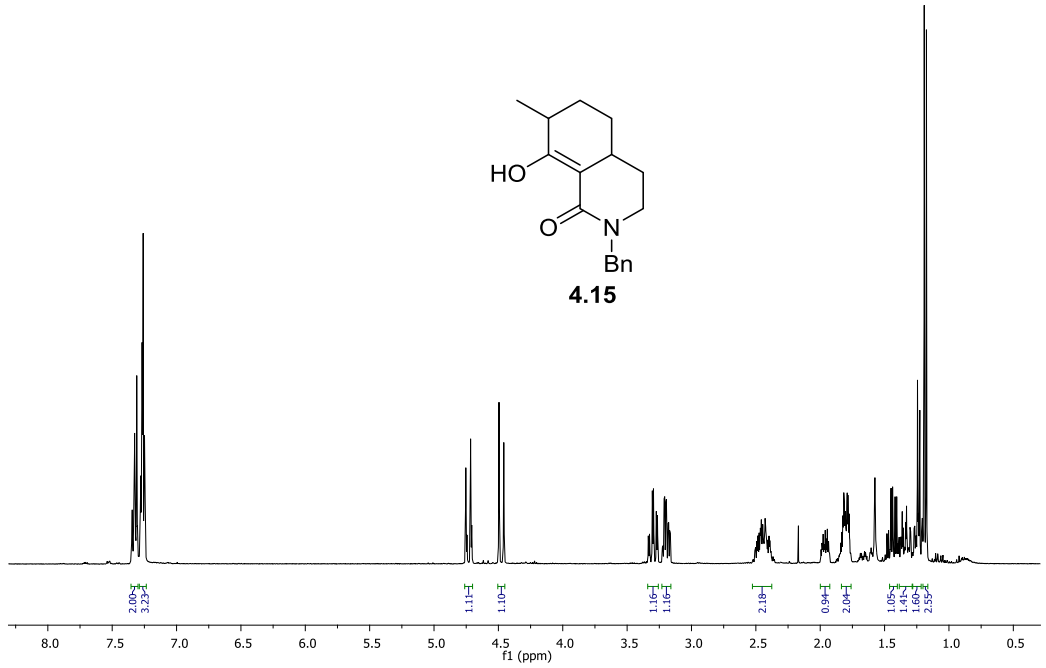
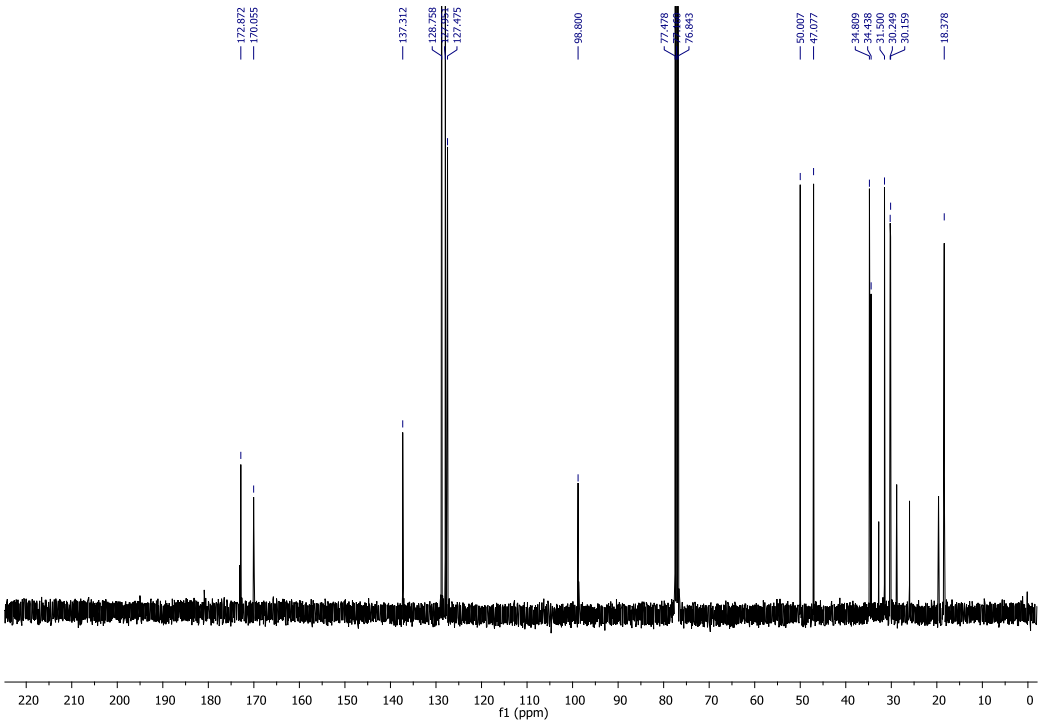
127.794
127.430
127.277
81.645
77.359
77.041
76.723
67.304
60.848
49.514
43.433
35.298
31.513
30.018
28.018
27.983
16.031
15.748
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(4a*S*)-2-Benzyl-8-hydroxy-7-methyl-3,4,4a,5,6,7-hexahydroisoquinolin-1(2*H*)-one. (4.15)

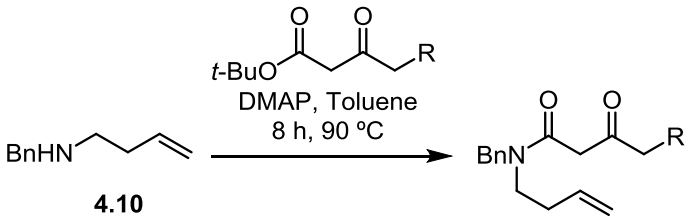


To a stirred solution of the mixture of **4.13** (90 mg, 0.188 mmol) in MeOH (1.5 mL) was added Pd/C (20% w/w, 18 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 for 3 h. The mixture was diluted with CH_2Cl_2 (≈ 30 mL), filtered through a pad of celite, washed through with CH_2Cl_2 and the filtrate was concentrated in *vacuo*. The crude product was essentially pure and was used in the next step without further purification. A solution of **4.14** in dioxane (5.5 mL) was stirred at reflux for 2 h. Concentration *in vacuo* and purification by column chromatography (0→25→50→100% EtOAc/hexane) gave **4.15** (12 mg, 23%) and **4.14** (14 mg, 22%) as yellow oils. **Data for 4.15:** ^{1}H NMR (400 MHz, COSY) δ 1.18 (d, *J* = 6.8 Hz, 3H, CH_3), 1.20-1.27 (masket, 1H, H-4), 1.34 (ddd, *J* = 13.2, 11.2, 2.8 Hz, 1H, H-5), 1.43 (dd, *J* = 12.8, 4.8 Hz, 1H, H-4), 1.78-1.83 (m, 2H, H-6), 1.93-1.99 (m, 1H, H-5), 2.38-2.51 (m, 2H, H-4a, H-7), 3.19 (ddd, *J* = 12.4, 7.2, 5.0 Hz, 1H, H-3ax), 3.30 (td, *J* = 12.4, 3.6 Hz, 1H, H-3eq), 4.48 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 4.73 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 7.24-7.28 (m, 3H, Ph), 7.31-7.35 (m, 2H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 18.4 ($ArCH_3$), 30.2 (C-4), 30.2 (C-6), 31.5 (C-5), 34.4 (C-7), 34.8 (C-4a), 47.1 (C-3), 50.0 (CH_2Ph), 98.8 (C-8a), 127.5 (*o*-Ph), 128.0 (*m*-Ph), 128.8 (*p*-Ph), 137.3 (*ipso*-Ph), 170.1 (C-8), 172.9 (CO); HRMS calcd for $C_{17}H_{22}NO_2$ $(M+H)^+$ 272.1589, found 272.1596. **Data for 4.14:** ^{1}H NMR (400 MHz, COSY) δ 1.03 (d, *J* = 6.5 Hz, 3H, CH_3), 1.48 (s, 1H, CH_3), 1.56-1.68 (m, 2H), 1.97 (dt, *J* = 6.6 4.8 Hz, 1H), 2.04 (ddd, *J* = 11.4, 5.4, 2.5 Hz, 1H), 2.22 (ddd, *J* = 17.5, 10.7, 6.4 Hz, 1H), 2.35 (dt, *J* = 12.6, 6.1 Hz, 1H), 2.62-2.75 (m, 3H), 3.03 (dd, *J* = 12.2. 1.0 Hz, 1H), 3.77 (d, *J* = 7.1 Hz, 2H, CH_2Bn), 7.20-7.36 (m, 10H); ^{13}C NMR (100 MHz, HSQC) δ 14.3 (CH_3), 28.1 (CH_3), 30.0 (C-5), 34.3 (C-1'), 35.7 (C-6), 40.1 (C-3), 45.0 (C-4), 46.5 (C-2'), 53.9 (CH_2), 64.4 (C-2), 81.3 (C), 126.9 (*o*-Ph), 128.1 (*m*-Ph), 128.4 (*p*-Ph), 140.3 (*ipso*-Ph), 169.2 (CO), 208.0 (C-1); HRMS calcd for $C_{23}H_{30}N_2O_2S$ $(M+H)^+$ 399.2101, found 399.2097.





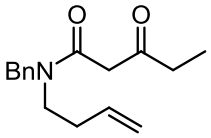
General Procedure A: Synthesis of β-keto amide.



4.10

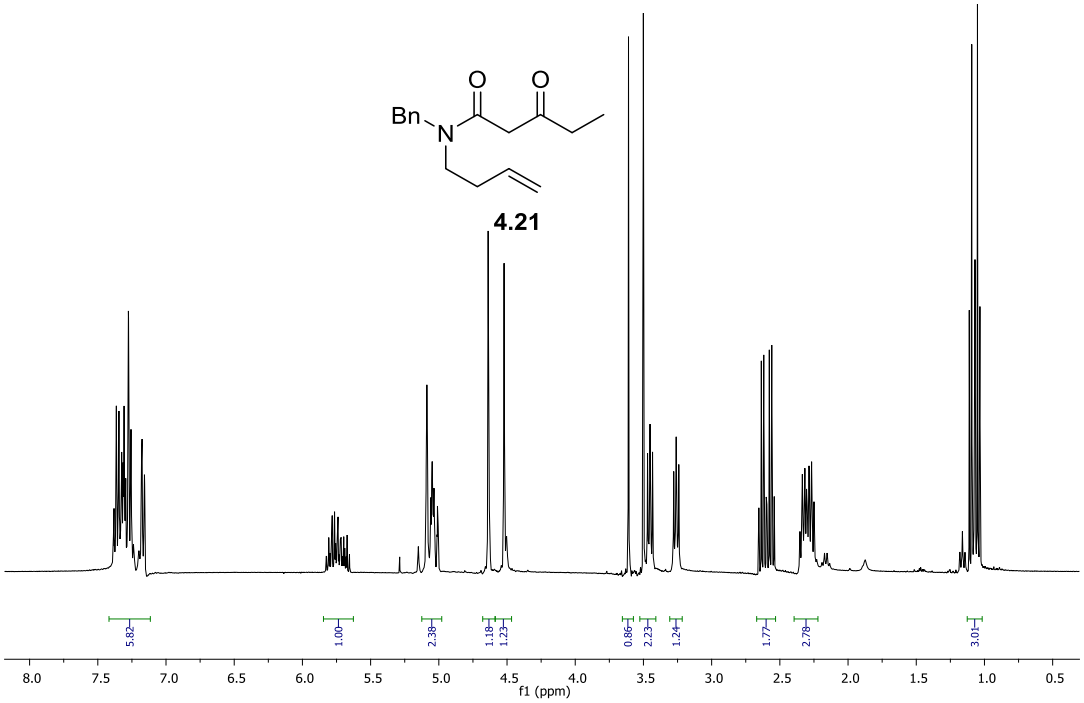
To a mixture of N-benzylbut-3-en-1-amine (1 equiv) and β-keto ester (2 equiv) in toluene (2.5 mL/mmol) was added 4-DMAP (0.3 equiv). The mixture was stirred at 80 ºC under Ar for 8 h. After cooling to room temperature, the solvent was removed *in vacuo*. Purification by column chromatography (EtOAc/hexane gradient) gave the corresponding β-keto amide.

_N_-Benzyl-_N_-(But-3-en-1-yl)-3-oxopentanamide. (4.21)



4.21

To a mixture of *N*-benzylbut-3-en-1-amine **4.10** (400 mg, 2.48 mmol) and *t*-butyl-3-oxopentanoate (879 mg, 4.96 mmol) in toluene (6.2 mL) was added 4-DMAP (91 mg, 0.744 mmol). The mixture was stirred at 80 ºC under Ar for 8 h. After cooling to room temperature, the solvent was removed *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave keto amide **4.21** (585 mg, 91%) as an orange oil. ***Rotamer A***. ^{1}H NMR (400 MHz, COSY) δ 1.04 (t, *J* = 4.0 Hz, 3H, H-5), 2.23-2.34 (m, 2H, H-2'), 2.61 (q, *J* = 7.2 Hz, 2H, H-4), 3.24 (t, *J* = 7.2 Hz, 2H, H-1'), 3.49 (s, 2H, H-2), 4.51 (s, 2H, CH_2Ph), 4.99-5.08 (m, 2H, H-4'), 5.64- 5.81 (m, 1H, H-3') 7.09 (d, *J* = 8.4 Hz, 1H, Ph), 7.22-7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 7.68 (C-5), 32.8 (C-2'), 36.4 (C-4), 47.2 (C-1'), 49.0 (C-2), 52.0 (CH_2Ph), 117.9 (C-4'), 127,0 (Ph), 134.0 (C-3'), 167.4 (C-3), 205.2 (C-1); ***Rotamer B*****:** ^{1}H NMR (400 MHz, COSY) δ 1.08 (t, *J* = 8.0 Hz, 3H, H-5), 2.23-2.34 (m, 2H, H-2'), 2.55 (q, *J* = 7.6 Hz, 2H, H-4), 3.44 (t, *J* = 7.2 Hz, 2H, H-1'), 3.59 (s, 2H, H-2), 4.62 (s, 2H, CH_2Ph), 4.99-5.08 (m, 2H, H-4'), 5.64-5.81 (m, 1H, H-3'), 7.09 (d, *J* = 8.4 Hz, 1H, Ph), 7.22-7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 7.60 (C-5), 32.0 (C-2'), 36.5 (C-4), 45.9 (C-1'), 48.2 (CH_2Ph), 48.7 (C-2), 116.9 (C-4'), 127,4 (C-Ph), 135.2 (C-3'), 167.1 (C-3), 205.1 (C-1); HRMS calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$ 260.1645, found 260.1650.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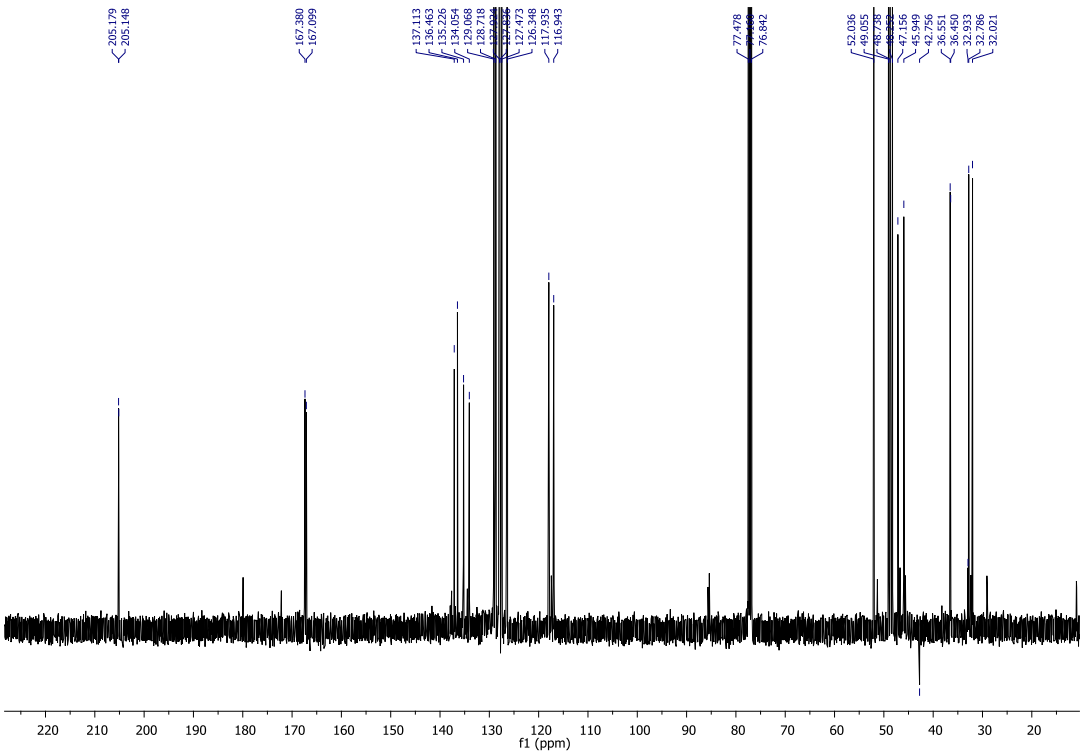
3.01
f1 (ppm)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77.478
76.842
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49.055
47.156
45.949
42.756
36.551
36.450
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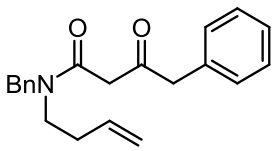
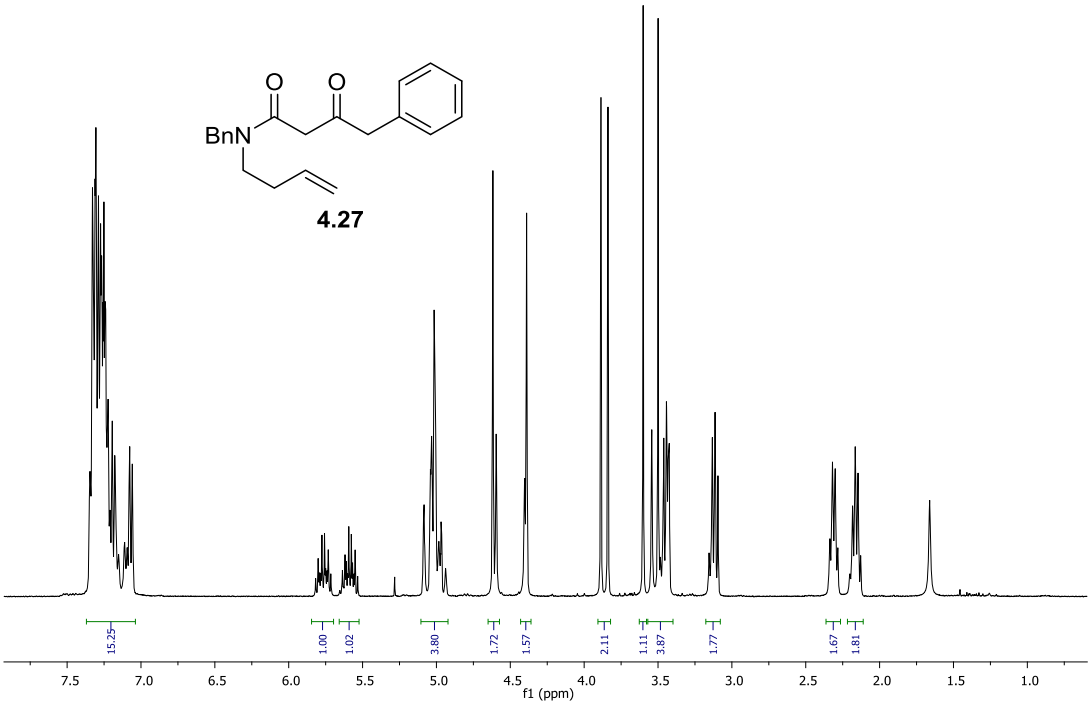
32.021
f1 (ppm)

N-Benzyl-*N*-(But-3-en-1-yl)-3-oxo-4-phenylbutanamide (4.27)



4.27

To a mixture of *N*-benzylbut-3-en-1-amine **4.10** (344 mg, 2.13 mmol), *t*-butyl-3-oxo-5-phenylpentanoate (1.00 g, 4.26 mmol) in toluene (5.3 mL) was added 4-DMAP (77 mg, 0.636 mmol). The mixture was stirred at 80 ºC under Ar for 8 h. After cooling to room temperature, the solvent was removed *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave keto amide **4.27** (0.685 g, 91%) as a yellow oil. ***Rotamer A*****:** ^{1}H NMR (400 MHz, COSY) δ 2.16 (q, *J* = 14.4, 7.2 Hz, 2H, H-2'), 2.16 (q, *J* = 9.2 Hz, 2H, H-1'), 3.50 (s, 2H, H-2), 3.84 (s, 2H, H-4), 4.40 (s, 2H, CH_2Ph), 5.01 (m, 2H, H-4'), 5.59 (m, 1H, H-3') 7.09 (m, 1H, Ph), 7.25 (m, 10H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 32.6 (C-2'), 46.7 (C-1'), 48.1 (C-2), 50.1 (C-4), 51.9 (CH_2Ph), 87.9, 117.8 (C-4'), 127,6 (Ph), 133.9 (C-3'), 167.1 (C-3), 202.2 (C-1); ***Rotamer B*****:** ^{1}H NMR (400 MHz, COSY) δ 2.31 (q, *J*= 7.2 Hz, 2H, H2'), 2.31 (m, 2H, H-1'), 3.60 (s, 2H, H-2), 3.89 (s, 2H, H-4), 4.54 (s, 2H, CH_2Ph), 5.01 (m, 2H, H-4'), 5.77 (m, 1H, H-3'), 7.09 (m, 1H, Ph), 7.25 (m, 10H, Ph); ^{13}C NMR (100 MHz, HSQC) δ 32.0 (C-2'), 46.0 (C-1'), 47.8 (C-2), 48.2 (CH_2Ph), 50.0 (C-4), 87.5, 116.9 (C-4'), 127,1 (C-Ph), 135.1 (C-3'), 166.8 (C-3), 202.1 (C-1); HRMS calcd for $C_{21}H_{24}NO_2$ $[M+H]^+$ 322.1802, found 322.1802.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O
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1.00
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1.67
1.81
7.5
7.0
6.5
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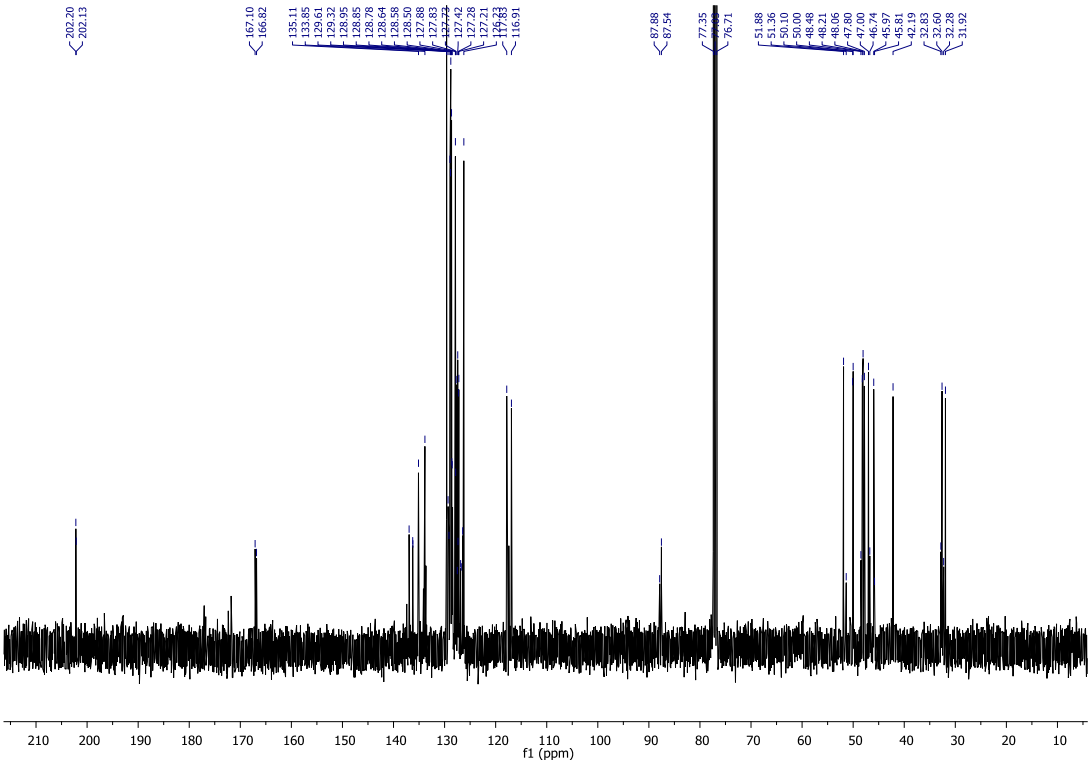
f1 (ppm)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50.00
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46.74
45.97
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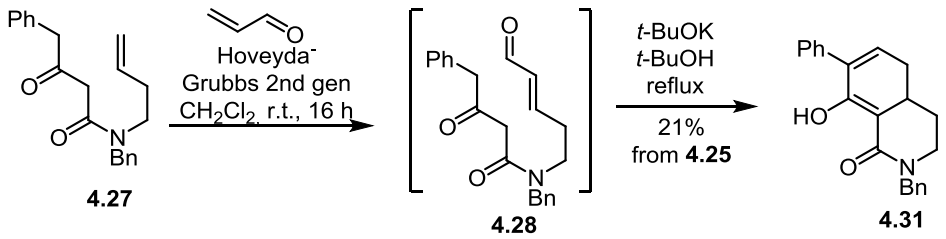
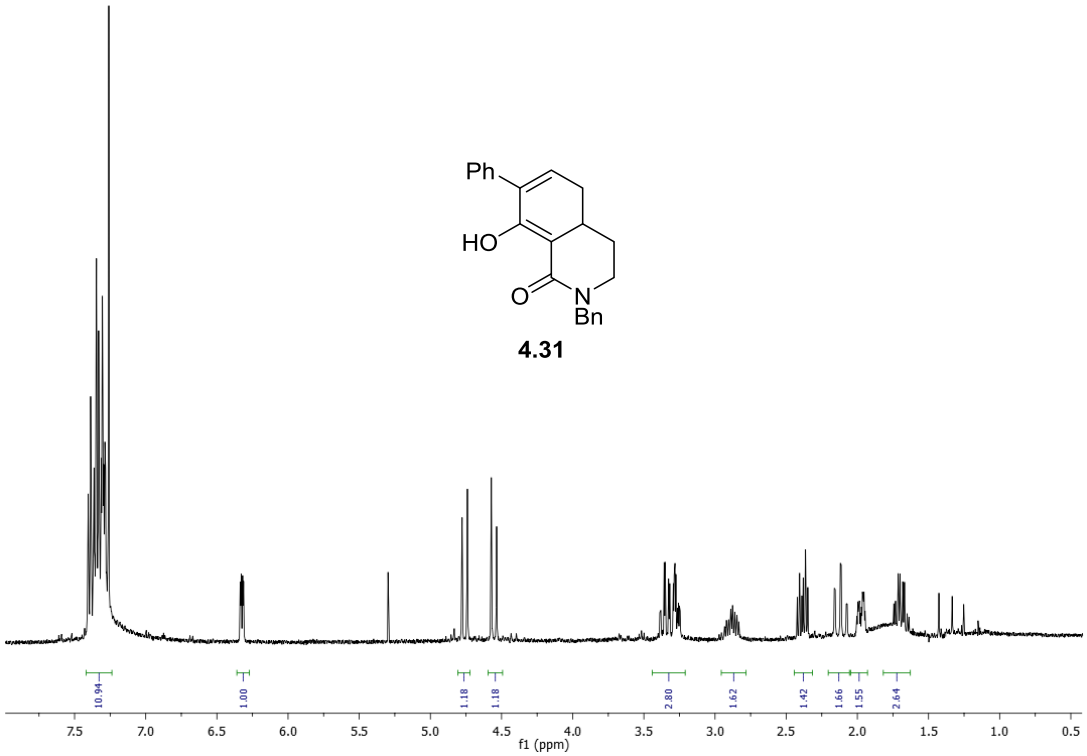
32.83
32.60
32.28
31.92
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

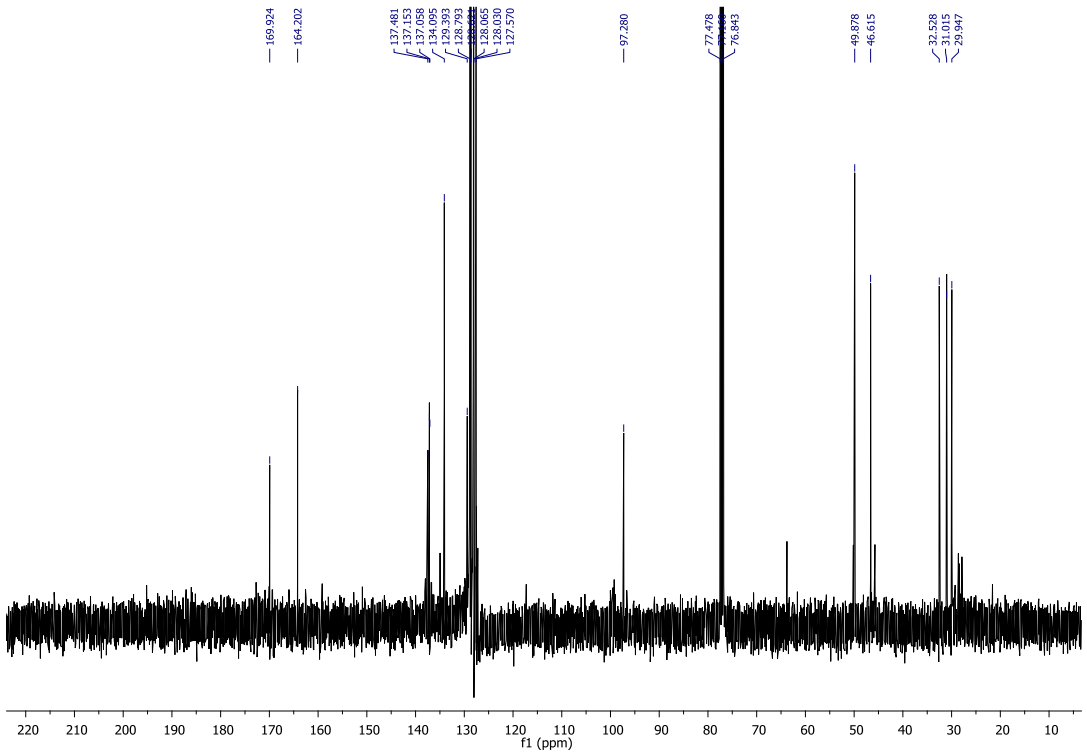
2-Benzyl-8-Hydroxy-7-phenyl-3,4,4a,5-tetrahydroisoquinolin-1(2*H*)-one. (4.31)



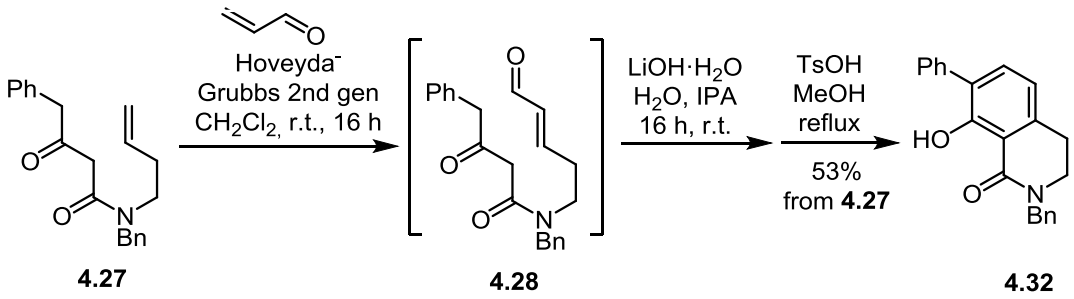
To a solution of β-keto amide **4.27** (250 mg, 0.777 mmol) in CH_2Cl_2 (8 mL) was added the Hoveyda-Grubbs 2nd generation catalyst (24 mg, 0.039 mmol) followed by acrolein (0.15 mL, 2.33 mmol). The resulting mixture was heated to reflux for 24 h, cooled to room temperature and the solvent removed *in vacuo*. The resulting crude oil was dissolved in *t*-BuOH (37 mL) and *t*-BuOK (26 mg, 0.233 mmol) was added. The resulting mixture was heated at reflux for 24 h, the reaction cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave **4.31** (54 mg, 21%) as a brown oil. ^{1}H NMR (400 MHz, COSY) δ 1.69 (dtd, *J* = 17.6, 12.8, 5.2 Hz, 1H, H-4), 1.98 (dq, *J* = 10.0, 7.2, 5.6, 2.8 Hz, 1H, H-4), 2.12 (td, *J* = 16.8, 2.4 Hz, 1H, H-5), 2.39 (dt, *J* = 16.6, 6.4 Hz, 1H, H-5), 2.83-2.93 (m, 1H, H-4a), 3.27 (ddd, *J* = 12.4, 7.2, 4.8, 2.4 Hz, 1H, H-3), 3.35 (td, *J* = 12.4, 3.2 Hz, 1H, H-3), 4.56 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 4.76 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 6.33 (dd, *J* = 6.8, 2.8 Hz, 1H, H-6), 7.25-7.42 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.8 (C-4), 30.9 (C-5), 32.4 (C-4a), 46.5 (C-3), 49.7 (CH_2Ph), 97.1 (C-8a), 127.4, 127.4, 127.9, 127.9, 128.5, 128.7, 129.3, 134.0, 136.9, 137.0, 137.3, 164.1 (C-8), 169.8 (C-1); HRMS calcd for $C_{22}H_{22}NO_2$ $[M+H]^+$ 332.1645, found 332.1647.


Ph
HO
O
N
Bn
10.94
1.00
1.18
1.18
2.80
1.62
1.42
1.66
1.55
2.64
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

4.31

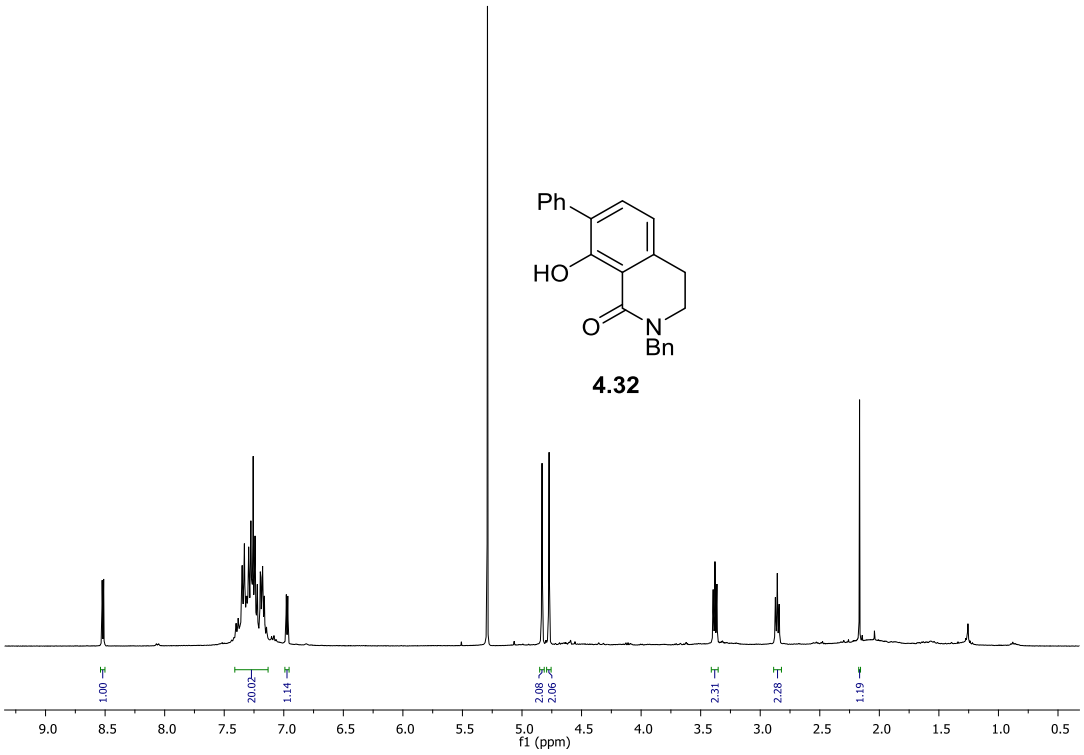

169.924
164.202
137.481
137.153
137.058
134.095
129.393
128.793
128.065
128.030
127.570
97.280
77.478
76.843
49.878
46.615
32.528
31.015
29.947
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2-Benzyl-8-Hydroxy-7-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one. (4.32)

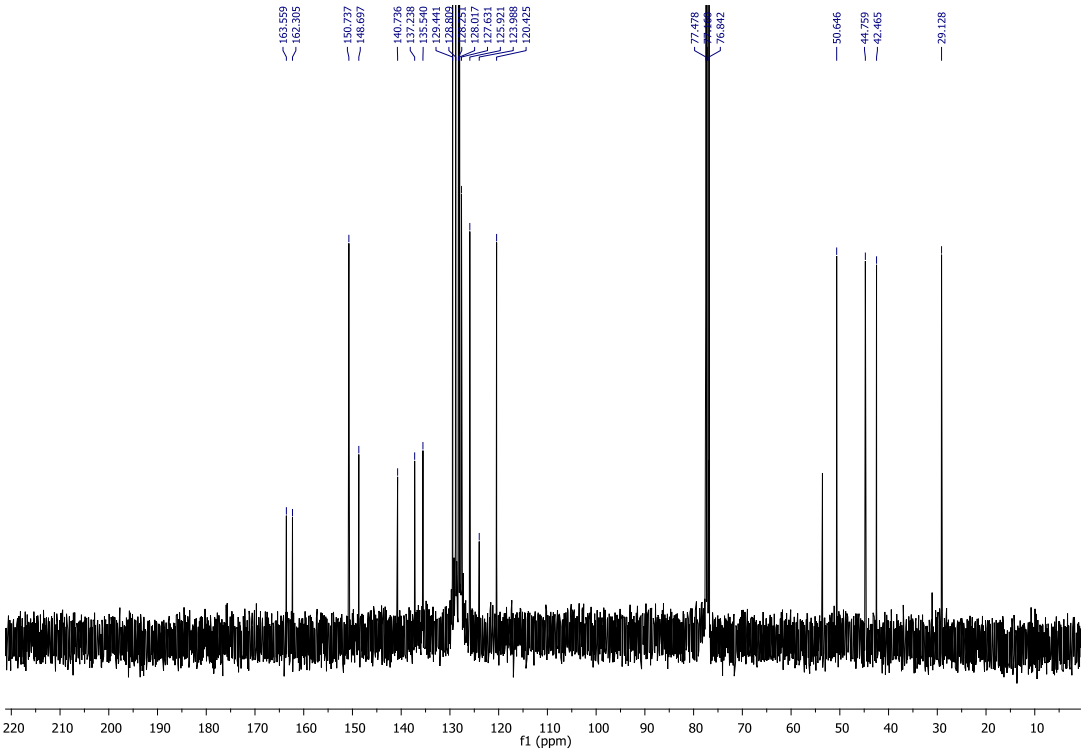


4.27 **4.28** **4.32**

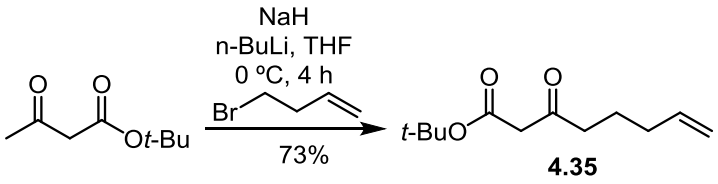
To a solution crude of cross methatesis product **4.28** (56 mg, 0.160 mmol) prepared as above in *i*PrOH (0.6 mL) was added H_2O (29 mg, 1.60 mmol), followed by $LiOH{\cdot}H_2O$ (7 mg, 0.160 mmol). The reaction mixture was stirred for 16 h at room temperature before being quenched by the addition of sat. NH_4Cl (aq), extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material **4.30** which was dissolved in methanol (1 mL), TsOH (6 mg, 0.031 mmol) was added and the mixture heated at reflux for 16 h. Purification by column chromtography (0→2.5→5→10% EtOAc/hexane) gave **4.32** (27 mg, 53%) as a brown oil. ^{1}H NMR (400 MHz, COSY) δ 2.86 (t, *J* = 6.4 Hz, 2H, CH_2), 3.38 (t, *J* = 6.0 Hz, 2H, CH_2), 4.77 (s, 2H, Ph-CH_2), 4.83 (s, 2H, Ph-CH_2), 6.97 (d, *J* = 4.9 Hz, 1H, Ar), 7.16-7.40 (m, 10H, Ph), 8.52 (d, *J* = 4.9 Hz, 1H, Ar); ^{13}C NMR (100 MHz, HSQC) δ 29.1 (C-3), 42.5 (Ph-CH_2), 44.8 (C-2), 50.6(CH_2Ph), 120.4 (C-4), 124.0, 125.9, 127.6, 128.0, 128.3, 128.8, 129.4, 135.5, 137.2, 140.2, 148.7, 150.7, (C-5), 162.3 (C-7), 163.6 (CO); HRMS calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$ 254.0845, found 254.0848.


Ph
HO
O
N
Bn
1.00
20.02
1.14
2.08
2.06
2.31
2.28
1.19
f1 (ppm)

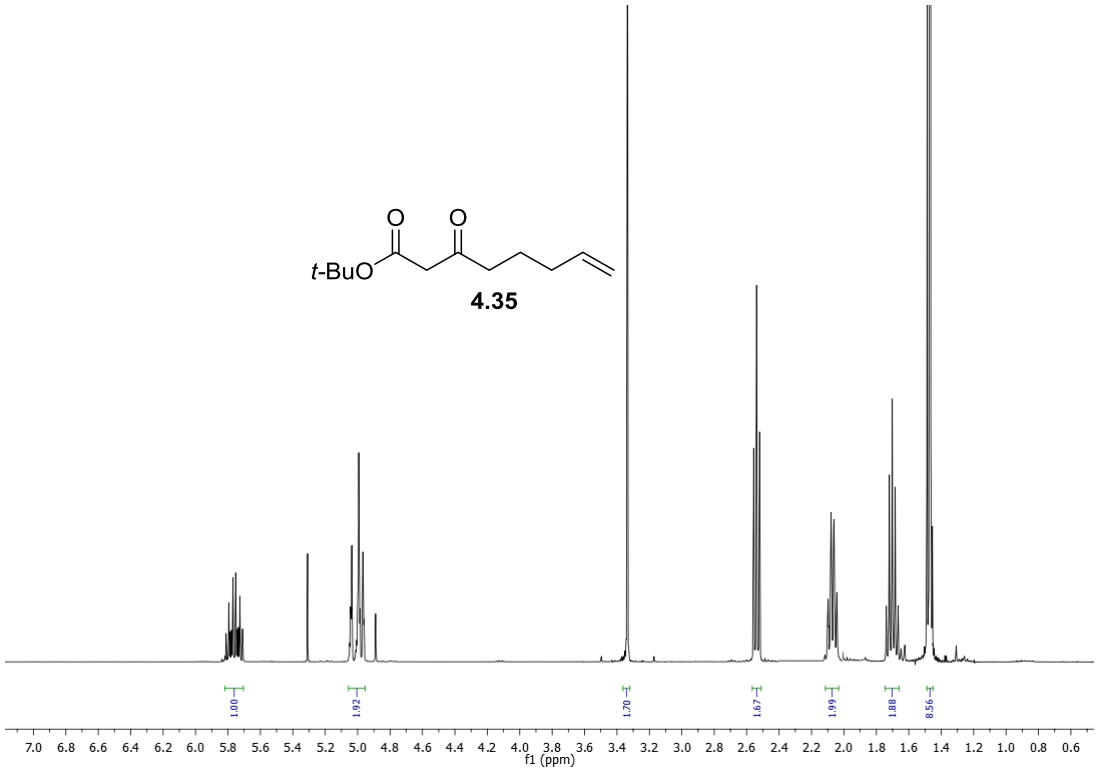
4.32

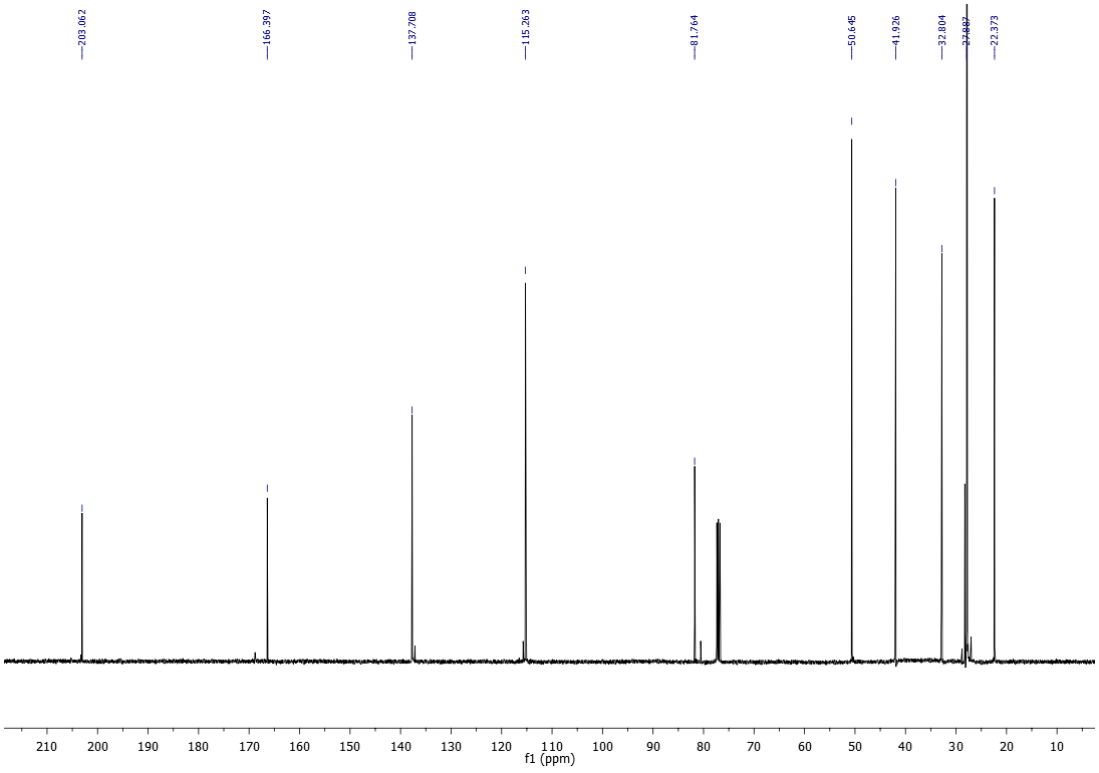

163.559
162.305
150.737
148.697
140.736
137.238
135.540
129.441
128.017
127.631
125.921
123.988
120.425
77.478
76.842
50.646
44.759
42.465
29.128
f1 (ppm)

tert-Butyl 3-Oxooct-7-enoate. (4.35)

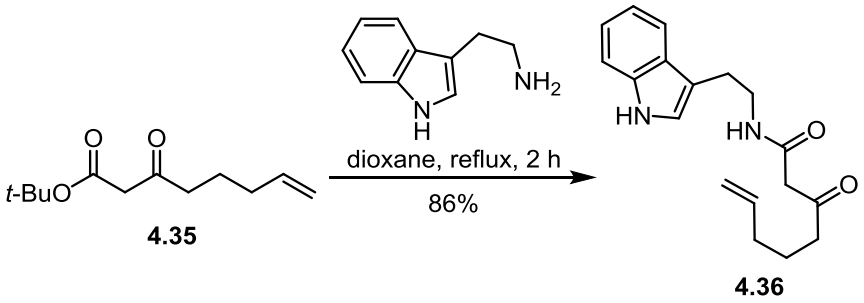


THF (20 mL) was added to NaH (60% mineral oil) (490 mg, 20.2 mmol) and the resulting suspension was cooled to 0°C. *tert*-butyl acetoacetate (6.74 mmol, 1.07 g) was added dropwise and the colorless solution was stirred at 0 ºC for 10 min. Then n-butyllithium (3.3 mL of 2.6 *M* in hexanes*,* 7.09 mmol*)* was added dropwise and the orange solution was stirred at 0 ºC for an additional 10 min. 4-bromo-1-butene (7.41 mmol, 1.00 g) in THF (1.5 ml) was added, The color of the dianion faded immediately on addition and the reaction mixture was stirred at room temperature for 15 min. The mixture was quenched with of sat. NH_4Cl (aq) (2 mL), water (5 mL) and diluted with 15 ml of ethyl ether. The organic phase was washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by chromatography (0→10→25→50% EtOAc/hexane) gave β-keto ester **4.35** (0.990 g, 73%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) δ 1.47 (s ,9H, CH_3), 1.70 (quint, *J* = 14.8, 7.6 Hz, 2H, H-6), 2.07 (qt, *J* = 8.4, 2.4, 1.2 Hz, 2H, H-5), 2.54 (t, *J* = 7.2 Hz, 2H, H-4), 3.33 (s, 2H, H-2), 5.00 (m, 2H, H-8), 5.76 (ddt, *J* = 13.6, 10.4, 6.8 Hz, 1H, H-7), ^{13}C NMR (400 MHz, HSQC) δ 22.4 (C-5), 27.9 (CH_3), 32.8 (C-6), 41.9 (C-4), 50.6 (C-2), 81.8 (C), 115.3 (C-8), 137.7 (C-7), 166.4 (C-1), 203.1 (C-3). HRMS calcd for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1486, found 213.1485.


O
O
t-BuO
4.35
1.00
1.92
1.70
1.67
1.99
1.88
8.56
7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

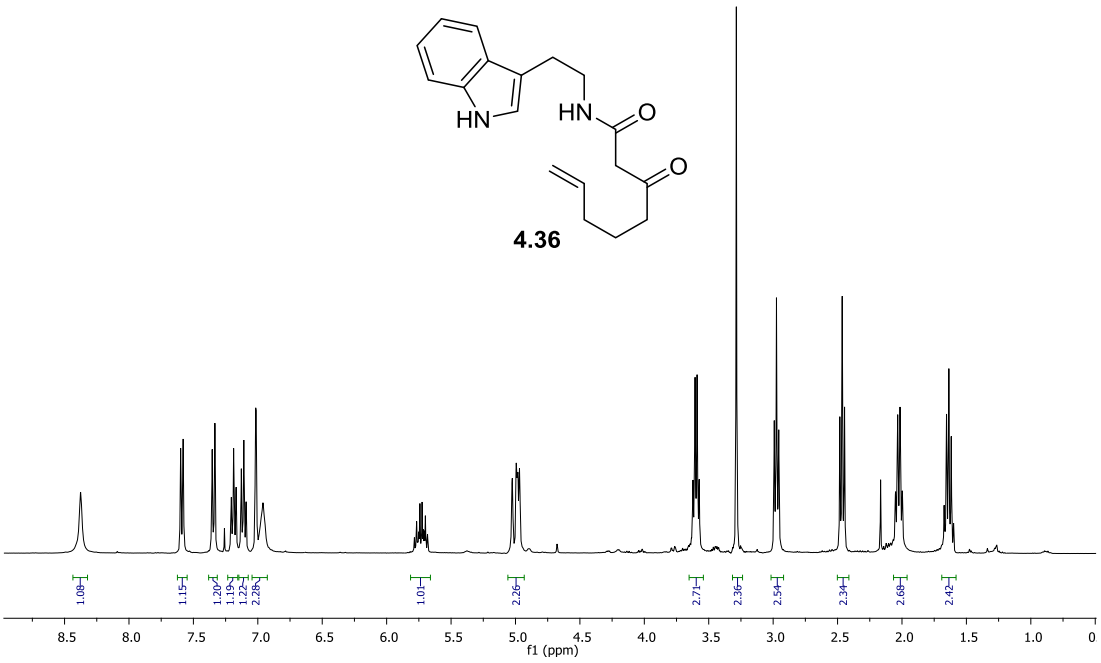

203.062
166.397
137.708
115.263
81.764
50.645
41.926
32.804
27.887
22.373
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

***N*-(2-(1*H*-Indol-3-yl)ethyl)-3-oxooct-7-enamide. (4.36)**

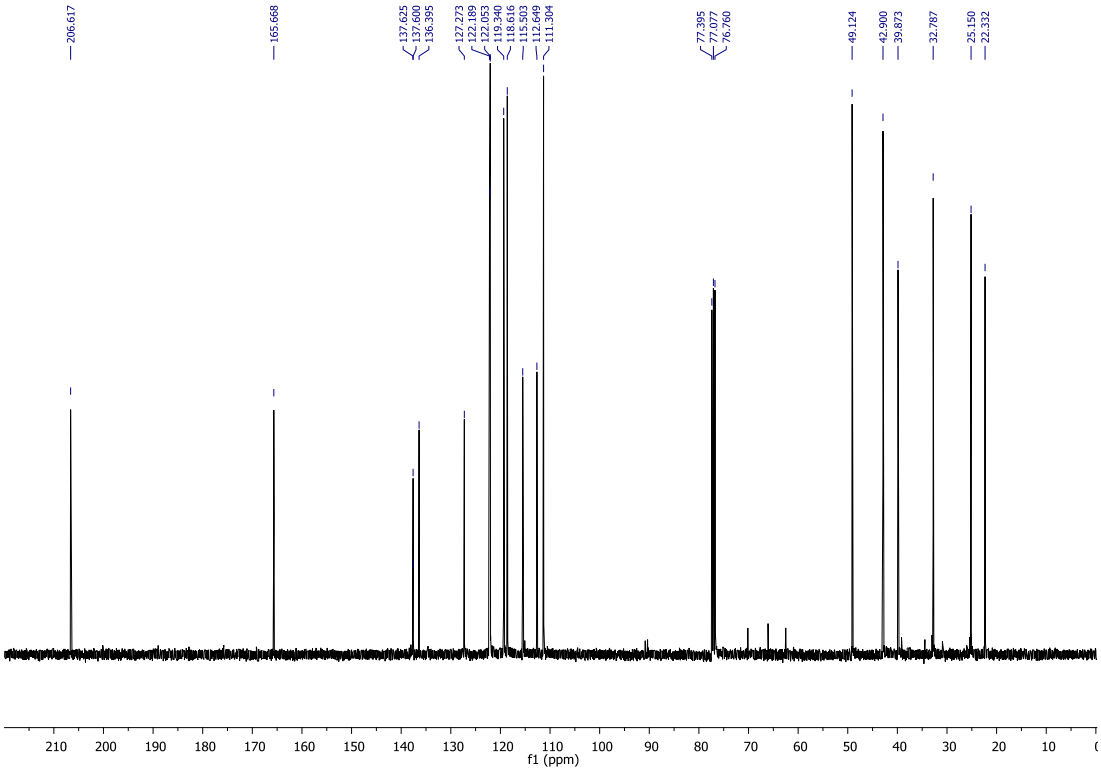


4.35 **4.36**

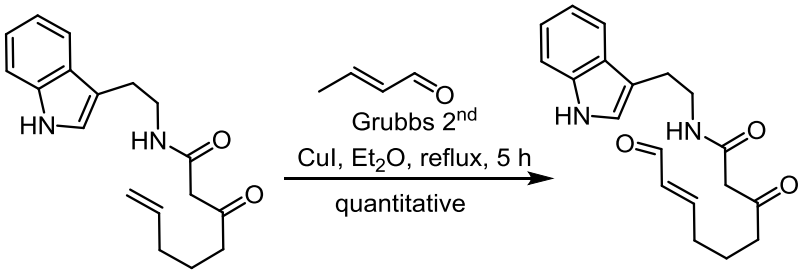
A solution of β-keto ester **4.35** (625 mg, 2.94 mmol) and tryptamine (471 mg, 2.94 mmol) in dioxane (100 mL) was stirred at reflux until all the amine was consumed (approximately 2 h, monitored by TLC). Evaporation *in vacuo* and purification by flash chromatography (0→25→50→100% EtOAc/hexane) gave **4.36** as a white solid (755 mg, 86%). ^{1}H NMR (400 MHz, COSY) δ 1.62 (quint, *J* = 14.8, 7.6 Hz, 2H, H-6), 2.01 (q, *J* = 6.8 Hz, 2H, H-5), 2.24 (t, *J* = 7.2 Hz, 2H, H-4), 2.96 (t, *J* = 6.8 Hz, 2H, NH-CH_2), 3.27 (s, 2H, H-2), 3.59 (q, *J* = 7.2 Hz, 2H, indol-CH_2), 4.99 (m, 2H, H-8), 5.72 (ddt, *J* = 13.6, 10.4, 6.8 Hz, 1H, H-7), 6.95 (br, 1H, NH), 7.00 (d, *J* = 2.0 Hz, 1H, H-indol), 7.10 (td, *J* = 8.0, 1.2 Hz, 1H, H-indol), 7.18 (td, *J* = 8.0, 1.2 Hz, 1H, H-indol), 7.33 (d, *J* = 8.4 Hz, 1H, H-indol), 7.58 (d, *J* = 8.0 Hz, 1H, H-indol), 8.36 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 22.3 (C-6), 25.2, 32.8 (C-5), 39.9, 42.9 (C-4), 49.1 (C-2), 111.3, 112.6, 115.5 (C-8), 118.6, 119.3, 122.0, 122.2, 127.3, 136.4, 137.6 (C-7), 165.7 (C-1), 206.6 (C-3). HRMS calcd for $C_{18}H_{23}N_2O_2$ $[M+H]^+$ 299.1759, found 299.1754.


HN
HN
O
O
1.08
1.15
1.20
1.19
1.22
2.28
1.01
2.26
2.71
2.36
2.54
2.34
2.69
2.42
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
f1 (ppm)

4.36

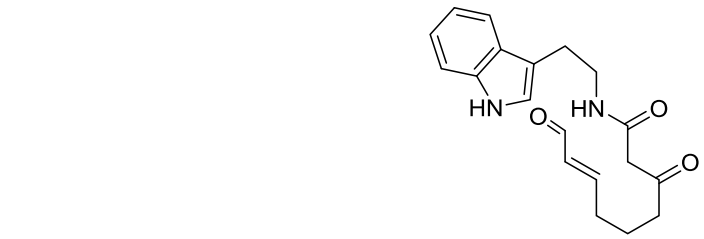

206.617
165.668
137.625
137.600
136.395
127.273
122.189
122.053
119.340
118.616
115.503
112.649
111.304
77.395
77.077
76.760
49.124
42.900
39.873
32.787
25.150
22.332
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(*E*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-3,9-dioxonon-7-enamide. (4.31)

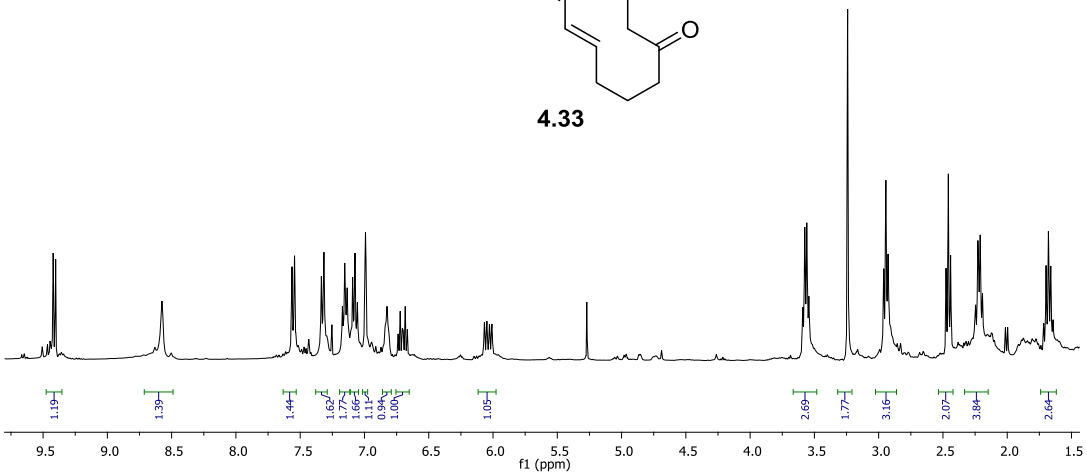


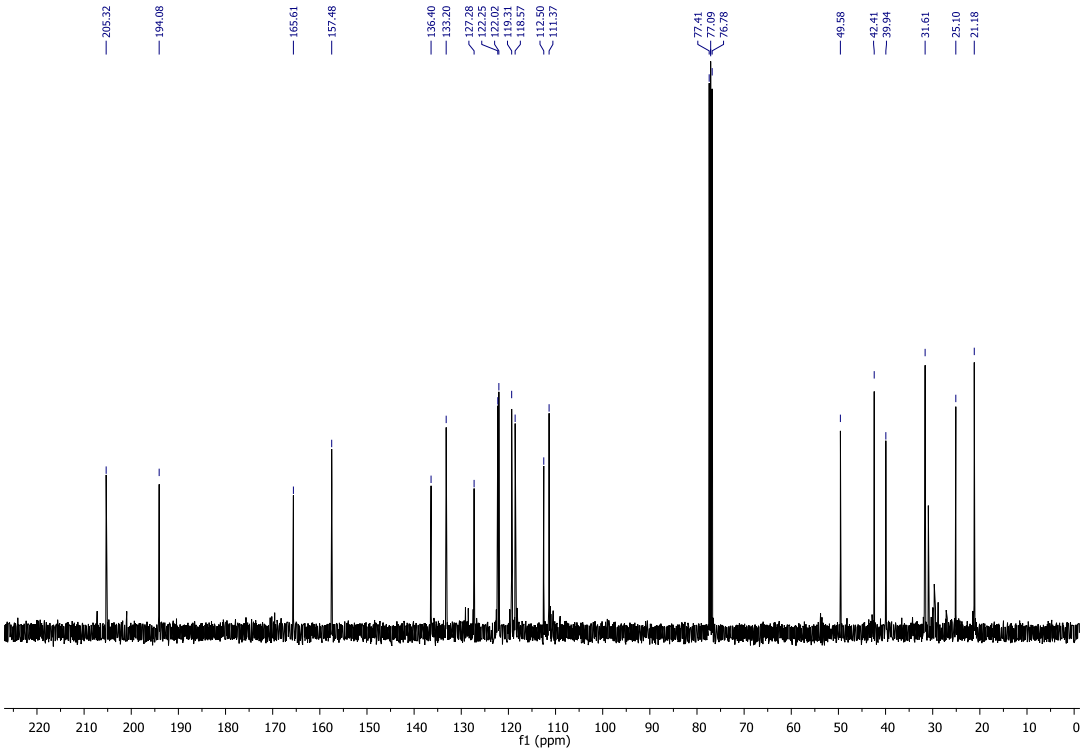
4.36 **4.33**

To alkene **4.36** (115 mg, 0.385 mmol), crotonaldehyde (81 mg, 1.156 mmol), Grubbs-2 catalyst (8.0 mg, 9.6 µmol), and CuI (3.0 mg, 15.4 µmol) was added diethyl ether (4.0 mL) and the solution was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the crude enal **4.33** (quantitative yield) was used directly without any further purification. ^{1}H NMR (400 MHz, COSY) δ 2.45 (t, *J* = 7.3 Hz, 2H, H-5), 2.68 (t, *J* = 7.4 Hz, 2H, H-4), 2.97 (t, *J* = 6.8 Hz, 2H, NH-CH_2), 3.30 (s, 2H, H-2), 3.60 (dd, *J* = 12.6, 6.7 Hz, 2H, indol-CH_2), 4.14-4.24 (m, 2H, H-9), 4.96 (d, *J* = 33.6 Hz, 2H, H-6'), 5.73-5.81 (m, 1H, H-8), 6.23 (d, *J* = 16.0 Hz, 1H, H-7), 6.88 (br, 1H, NH), 7.05 (br, 1H, H-indol), 7.11 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H, H-indol), 7.19 (ddd, *J* = 8.2, 8.2, 1.2 Hz, 1H, H-indol), 7.36 (d, *J* = 8.1 Hz, 1H H-indol), 7.59 (d, *J* = 7.6 Hz, 1H, H-indol), 8.42 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 21.2 (C-6), 25.1, 31.6 (C-5), 39.9, 42.4 (C-4), 49.6 (C-2), 111.4, 112.5, 118.6, 119.3, 122.10 122.3, 127.3, 133.2, 136.4 (C-8), 157.5 (C-7), 165.6 (C-1), 194.1 (C-9), 205.3 (C-3). HRMS calcd for $C_{24}H_{44}NaO_3$ $[M+Na]^+$ 403.3183, found 403.3171.

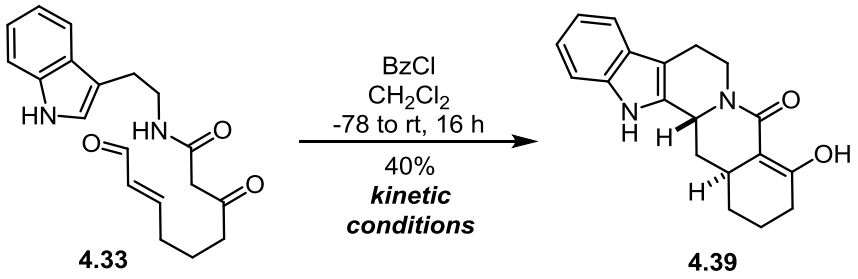

HN
O
HN
O
O

4.33


1.19
1.39
1.44
1.62
1.77
1.66
1.11
0.94
1.00
1.05
2.69
1.77
3.16
2.07
3.84
2.64
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)

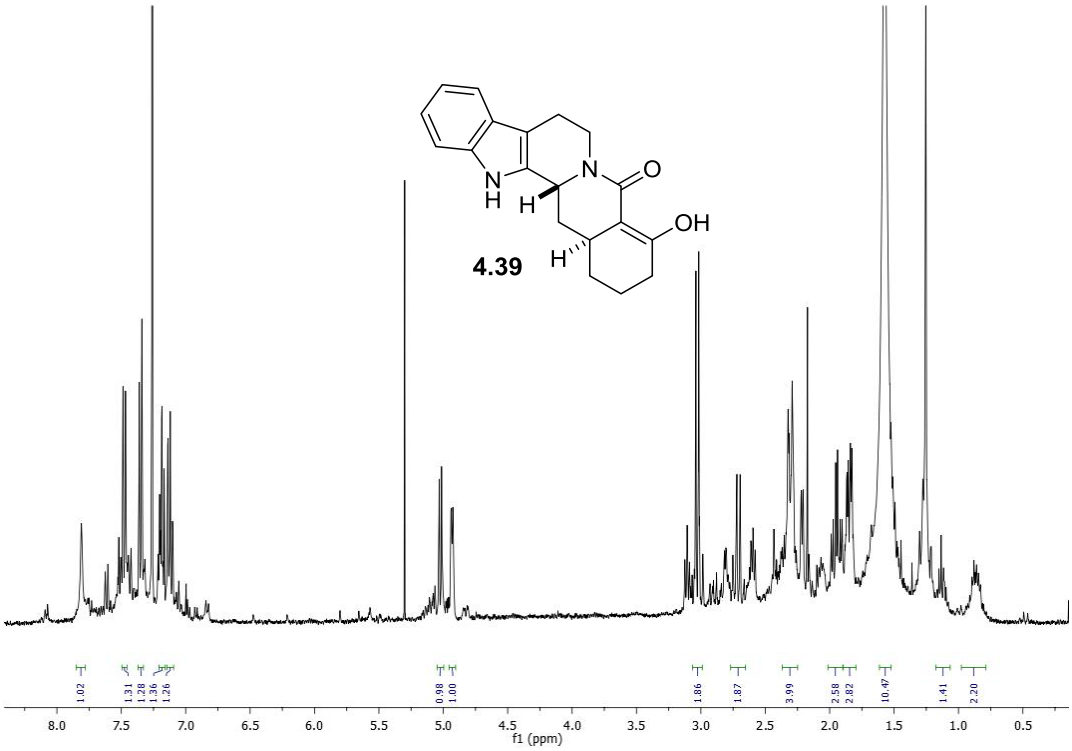

205.32
194.08
165.61
157.48
136.40
133.20
127.28
122.25
122.02
119.31
118.57
112.50
111.37
77.41
77.09
76.78
49.58
42.41
39.94
31.61
25.10
21.18
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Compound 4.39 (kinetic conditions) (4.39)

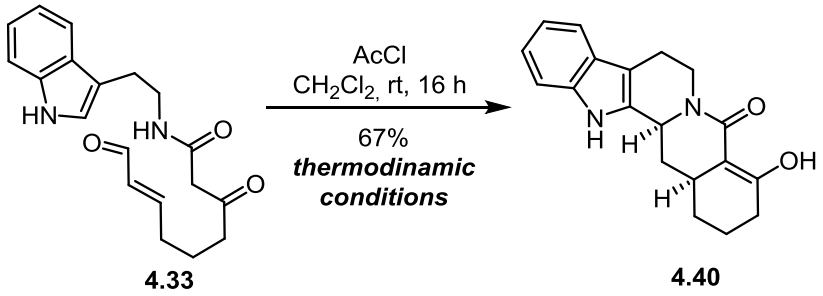


4.33 **4.39**

To the crude enal **4.33** (92 mg, 0.282 mmol) in dichloromethane (0.3 mL) at -78 ºC was added benzoyl chloride (48 mg, 0.338 mmol). The resulting mixture was stirred for 3 h then slowly warmed to room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 washed with 2N NaOH (aq) (3 x 2 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by chromatography (0→10→25→50→100% EtOAc/hexane) gave a **4.39** (24 mg, 40%) as a yellow solid in a ratio 2:1 of **4.39** and **4.40**. ^{1}H NMR (400 MHz, COSY)) δ 1.24-1.31 (m, 3H, H-16 and H-17), 1.49-1.60 (m, 1H, H-14), 1.85 (dd, *J* = 10.4, 3.6 Hz, 1H, H-18), 1.95 (m, 1H, H-18), 2.23-2.15 (m, 1H, H-15), 2.27-2.33 (m, 2H, H-14, H-17) 2.73 (masked, 2H, H-6), 3.03 (masked, 1H, H-5), 4.92-4.95 (dm, 1H, H-3), 5.10 (dm, 1H, H-5), 7.12 (td, *J* = 7.2, 0.8 Hz, 1H, H-10), 7.19 (td *J* = 6.8, 1.2 Hz, 1H, H-11), 7.35 (d, *J* = 8.0 Hz, 1H, H-12), 7.48 (d, *J* = 7.6 Hz, 1H, H-9), 7.81 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 21.2 (C-6), 21.6 (C-16), 28.9 (C-17), 29.0 (C-14), 29.9 (C-18), 31.9 (C-15), 43.1 (C-5), 53.9 (C-3), 99.3 (C-20), 111.1 (C-7), 111.2 (C-12), 118.5 (C-9), 120.1 (C-10), 122.2 (C-11), 127.4 (C-8), 132.9 (C-2), 135.7 (C-13), 169.9 (C-19), 170.1 (C-21). HRMS calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1602, found 309.1598.

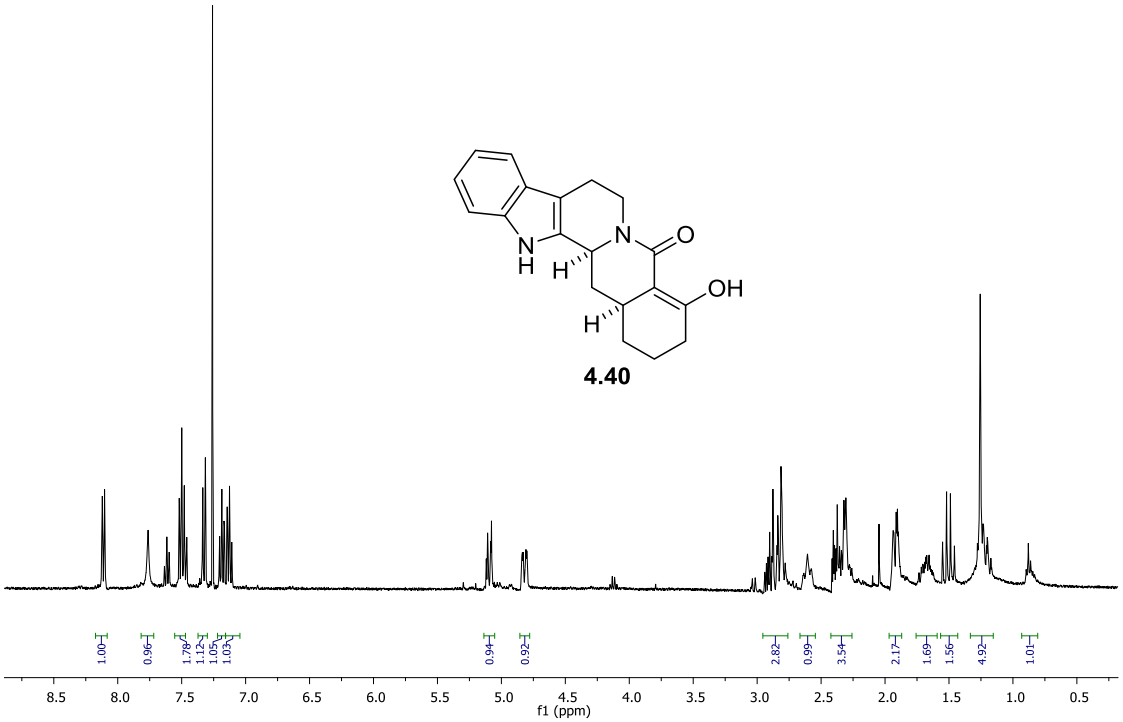

N
H
H
N
O
OH
H
4.39
1.02
1.31
1.28
1.36
1.26
0.98
1.00
1.86
1.87
3.99
2.58
2.82
10.47
1.41
2.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

Compound 4.38 (thermodynamic conditions). (4.40)

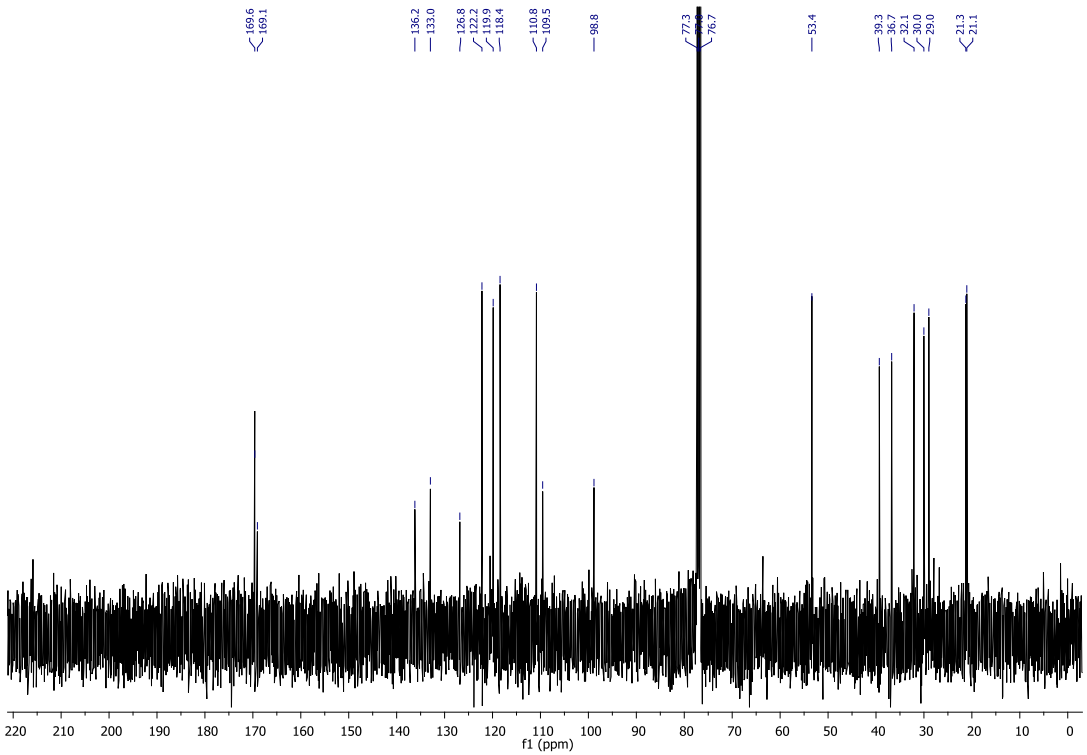


4.33 **4.40**

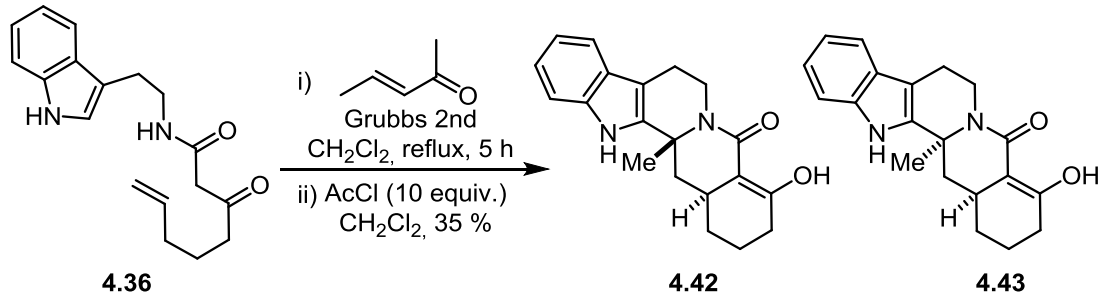
To crude enal **4.33** (27 mg, 0.083 mmol) in dichloromethane (0.1 mL) at room temperature was added acetyl chloride (65 mg, 0.827 mmol) and the resulting mixture stirred overnight. The reaction mixture was diluted with CH_2Cl_2 washed with 2N NaOH (aq) (3 x 1 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50→100% EtOAc/hexane) gave a **4.40** (17 mg, 67%) as a yellow solid in a ratio 1:10 of **4.39** and **4.40**. ^{1}H NMR (400 MHz, COSY)) δ 1.18-1.25 (m, 1H, H-16), 1.25-1.32 (m, 1H, H-17), 1.50 (q, *J* = 12.8 Hz, 1H, H-14), 1.62-1.71 (m, 1H, H-18), 1.87-1.94 (m, 2H, H-16 and H-18), 2.26-2.36 (m, 1H, H-17), 2.39 (dt, *J* = 7.6, 3.6 Hz, 1H, H-14), 2.61 (t, *J* = 12.8 Hz, 1H, H-15), 2.82 (ddt, *J* = 6.0, 4.0, 2.0 Hz, 2H, H-6), 2.85-2.93 (m, 1H, H-5eq), 4.82 (dd, *J* = 11.6, 2.8 Hz, 1H, H-3), 5.10 (ddd, *J* = 4.0, 2.0 Hz, 1H, H-5ax), 7.13 (td, *J* = 7.6, 0.8 Hz, 1H, H-10), 7.19 (td *J* = 7.2, 1.2 Hz, 1H, H-11), 7.33 (d, *J* = 8.0 Hz, 1H, H-12), 7.51 (d, *J* = 7.2 Hz, 1H, H-9), 7.75 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 21.1 (C-6), 21.3 (C-16), 29.0 (C-17), 30.0 (C-18), 32.1 (C-15), 36.7 (C-14), 39.3 (C-5), 53.4 (C-3), 98.8 (C-20), 109.5 (C-7), 110.8 (C-12), 118.4 (C-9), 119.9 (C-10), 122.2 (C-11), 126.8 (C-8), 133.0 (C-2), 136.2 (C-13), 169.1 (C-19), 169.6 (C-21). HRMS calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1602, found 309.1598.


N
H
H
N
O
OH
H
1.00
0.96
1.79
1.12
1.05
1.03
0.94
0.92
2.82
0.99
3.54
2.17
1.69
1.56
4.92
1.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

4.40

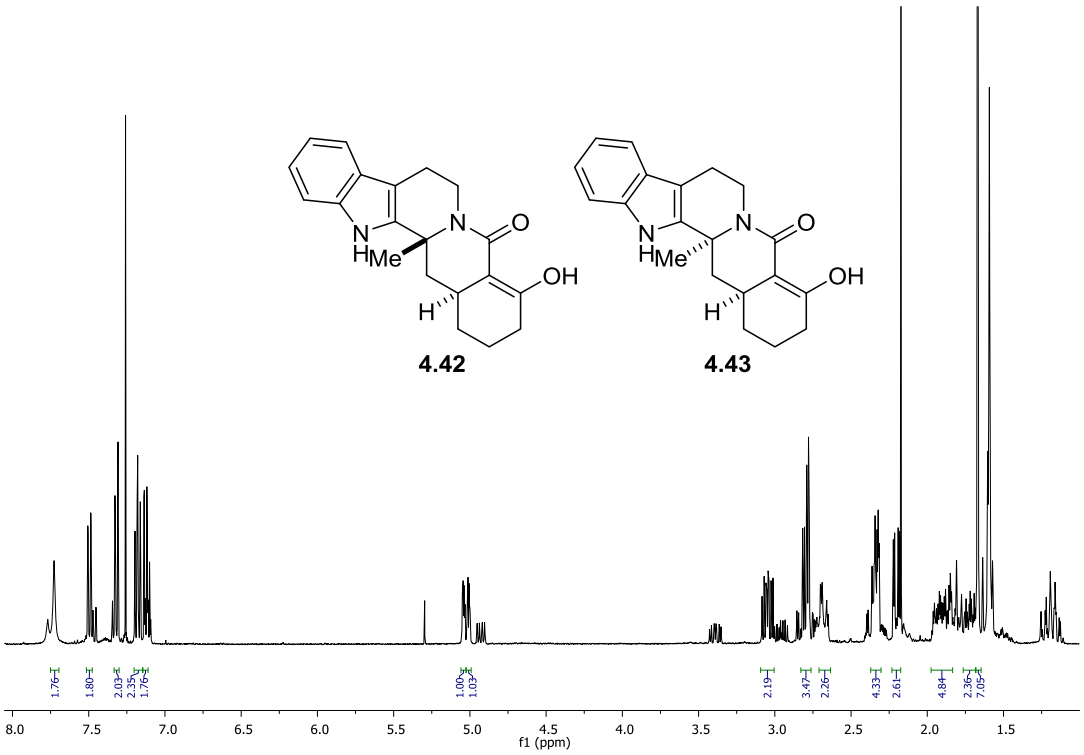

169.6
169.1
136.2
133.0
126.8
122.2
119.9
118.4
110.8
109.5
98.8
77.3
76.7
53.4
39.3
36.7
32.1
30.0
29.0
21.3
21.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

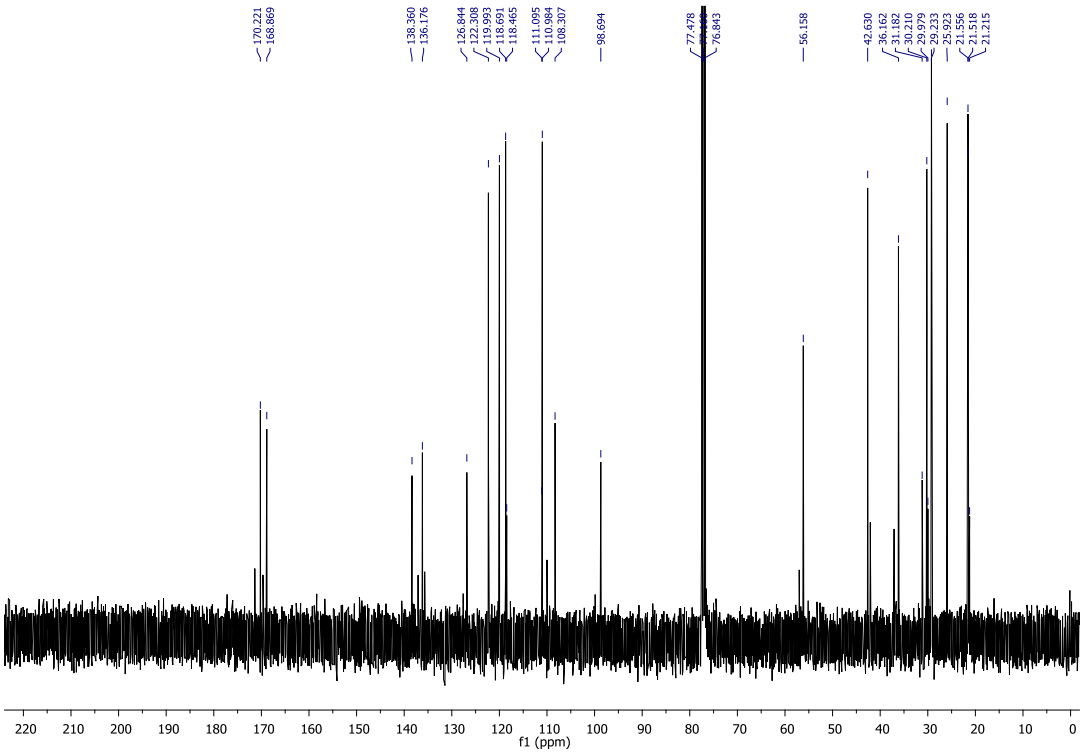
(*E*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-3,9-dioxonon-7-enamide. (4.42)



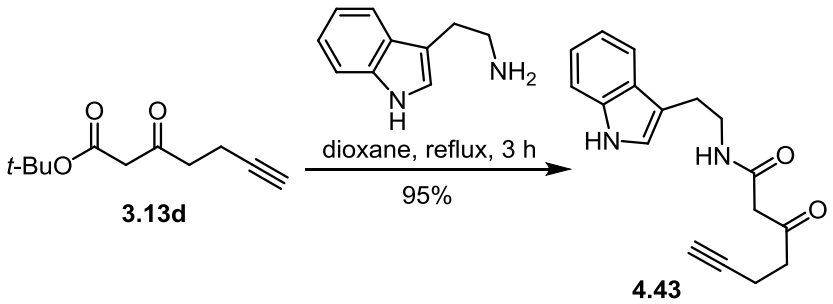
4.36 **4.42** **4.43**

To amine **4.36** (150 mg, 0.503 mmol), crotonaldehyde (176 mg, 2.515 mmol) in CH_2Cl_2 (5 mL), was added Grubbs-2 catalyst (11 mg, 12.5 µmol) under an Ar atmosphereand the resulting solution was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the crude material was dissolved CH_2Cl_2 (1 mL). AcCl (395 mg, 5.03 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 washed with 2N NaOH dried, and concentrated *in vacuo*. Purification by column chromatography (0→10→25→50% EtOAc/hexane) gave compounds **4.42** : **4.43** (56 mg, 35%) in a ratio of 1:2.4 as a brown oil. ^{1}H NMR (400 MHz, COSY) δ 1.13-1.25 (m, 1H, H-18), 1.60 (s, 3H, CH_3), 1.57-1.64 (masked, 1H, H-14), 1.69-1.76 (m, 1H, H-16), 1.83-1.90 (m, 1H, H-18), 1.90-1.96 (m, 1H, H-16), 2.22 (dd, *J* = 12.8, 3.6 Hz, 1H, H-14), 2.33 (dt, *J* = 7.6, 4.8, 2.4 Hz, 2H, H-17), 2.65-2.73 (m, 1H, H-15), 2.77-2.82 (m, 2H, H-6), 3.05 (ddd, *J* = 13.2, 10.4, 5.6 Hz, 1H, H-5), 5.03 (ddd, *J* = 13.2, 4.4, 2.4 Hz, 1H, H-5), 7.13 (dd, *J* = 7.6, 1.2 Hz, 1H, H-10), 7.18 (td *J* = 6.8, 1.2 Hz, 1H, H-11), 7.32 (dt, *J* = 8.0, 1.6 Hz, 1H, H-12), 7.50 (dt, *J* = 7.6, 1.2 Hz, 1H, H-9), 7.73 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 21.4 (C-6), 21.4 (C-16), 25.8 (CH_3), 29.0 (C-17), 29.1 (C-15), 30.0 (C-18), 36.0 (C-5), 42.5 (C-14), 56.0 (C-3), 98.5 (C-20), 108.1 (C-7), 110.8 (C-12), 118.5 (C-9), 119.8 (C-10), 122.1 (C-11), 126.7 (C-8), 136.0 (C-13), 138.2 (C-2), 168.7 (C-19), 170.1 (C-21). HRMS calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1773, found 323.1786.

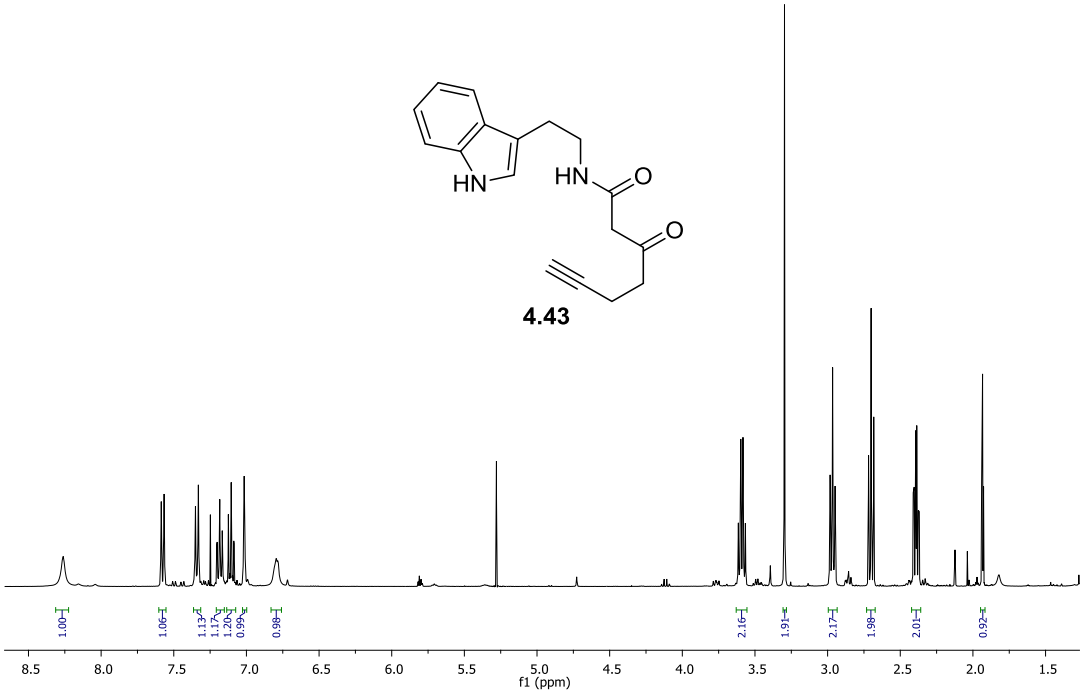

4.42
4.43
f1 (ppm)


f1 (ppm)

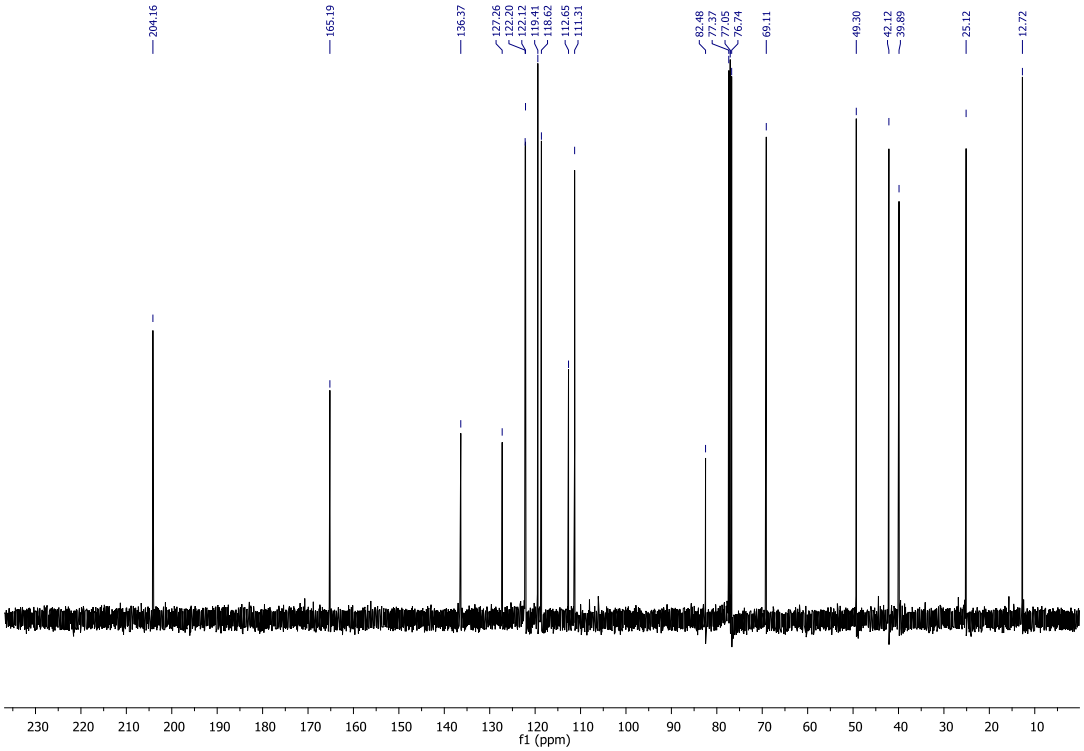
N-(2-(1*H*-Indol-3-yl)ethyl)hept-6-ynamide (4.43)



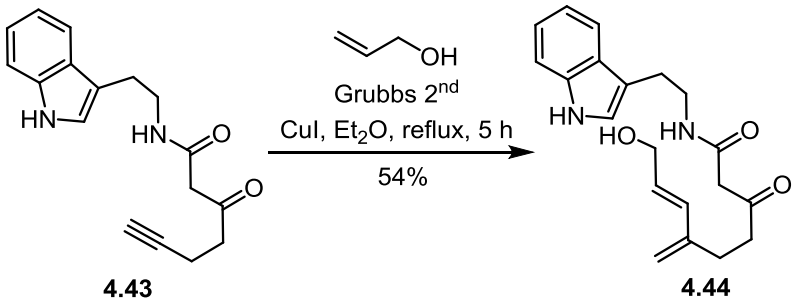
A solution of β-keto ester **3.13d** (450 mg, 2.29 mmol) and tryptamine (367 mg, 2.29 mmol) in dioxane (78 mL) was stirred at reflux until all amine was consumed (approximately 3 h, monitored by TLC). Concentration *in vacuo* and purification by column chromatography (0→25→50→100% EtOAc/hexane) gave **4.43** as a white solid (615 mg, 95%). ^{1}H NMR (400 MHz, COSY) δ 1.93 (t, *J* = 2.7 Hz, 1H, H-7), 2.39 (td, *J* = 7.0, 2.6 Hz, 2H, H-5), 2.70 (t, *J* = 7.1 Hz, 2H, H-4), 2.97 (t, *J* = 6.8 Hz, 2H, NH-CH_2), 3.30 (s, 2H, H-2), 3.59 (dd, *J* = 12.7, 6.8 Hz, 2H, indol-CH_2), 6.79 (br, 1H, NH), 7.02 (br, 1H), 7.10 (td, *J* = 7.6, 0.4 Hz, 1H, indol) 7.18 (td, *J* = 7.2, 1.2 Hz, 1H, indol), 7.34 (d, *J* = 8.1 Hz, 1H, indol), 7.58 (d, *J* = 7.8 Hz, 1H, indol), 8.26 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 12.7 (C-5), 25.1 (C-indol), 39.9 (C-indol), 42.1 (C-4), 49.3 (C-2), 69.1 (C-7), 82.5 (C-6), 111.3, 112.7, 118.6, 119.4, 122.1, 122.3, 127.3, 136.4, 165.2 (C-1), 204.2 (C-3). HRMS calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ 283.1439, found 283.1441.


HN
HN
O
O
1.00
1.06
1.13
1.17
1.20
0.99
0.98
2.16
1.91
2.17
1.98
2.01
0.92
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

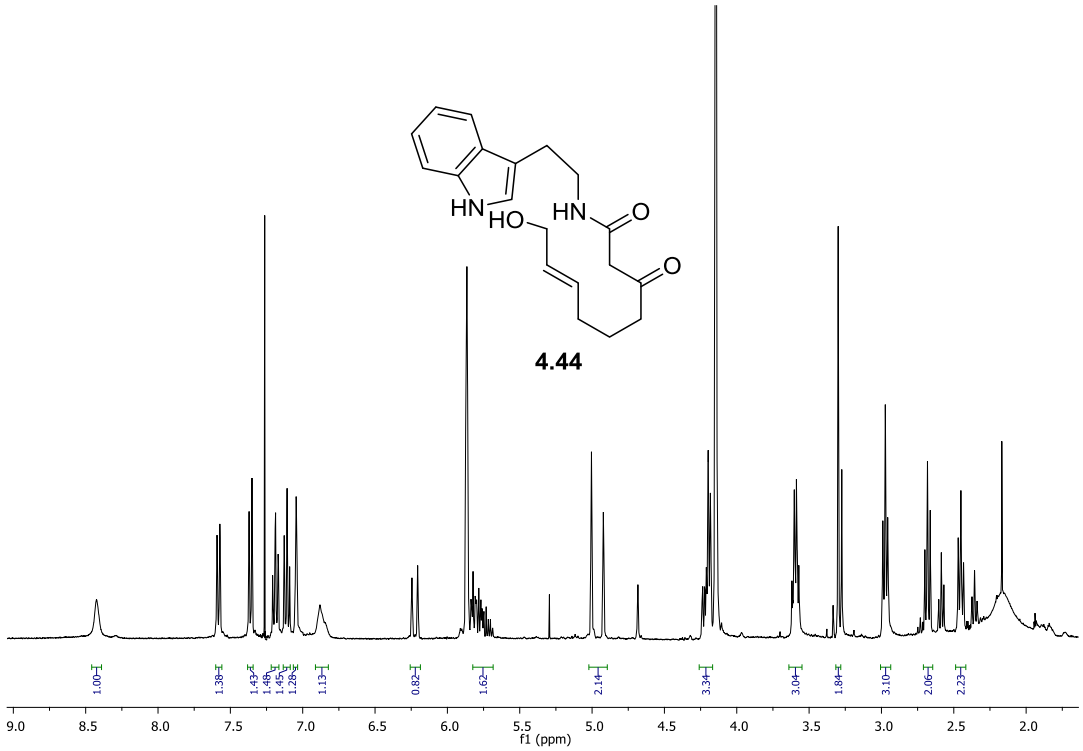
4.43

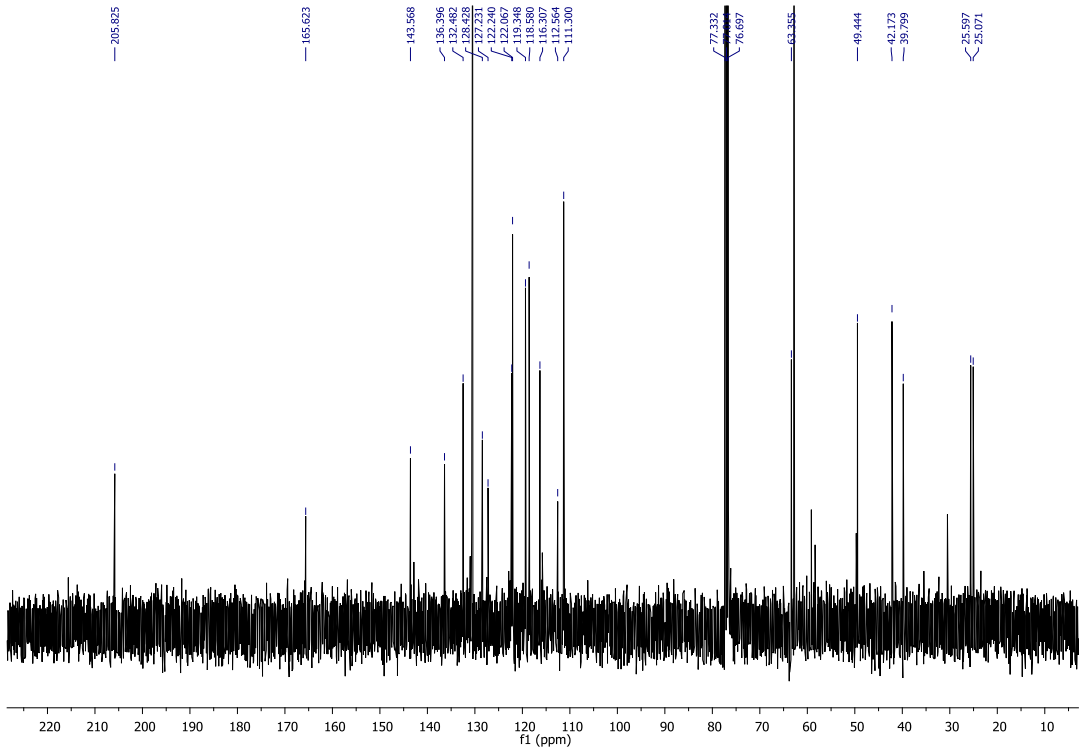

204.16
165.19
136.37
127.26
122.20
122.12
119.41
118.62
112.65
111.31
82.48
77.37
77.05
76.74
69.11
49.30
42.12
39.89
25.12
12.72
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(*E*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-9-hydroxy-6-methylene-3-oxonon-7-enamide (4.44)



To Alkyne **4.43** (100 mg, 0.354 mmol), allyl alcohol (123 mg, 2.125 mmol), Grubbs-2 catalyst (6 mg, 7.0 µmol), and CuI (2 mg, 11.0 µmol) under an Ar atmosphere weas added diethyl ether (4.0 mL) and the resulting mixture was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* purified by column chromatography (0→25→50→100% EtOAc/hexane) to give **4.44** as brown oil (65 mg, 54%) ^{1}H NMR (400 MHz, COSY) δ 1.93 (t, *J* = 2.7 Hz, 1H, H-7), 2.39 (td, *J* = 7.0, 2.6 Hz, 2H, H-5), 2.70 (t, *J* = 7.1 Hz, 2H,H-4), 2.97 (t, *J* = 6.8 Hz, 2H, NH-CH_2), 3.30 (s, 2H, H-2), 3.59 (dd, *J* = 12.7, 6.8 Hz, 2H, indol-CH_2), 6.79 (br, 1H, NH), 7.02 (br, 1H), 7.10 (td, *J* = 7.6, 0.4 Hz, 1H, indol) 7.18 (td, *J* = 7.2, 1.2 Hz, 1H, indol), 7.34 (d, *J* = 8.1 Hz, 1H, indol), 7.58 (d, *J* = 7.8 Hz, 1H, indol), 8.26 (br, 1H, NH) ^{13}C NMR (400 MHz, HSQC) δ 12.7 (C-5), 25.1 (C-indol), 39.9 (C-indol), 42.1 (C-4), 49.3 (C-2), 69.1 (C-7), 82.5 (C-6), 111.3, 112.7, 118.6, 119.4, 122.1, 122.3, 127.3, 136.4, 165.2 (C-1), 204.2 (C-3). HRMS calcd for $C_{20}H_{25}N_2O_3$ $[M+H]^+$ 341.1865, found 341.1860.

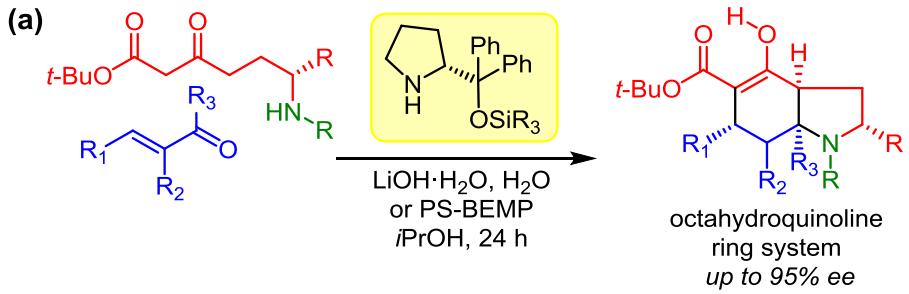

HN
HO
HN
O
O
4.44
1.00
1.38
1.43
1.45
1.45
1.28
1.13
0.82
1.62
2.14
3.34
3.04
1.84
3.10
2.06
2.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)


205.825
165.623
143.568
136.396
132.482
128.428
127.231
122.260
121.067
119.348
118.580
116.307
112.564
111.300
77.332
76.697
63.355
49.444
42.173
39.799
25.597
25.071
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

ANNEX I
CONCLUSIONES EN CASTELLANO

Octahidroindoles:

Se ha desarrollado una metodología general para la síntesis del núcleo octahidroindolico utilizando materiales de partidas sencillos mediante (*a*) el tratamiento de un β-ceto éster *tert*-butilico que presenta en su estructura un grupo amino monoprotegido y crotonaldehído en condiciones básicas ($LiOH.H_2O$, *t*-BuOK o *n*-Bu_4NOH) extrapolando las condiciones utilizadas para la formación de compuestos del tipo 5-oxodecahidroquinolinas mediante una secuencia tándem/domino *one-pot* de reacciones (Michael intermolecular, aldolica intramolecular y aza-Michael intramolecular). Con el objetivo de simplificar las etapas de manipulación de la reacción se encontró que la utilización de una resina básica como el PS-BEMP aumenta el potencial de la reacción y se obtiene de forma rápida y directa en un escaso número de pasos el sistema octahidroindolico. (*b*) Los criterios aplicados para la obtención de decahidroquinolinas organocatalíticas (adición de Michael) fueron totalmente trasferibles a la serie octahidroindolica. Sin embargo, se encontró que el *n*-BuNOH o PS-BEMP dan excesos enantiomericos ligeramente mejores en comparación a la utilización del $LiOH{\cdot}H_2O$ para la reacción tándem de cierre de anillo. La utilización de diferentes aceptores de Michael sustituidos en las posiciones 2 y/o 3 permite la formación de una amplia gama de análogos de forma asimétrica con excelentes ee y rendimientos moderados, otorgando una mayor robusteza a la metodología desarrollada.



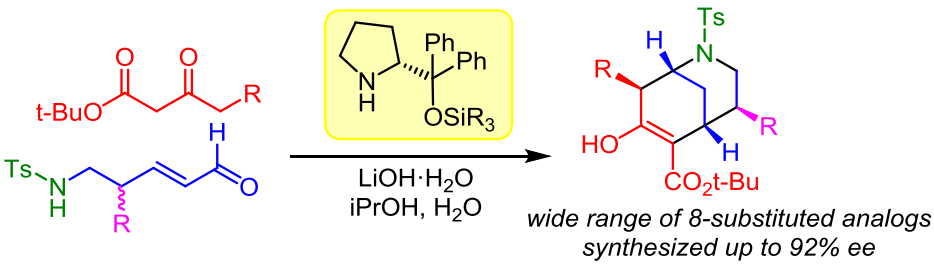
Esquema 1 Síntesis del sistema octahidroindolico multi-sustituido.

(*c*) Los intentos de sintetizar compuestos análogos que presenten en su estructura 7 miembros en el anillo nitrogenado (perhidro[*b*]azepinas) no tuvieron éxito conduciendo sólo al aducto Robinson. Se ensayaron una serie de condiciones para la ciclación, pero en ningún caso fue observado el compuesto bicíclico.

Presumiblemente, mientras que en la serie de anillos de 5 y 6 miembros se forma una pequeña cantidad de ciclohexenona en equilibrio con la forma enolato, esto permite el ataque para dar el producto de adición aza-Michael desplazando el equilibrio hacia la formación del producto. Sin embargo, en la serie del anillo de 7 miembros esto no ocurre debido a las dificultades entrópicas para la formación de la enona ya que se genera una nueva desprotonación de β-ceto ester lo cual inhibe completamente el progreso de la reacción.

Morfanos:

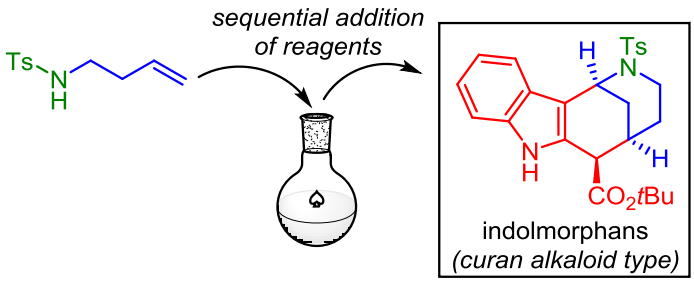
En esta tesis se describe una síntesis asimétrica de carácter general para la obtención compuestos morfánicos. La aplicación a morfanos es diferente y requiere un cambio más sustancial yaque el átomo de N tosilado se incorpora en la unidad del aceptor de Michael α,β-insaturado en lugar del β-ceto ester como en el protocolo anterior para generar azabiciclos fusionados. (*a*) La metodología que se presenta para la obtención de sistemas de 2-azabiciclo[3.3.1]nonano (morfano) implica un proceso tándem basado en una reacción organocatalizada. La secuencia sintética, a partir de materiales de partida fácilmente disponibles, comporta la formación de tres nuevos enlaces: i) el primero en una reacción intermolecular de Michael que genera de manera organocatalizada y asimétrica un enlace C-C; ii) el segundo implica la formación de una ciclohexenona en medio básico completando una anelación de Robinson enantiocontrolada y iii) una reacción aza-Michael intramolecular para generar el sistema azabicíclico.



Esquema 2 Síntesis del sistema morfanico C8-sustituido.

(*b*) Para ampliar aún más el potencial de la reacción, se puede añadir una ulterior reacción tándem a partir del núcleo morfánico adecuadamente sustituído en C-8. Así, ha sido posible la síntesis de indolomorfanos, que contienen la subestructura del núcleo de los alcaloides curano, como ejemplo del potencial de esta metodología

para acceder rápidamente a complejas estructuras moleculares de una manera simple y directa

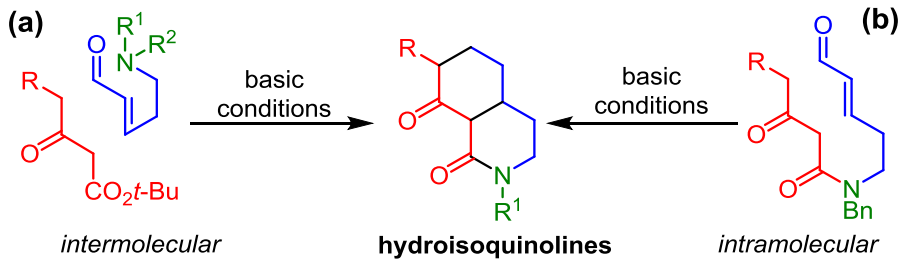


Esquema 3 Síntesis del sistema indolomorfanos “one-pot”.

Hidroisoquinolinas:

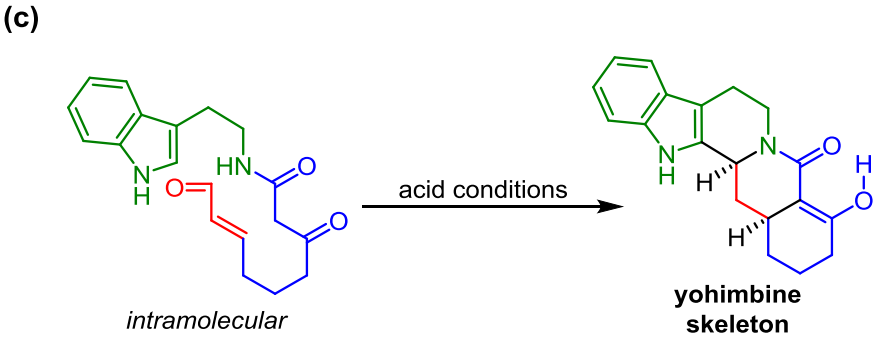
Para ampliar el alcance de la reacción, se evaluaron 3 enfoques diferentes para la formación del núcleo hidroisoquinolinico:

(*a*) El enfoque intermolecular se basa en el re-direccionamiento de la reacción de morfano, utilizando un intermedio en común que dependiendo de las condiciones conduce a una estructura u otra. Sin embargo, en comparación a las series desarrolladas hasta ahora (decahidroquinolinas y octahidroindoles) se encontró que de forma inesperada la utilización de carbamatos se ve favorecida la reacción aza-Michael generando de esta manera una nueva serie morfanos. Se emplearon aceptores de Michael donde el átomo de nitrógeno estuviera bis-protegido, permitiendo la formación de un anillo de ciclohexenona que seguido de una hidrogenación que escinde del grupo carbamato y reduce la funcionalidad enona. Tras utilizar condiciones de reflujo, se produce una condensación entre el grupo ester y la amina bencil-protegida dando como resultado la ciclación que da paso a la formación del sistema hidroisoquinolinico.



Esquema 4 Síntesis del sistema perhidroisoquinolinico via reacción intra- e intermolecular.

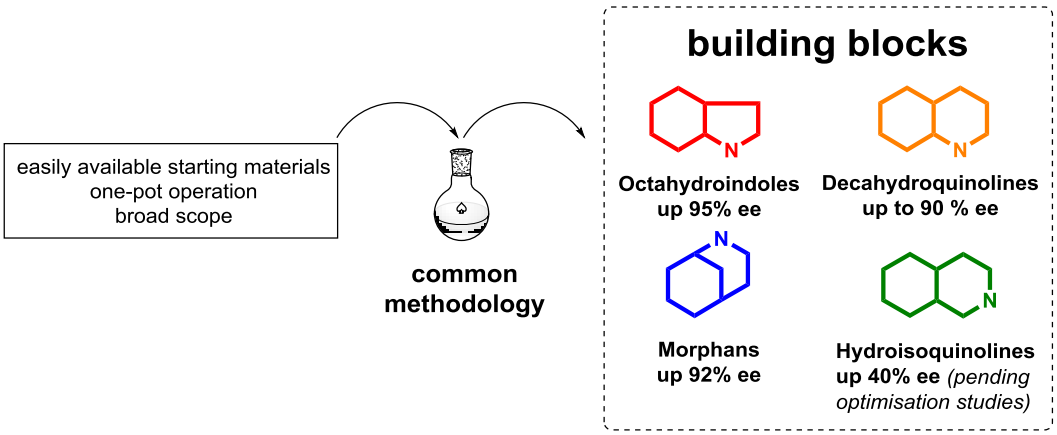
(*b*) Invirtiendo el orden de formación de los anillos involucrados en la reacción (formando del anillo piperidona/ciclohexenona) mediante un enfoque intramolecular, también fue observada la formación del sistema de anillos hidroisoquinolinicas. Sin embargo, la formación controlada de los anillos se complicó debido la espontánea y lábil ciclación mediante una adición de Michael intramolecular.



Esquema 5 Síntesis del sistema pentaciclico de yohimbinano.

(*c*) Una nueva orientación de la reacción intramolecular desarrollada anteriormente permitió la formación del esqueleto pentacíclico yohimbinano de manera directa en una reacción domino. Donde esta vez, en lugar de una reacción aza-Michael se empleó una reacción de Mannich/indol. Tras la formación del enal (a través de una metátesis cruzada), la estructura pentacíclica fue generándose de manera espontánea, donde una vez más, por la naturaleza lábil y favorecida de la ciclación intramolecular permite la obtención de la estructura deseada en condiciones de preparación de material de partida o a través de etapas de purificación posteriores.

El trabajo realizado en esta tesis, amplía el potencial de la reacción tándem inicialmente desarrollado y demuestra que es un proceso general que puede permitir la síntesis de diversos anillos de manera asimétrica.



Esquema 6 Metodología en común para la preparación de importantes núcleos asimetricos.

ANNEX II
PUBLISHED ARTICLES

ORGANIC LETTERS

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Organocatalyzed Asymmetric Synthesis of Morphans

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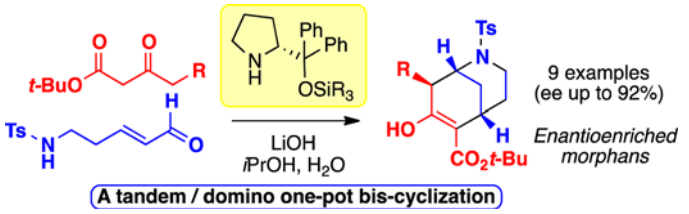
ABSTRACT



A general effective organocatalyzed synthesis of enantioenriched morphans with up to 92% ee was developed. The morphan scaffold was constructed in a one-pot tandem asymmetric organocatalyzed Michael addition followed by a domino Robinson annulation/aza-Michael intramolecular reaction sequence from easily available starting materials.

The morphan ring system (2-azabicyclo[3.3.1]nonane) features prominently in many complex and biologically active natural products as well as medicinal compounds of significant interest, including *Strychnos*,[1] madangamines,[2] some *Daphniphyllum* alkaloids[3] and the immunosuppressant FR901483[4] (Figure 1).

Despite the plethora of methods that have been developed for the formation of the morphan nucleus, to date[5] no general catalytic asymmetric strategy to polyfunctionalized enantiopure morphan ring systems has been developed.[6,7] Here, we outline an effective asymmetric organocatalyzed strategy to this nucleus, based on a tandem Michael addition/domino Robinson annulation and aza-Michael intramolecular reaction.

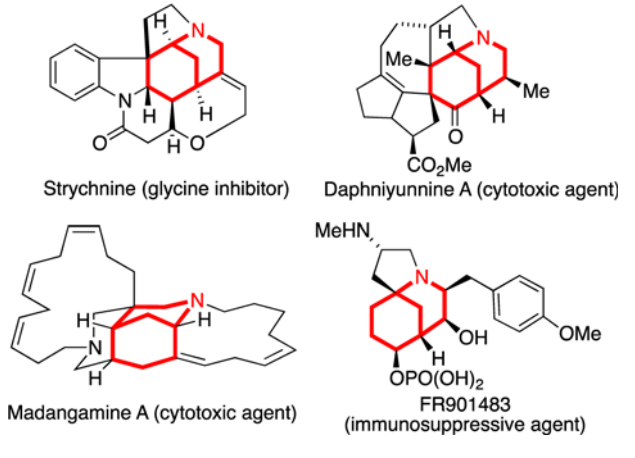


Figure 1. Natural products containing the morphan (2-azabicyclo-[3.3.1]nonane) nucleus.

Recently, we reported the synthesis of enantiopure decahydroquinolines via an organocatalyzed Robinson annulation/aza-Michael reaction, which constructed the ring system in one pot, generating three stereogenic centers

(1) (a) Cannon, J. S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288–4311. (b) Solé, D.; Bonjoch, J. *Chem. Rev.* **2000**, *100*, 3455–3482.

(2) (a) Amat, M.; Ballette, R.; Proto, S.; Pérez, M..; Bosch, J. *Chem. Commun.* **2013**, *49*, 3149–3151. (b) Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem.* **2008**, *73*, 768–771.

(3) Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499–5501.

(4) (a) Huo, H.-H.; Xia, X.-E.; Zhang, H.-K.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 455–465. (b) Bonjoch, J.; Diaba, F. *Stud. Nat. Prod. Chem.* **2005**, *32*, 3–60.

(5) For a review of approaches to morphan-containing natural products, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, *7*, 993–1018. For a recently reported approach, see: Garrido, N. M.; Nieto, C. T.; Díez, D. *Synlett* **2013**, *24*, 169–172.

(6) For an organocatalyzed enantioselective method using a desymmetrization reaction, see: Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517–2519.

(7) For synthesis of enantiopure morphans using a chiral auxiliary, see: (a) G. Karig, G.; Fuchs, A.; Büsing, A.; Brandstetter, T.; Scherer, S.; Bats, J. W.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1049–1078. (b) Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J.; Lago, E.; Molins, E. *C. R. Acad. Sci.* **2001**, *4*, 513–521. (c) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923.

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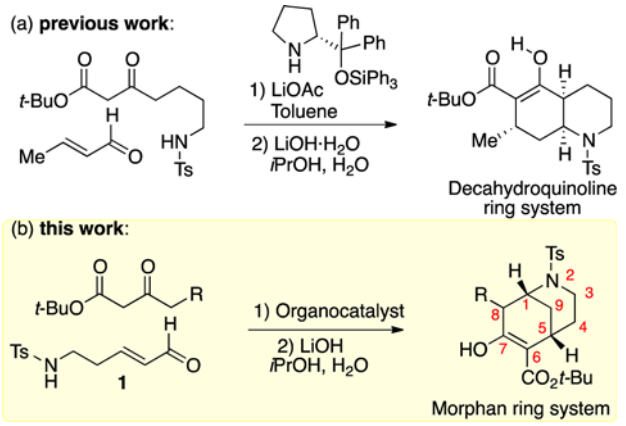
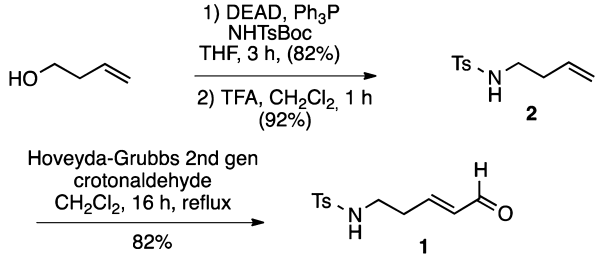
Scheme 1. Synthesis of Nitrogen-Containing Heterocycles by Forming Three Bonds in a One-Pot Reaction



in the process[8] (Scheme 1a). We postulated that this method could be adapted to access the morphan ring system by moving the tethered nucleophilic *N*-Tosyl group from the keto ester to the enal component (Scheme 1b). However, it was not clear at the outset that the direct application of the original method would be feasible, since the resulting enal **1** would now bear both nucleo- and electrophilic centers. Indeed, similar compounds separated by additional carbons have been used in organocatalyzed intramolecular aza-Michael reactions.[9] We hoped that in our case the formation of the azetidine ring by intramolecular cyclization would be sufficiently disfavored to allow the intermolecular Michael reaction.

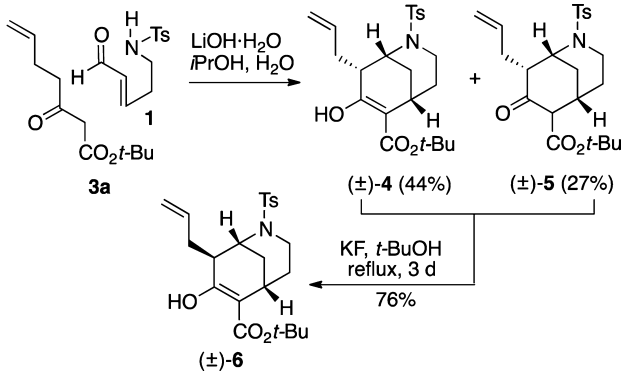
Scheme 2. Synthesis of Enal **1**



The required enal **1** was synthesized in a straightforward manner from 3-buten-1-ol via Mitsonobu coupling with *tert*-butyl tosylcarbamate[10] and removal of the Boc group with TFA, followed by a cross metathesis reaction of the resultant alkene **2** with the Hoveyda–Grubbs second generation catalyst and crotonaldehyde[11] (Scheme 2).

With enal **1** in hand, we began our studies by investigating the coupling reaction in the nonasymmetric form. Upon treatment of an equimolar mixture of **1** and the keto ester **3a** with $LiOH \cdot H_2O$ in *i*PrOH/H_2O, we were pleased to observe the formation of the desired morphan **4** (Scheme 3). A second, more polar compound **5** was also isolated, which was identified as the same cyclized product in its keto tautomeric form. Surprisingly, it was possible to separate these two compounds by column chromatography, and once isolated they did not undergo equilibration in solution,[12] allowing their NMR structures to be determined. In both cases, the allyl substituent was determined to be equatorial.

Scheme 3. Evaluation of Feasibility of Robinson/Aza-Michael Reaction in Racemic Form



Access to the axially positioned substituent product **6** was achieved by refluxing the mixture of **4** and **5** with KF in *t*-BuOH for 3 days.[13] To rationalize the observed stereochemistry of the allyl substituent, it was presumed that upon attack of the *N*-Tosyl group, the resulting enolate protonates from the less hindered top face to give **4** and **5**, with the allyl in the equatorial position (kinetic products). The resulting steric compression suffered by the allyl substituent with the tosyl group[14] was minimized in the kinetic isomer **4** by nitrogen inversion. The axial orientation of the *N*-tosyl group relieved the steric crowding with the equatorial side chain at C-8. This conformational change was deduced from a shielding at C-4 observed when comparing the ^{13}C NMR spectra of **4** and the thermodynamic isomer **6**. In the latter, the allyl group axially located at C-8 allowed the *N*-tosyl to adopt an equatorial disposition (Figure 2).

(8) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326–329.

(9) For the use of this type of compound for the formation of piperidines via organocatalysis, see: Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. For a general review on organocatalytic asymmetric aza-Michael reactions, see: Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058–11076.

(10) Teichert, J. F.; Zhang, S.; Zijl, A. W. v.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658–4660.

(11) For a related procedure, see: Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xaiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492.

(12) It should be noted, however, that upon prolonged standing the pure compounds would revert to mixtures of the enol/keto forms.

(13) For thermodynamic isomerization of α-substituted cycloalkanones using KF, see: Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010**, *132*, 5966–5967.

(14) For a related 1,3-syn interaction within the *N*-substituent and alkyl side chain in C-8 in morphan compounds, see: Bonjoch, J.; Casamitjana, N.; Quirante, J.; Torrens, A.; Paniello, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 377–381.

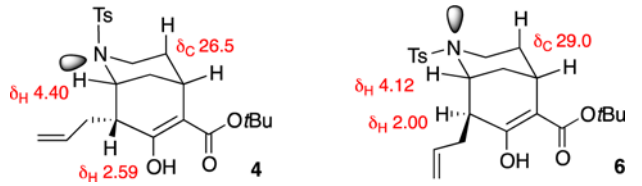
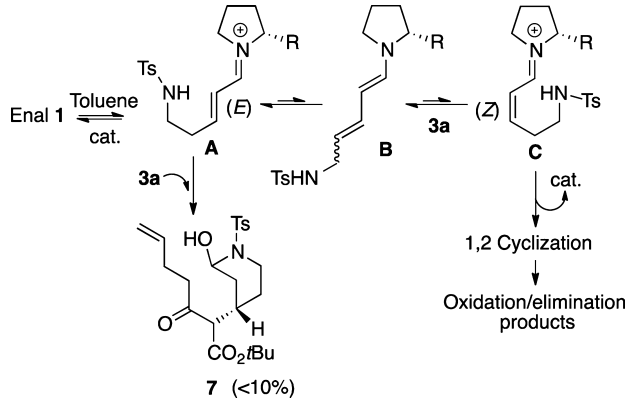


Figure 2. Stereochemical assignment of compounds **4** and **6**.

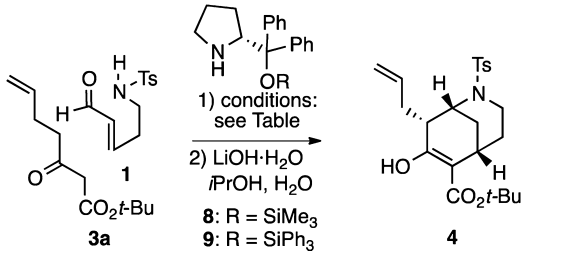
Having proof of concept, we then turned to investigate the reaction in asymmetric form. Unfortunately, upon treatment of keto ester **3a** with enal **1** in the presence of the Hayashi–Jorgensen catalyst **8**[15] in a range of organic solvents,[16] we observed only trace amounts of the Michael addition product **7**, which existed exclusively in its hemiaminal form (Scheme 4). While the keto ester **3a** was stable under the reaction conditions, enal **1** was slowly consumed into an unidentified product. We believe that the side reaction is a result of an isomerization of the double bond of **A** via the dienamine **B**[17] to form the cis isomer **C**, which

Scheme 4. Organocatalyzed Michael Reaction of **1** and **3a** and Loss of Enal **1** via a Parasitic Catalytic Cycle



then cyclizes to form a six-membered ring, followed by subsequent oxidation.[18] It should be noted that this side reaction did not occur in the absence of **3a**, indicating that the keto ester must somehow facilitate the isomerization by proton transfer processes. To prevent the undesired intramolecular reaction, protection of the free NH of **1** as an acetamide[19] was investigated. Unfortunately, only trace quantities of the coupled product were observed,[20] indicating that the Michael reaction is generally unfavorable. By carrying out the coupling reaction of **1** and **3** in the absence of any solvent, the reaction was noticeably accelerated and we were able to obtain moderate quantities of the coupled product **7**. Treatment of the crude mixture with LiOH in *i*PrOH/H_2O led to the cyclized product in 79% ee and moderate 38% overall yield for the two steps (Table 1, entry 1). Again, the product was isolated as a mixture of enol/keto forms (~3:1 ratio; only the enol form is shown for clarity). To improve the reaction, a series of additives (BzOH, TBAB,[21] $NaHCO_3$, LiOAc) were investigated, with significantly improved yields being obtained with the LiOAc (Table 1, entry 3). The use of water as an additive (10 equiv) led to both an increase in yield and ee (Table 1, entry 7). Carrying out the reaction at reduced temperature, however, proved to be detrimental (Table 1, entry 9). Switching to the more impeded catalyst **9**[8,22] gave

Table 1. Screening of Conditions[a] for Organocatalyzed Synthesis of Morphans



entry	additive (equiv)	R	temp	yield (%)[b]	ee (%)
1	–	TMS	rt	38	79
2	BzOH (0.1)	TMS	rt	34	51
3	LiOAc (0.1)	TMS	rt	61	79
4	$NaHCO_3$ (0.1)	TMS	rt	37	81
5	TBAB (0.1)	TMS	rt	43	75
6	H_2O (0.1)	TMS	rt	28	83
7	H_2O (10)	TMS	rt	69	88
8[c]	H_2O (10)	TMS	rt	41	80
9	H_2O (10)	TMS	0 °C	52	73
10	H_2O (10)	$SiPh_3$	rt	67	88
11	LiOAc (0.1)	$SiPh_3$	rt	66	86
12	LiOAc (0.1)	$SiPh_3$	0 °C	62	64
13	LiOAc(0.1)/H_2O(10)	$SiPh_3$	rt	52	90
14[d]	LiOAc(0.1)/H_2O(10)	$SiPh_3$	rt	55	92

[a] Conditions: 2 equiv of keto ester **3a**, 1 equiv of enal **1**, 10% catalyst, 3 h then add *i*PrOH (4 mL/mmol of enal), LiOH·H_2O (3 equiv), H_2O (10 equiv), 16 h. [b] Yield is given for enol and keto forms combined. [c] 1:1 Ratio of keto ester and enal used. [d] Reaction time 24 h for the initial step.

(15) (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215. (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.

(16) Solvents screened were toluene, CH_2Cl_2, and MeOH; all gave equally poor results so a detailed solvent screen was not undertaken.

(17) For isomerization of enals to dienamines via organocatalysis, see: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

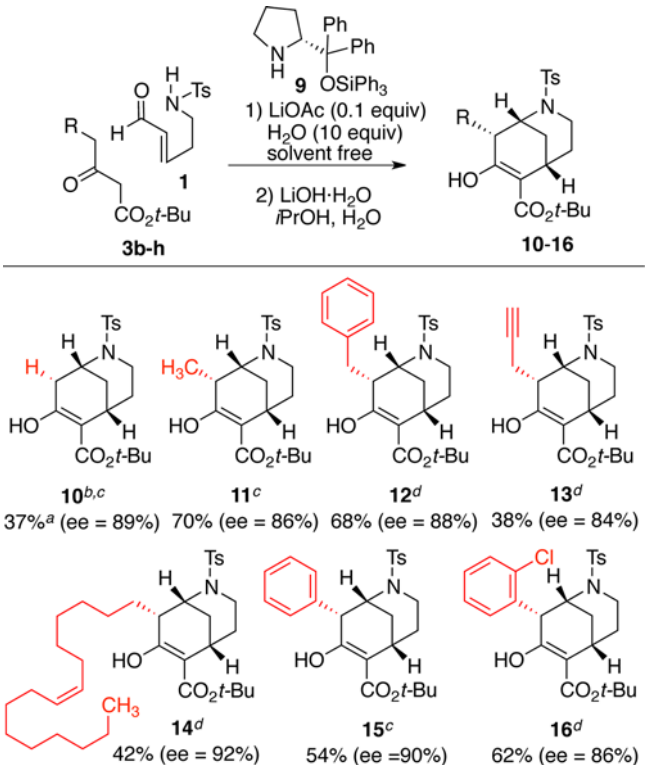
(18) For related intramolecular cyclization of N-Ts derivatives to form pyridines, see: Donohoe, T. J.; Bower, J. F.; Baker, D. B.; Basutto, J. A.; Chan, L. K. M.; Gallagher, P. *Chem. Commun.* **2011**, *47*, 10611–10613.

(19) Since N-Ts acetamides can be cleaved under mildly basic conditions, it was planned to liberate the NH-Ts group under the cyclization conditions, thus eliminating the need for a separate deprotection step.

(20) Presumably the formation of the hemiaminal (e.g., **7**) is important since it helps drive the reaction forward by removing the formed aldehyde from competition with the organocatalyst, as well as preventing a possible retro-Michael reaction.

(21) TBAB refers to tetrabutylammonium bromide. For its use, see: Duce, S.; Mateo, A.; Alonso, I.; Garcia Ruano, J. L.; Cid, M. B. *Chem. Commun.* **2012**, *48*, 5184–5186.

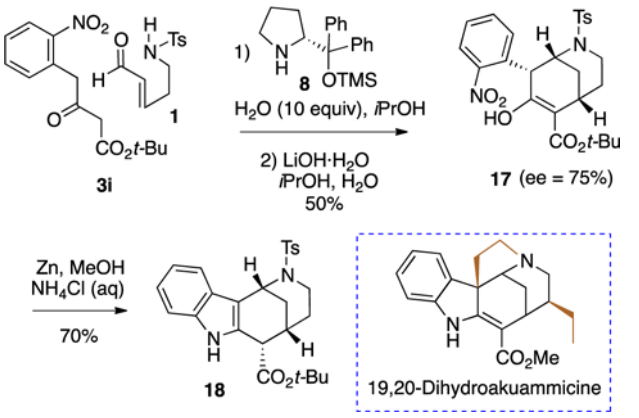
Scheme 5. Synthesis of C-8 Substituted Morphans[a]



[a] Conditions: 2 equiv of ketoester **3**, 1 equiv of enal, 10% catalyst, 24 h then add *i*PrOH (4 mL/mmol of enal), LiOH·H_2O (3 equiv), H_2O (10 equiv), 24 h. [b] Step ii required 48 h to reach completion. [c] Forms predominantly or exclusively as the enolic form. [d] Forms as a mixture of enol/keto forms; yields are given for both forms combined. For the tautomer ratio, see Supporting Information.

similar results to catalyst **8** when water was used as the additive (Table 1, entry 10), but it proved to be superior when LiOAc was used (in Table 1, compare entry 3 vs 11). Again, reducing the temperature resulted in significantly inferior results (entry 12). The use of both additives together, as opposed to individually, proved to be superior (Table 1, entry 14), with the enantioselectivity increasing to 92%.[23]

Scheme 6. Synthesis of Indolomorphan **18**



To explore the scope of the reaction, a number of varied keto ester substrates (**3b**–**h**)[24] were used in the coupling reaction. As can be seen in Scheme 5, the reaction works with a wide range of substrates, including both aliphatic and aromatic substituents, with some compounds being isolated predominantly in the enol form. Although in some cases the yields were moderate, we believe this reflects difficulties in mixing the reagents under solvent-free conditions.

To further expand the potential of the reaction, we proposed it should be possible to add a third tandem reaction using the C-8 substituent in an additional ring-forming step. The 2-nitrophenyl keto ester **3i** was coupled with enal **1** under modified conditions[25] to give morphan **17** possessing a latent indole moiety (Scheme 6). Treatment with Zn, NH_4Cl(aq)[26] gave indole **18**, which contains the core structure of curan-type alkaloids,[27] showing the potential of this methodology to rapidly access complex molecular scaffolds in a simple, straightforward manner.

In conclusion, the first effective catalytic route to poly-functionalized enantiopure morphans has been developed using a one-pot organocatalyzed Robinson/aza-Michael reaction. The convergency and potential flexibility of this method should open up new effective disconnection approaches for the total synthesis of morphan-containing natural products. Work in this direction is currently in progress.

Acknowledgment. Support of this research was provided by the Spanish Ministry of Economy and Competitiveness (Project CTQ2010-14846/BQU). C.P. is a recipient of a predoctoral fellowship (CONICYT, Chile).

Supporting Information Available. Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353–357.

(23) The absolute configuration proposed for morphan **4** is based on the accepted mechanism of organocatalyzed Michael addition of β-keto esters upon enals: Jensen, K. L.; G. Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

(24) Keto esters **3** were prepared by coupling the correpsponding carboxylic acid with Meldrum's acid using DCC, followed by refluxing in *t*-BuOH. For an early use of this methdology, see: Li, B.; Franck, R. W: *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629–2634.

(25) Due to the highly crystalline nature of **17** and the coupled product, mixing of the reagents proved difficult and the conditions of the initial organocatalytic step had to be modified. Heating was used to melt the substrates and the catalyst was switched to catalyst **8**, which, unlike catalyst **9**, exists as an oil.

(26) Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *Org. Biomol. Chem.* **2008**, *6*, 772–778.

(27) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230–7240.