Asymmetric synthesis of heterocycles using sulfinimines (*N*-sulfinyl imines)

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Abstract
The efficient asymmetric synthesis of nitrogen heterocycles including the quinolizidine alkaloid (-)-epimyrtine, indolizidine alkaloids 209B and 223A, and (-)-agelastatin A using easily prepared sulfinimine-derive chiral building blocks is described.

Keywords: Asymmetric synthesis, sulfinimine, nitrogen heterocycles

Contents

1. Introduction

Sulfinimines, *N*-sulfinyl imines (R^1-S(O)N=CR^2R^3), developed in our laboratory, provide a general solution to the problem of addition of organometallic reagents to chiral imines. The electron-withdrawing sulfinyl group activates the C=N bond for addition, is highly stereodirecting, and is easily removed to give the enantiopure amine product.[1] In fact the most direct and reliable method for the asymmetric construction of diverse amine derivatives having nitrogen attached to a stereogenic center is the addition of an organometallic reagent to the C=N

bond of an enantiopure sulfinimine. This includes the asymmetric synthesis of nitrogen heterocycles.

The current focus of our research is the design and synthesis of sulfinimine-derived polyfunctionalized chiral building blocks for the asymmetric synthesis of multi-substituted nitrogen heterocycles. We required these building blocks to be easily prepared in both enantiomerically pure forms and provide access to diverse classes of nitrogen heterocycles with a minimum of chemical manipulation and protecting group chemistry. In this context we have prepared *N*-sulfinyl δ-amino β-ketoesters for the asymmetric synthesis of 2,4,6-trisubstituted piperidines[2] and 2,3,5-trisubstituted pyrrolidines (prolines);[3] *N*-sulfinyl δ-amino β-ketoester enaminones for the synthesis of 2,4,6-trisubstituted piperidines;[4] β-amino Weinreb amides and β-amino ketones for the synthesis of 2,3,4,6-tetrasubstitued piperidines[5,6] and 2,3,4,5,6-pentasubstituted piperidines;[7] aziridine 2-carboxylates for the synthesis of 2*H*-azirine 2-carboxylates;[8] and aziridine-2-phosphonates for 2*H*-azirine-3-phosphonates (Figure 1).[9] Generally these building blocks are prepared in one pot by addition of an enolate species to a sulfinimine.

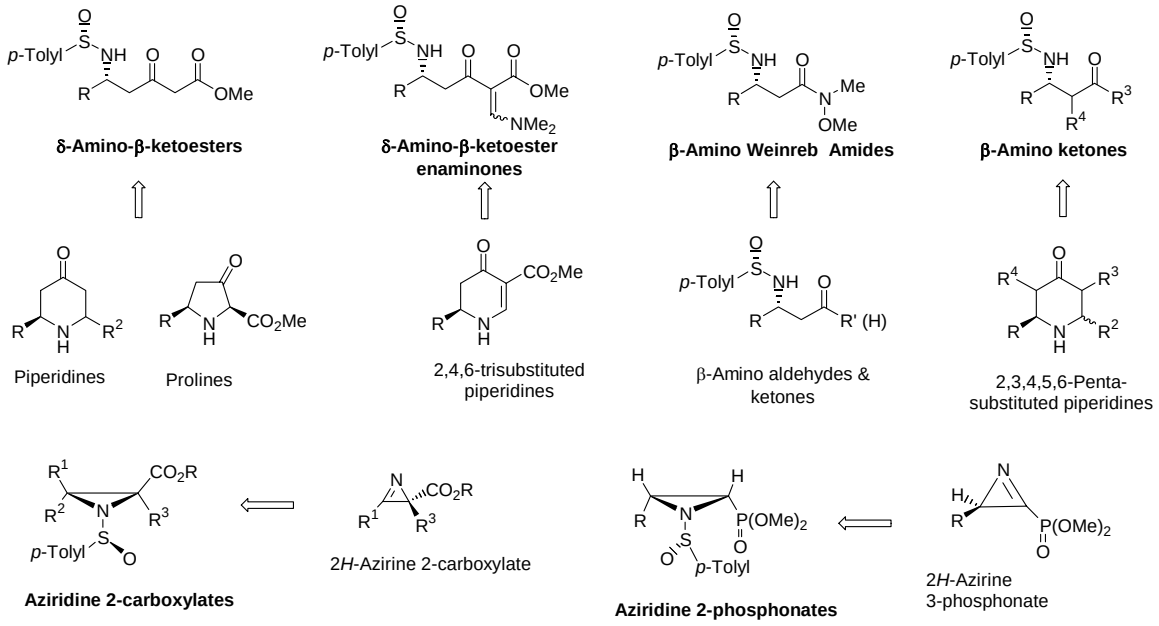
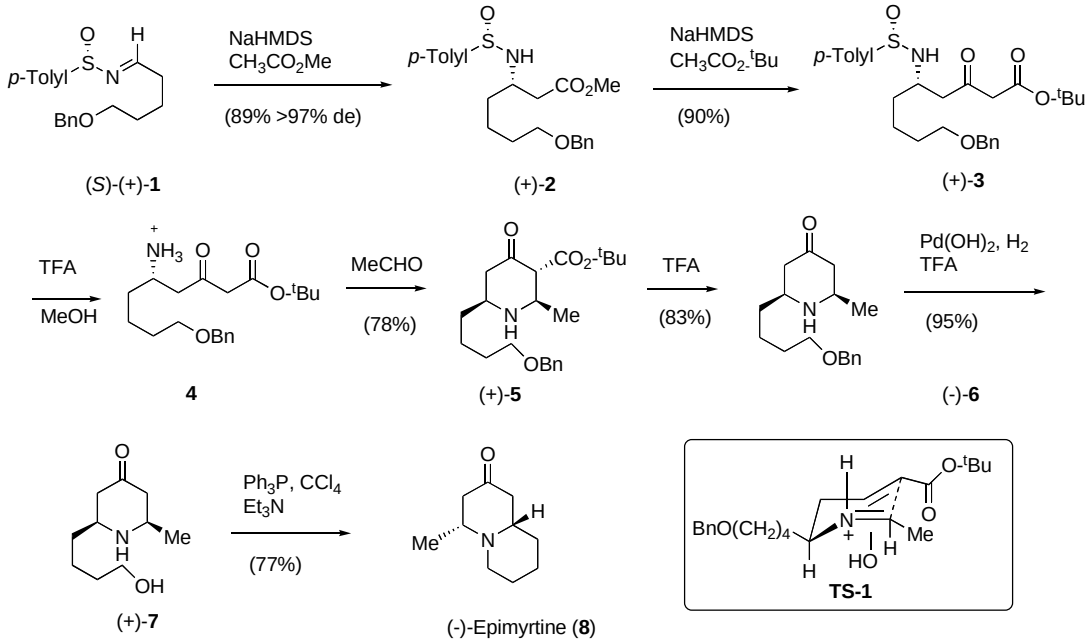


Figure 1. Examples of sulfinimine-derived chiral building blocks for the asymmetric synthesis of nitrogen heterocycles.

The following examples demonstrate the utility of δ-amino β-ketoesters and β-amino ketones for the asymmetric synthesis of piperidine alkaloids. The piperidine ring system is a common motif found in many natural products, as well as drugs and drug candidates. Furthermore piperidines are precursors of more elaborate heterocycles including the quinolizidine and indolizidine ring systems.

2. Asymmetric Synthesis of (-)-Epimyrtine

The intramolecular Mannich reaction is a particularly useful transformation for the rapid and stereoselective assembly of functionalized piperidines and is illustrated by a short asymmetric synthesis of the quinolizidine alkaloid (-)-epimyrtine (**8**) (Scheme 1).[2f] Our synthesis employs δ-amino β-ketoester (+)-**3** as a key intermediate. This sulfinimine-derived chiral building block is readily prepared by reacting *N*-sulfinyl β-amino ester (+)-**2** with the sodium enolate of *tert*-butyl acetate. The β-amino ester (+)-**2** is prepared in excellent yield and de by treating sulfinimine (+)-**1** with the sodium enolate of methyl acetate. Removal of the sulfinyl group in (+)-**3** with TFA/MeOH affords salt **4** that on reaction with acetaldehyde gives tetrasubstituted piperidine (+)-**5** in 78% isolated yield for the two-step sequence. The fact that a single isomer was obtained is in accord with an intramolecular Mannich transition state **TS-1**. Decarboxylation of (+)-**5**, followed by deprotection and cyclization affords (-)-epimyrtine (Scheme 1) and represents a general route to this class of heterocycles.



Scheme 1

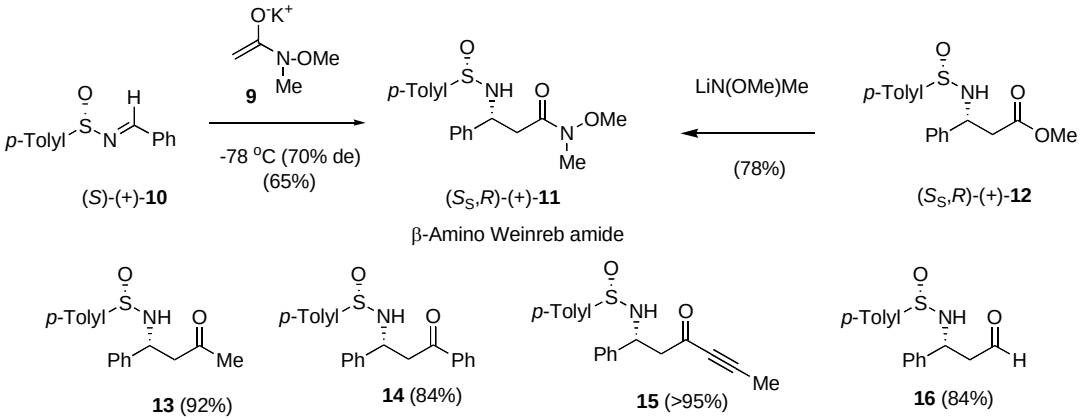
3. Asymmetric Synthesis of (-)-Indolizidine 209B

To prepare a 2,3,6-trisubstituted piperidine employing the intramolecular Mannich protocol requires access to β-amino ketones. While β-amino ketones are found in several natural products and are precursors of the 1,3-amino alcohols they have been under utilized as chiral

building blocks because of the lack of methods to prepare them in enantiomerically pure form. We solved this problem by introducing β-amino Weinreb amides.[5]

3.1 β-Amino Weinreb amides

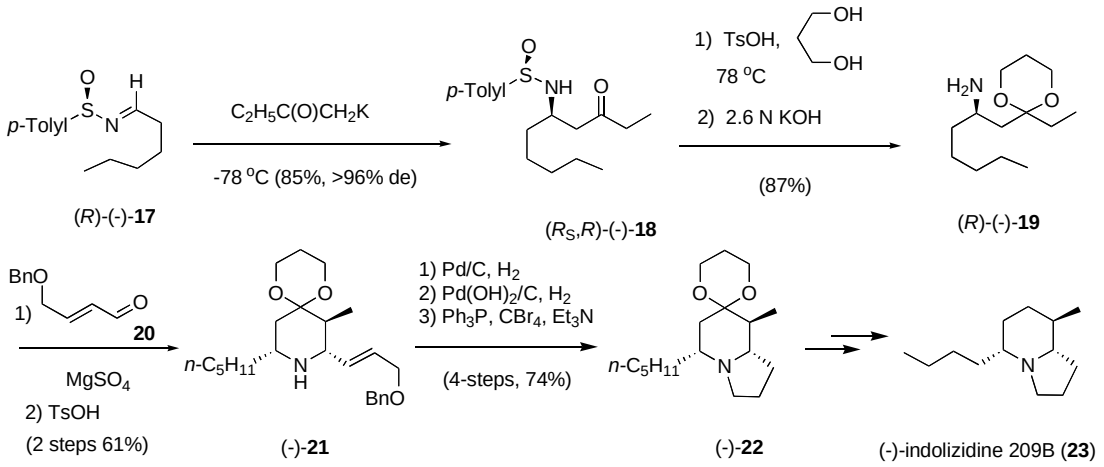
N-Sulfinyl β-amino Weinreb amides such as (+)-**11** are prepared by reaction of the potassium enolate of *N*-methoxy-*N*-methylacetamide (**9**) with sulfinimine (*S*)-(+)-**10** or lithium *N*,*O*-dimethylhydroxylamine with the corresponding β-amino ester (+)-**12** (Scheme 2).[5] This Weinreb amide reacts with excess methylmagnesium bromide to give the methyl ketone **13**, with phenylmagnesium bromide to give the phenyl ketone **14**; with 1-propynylmagnesium bromide to give the alkynyl ketone **15**; and with DIBAL-H to give the aldehyde **16** (Scheme 2). These β-amino ketones are stable, can be stored for long periods of time, and provide additional evidence for superb amine protecting group ability of the *N*-sulfinyl group.



Scheme 2

3.2 β-Amino ketones

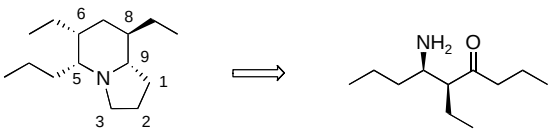
β-Amino ketones can be prepared directly, with excellent diastereoselectivity, by reacting the potassium enolates of methyl ketones with sulfinimines.[6] For example, the potassium enolate of methyl ethyl ketone reacts with sulfinimine (*R*)-(-)-**17** to give β-amino ketone (-)-**18** in >96% de (Scheme 3). One-pot deprotection/protection of **18** with TsOH and 1,3-propanediol afforded the corresponding β-amino ketal (-)-**19** in 87% isolated yield. This protected amino ketone is a valuable chiral building block for the asymmetric synthesis of polysubstituted, *cis*-2,6-disubstitute piperidines: on reaction with aldehydes such as **20** it undergoes a facile, highly stereoselective intramolecular Mannich cyclization to give piperidine (-)-**21** in 61% yield for the two steps (Scheme 3). Deprotection of the benzyloxy group and cyclization gave (-)-**22**. Removal of the keto group afforded the dendrobatide frog skin toxin (-)-indolizidine 209B (**23**).[6] This synthesis represents the most efficient asymmetric synthesis of this alkaloid recorded to date.



Scheme 3

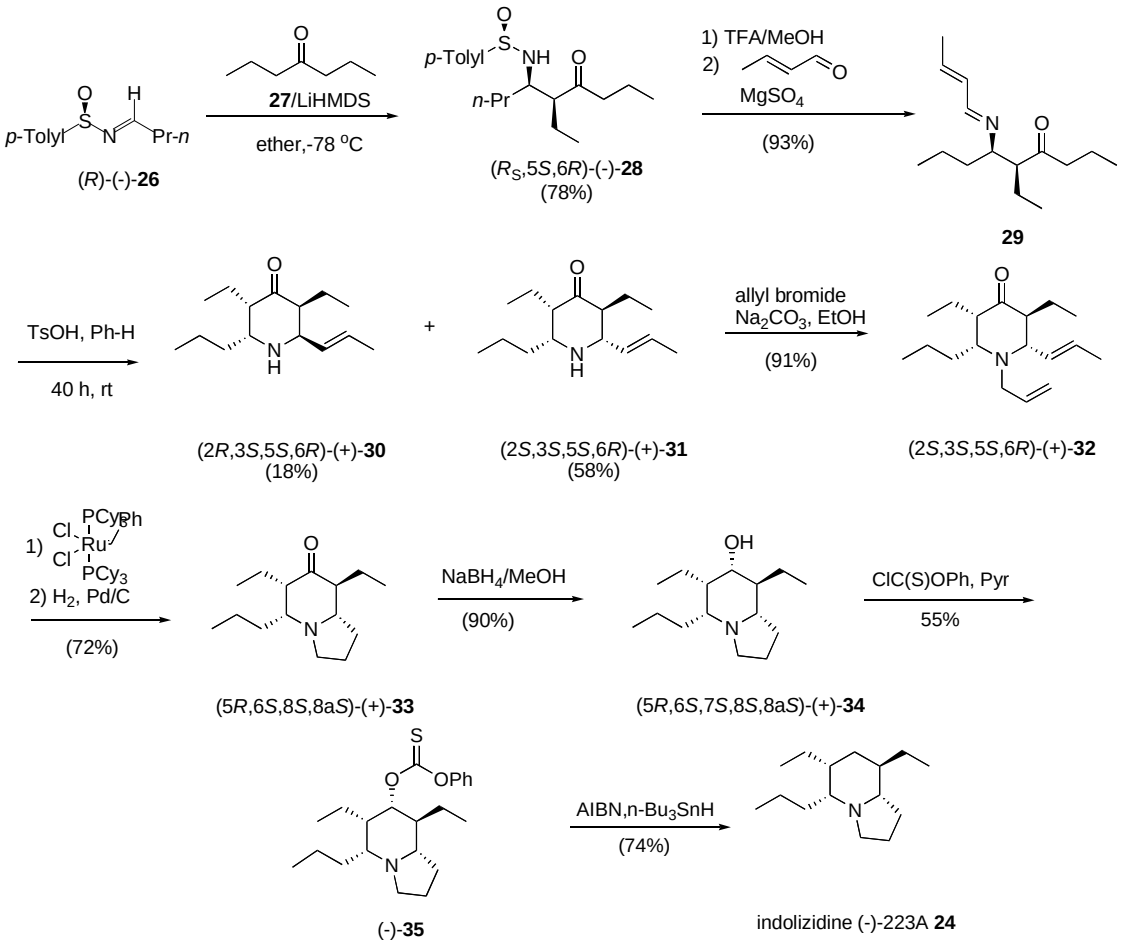
4. Asymmetric Synthesis of (-)-Indolizidine 223A

While most of the isolated indolizidine alkaloids have the 3,5- or 5,8-disubstituted structure, e.g. **23**, (-)-223A (**24**) was the first trisubstituted indolizidine alkaloid to have been isolated from the skin of toxic dendrobatide frogs.[10] To prepare 223A (**24**) using the intramolecular Mannich protocol requires access to (5*S*,6*R*)-6-amino-5-ethylnonan-4-one (**25**), a *syn*-α-substituted β-amino ketone (Scheme 4).



Scheme 4

We found that addition of the lithium enolate of 4-heptanone (**27**) to sulfinimine (*R*)-(-)-**26** gave two of a possible four stereoisomeric products (Scheme 5).[7]



Scheme 5

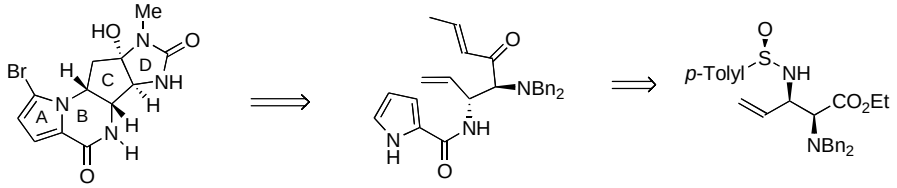
The major product was the *syn*-β-amino ketone (-)-**28** isolated in 78% yield with the anti isomer being obtained in less than 8% yield. We noted an unusual solvent effect on the formation of the syn- and anti-isomers. The E enolate of **27** is believed to give to the syn-product **28**. In diethyl ether the syn/anti-ratio was 10:1, but dropped to 4:1 in THF. These results were rationalized in terms of Ireland's transition state model: in the poorly coordinating diethyl ether solvent, increased steric interactions between the ethyl group and the carbonyl-$LiN(TMS)_2$ moiety destabilized the transition state leading to the Z enolate.[11]

With the *syn*-β-amino ketone (-)-**29** in hand the *N*-sulfinyl group was removed and free amine was immediately treated with crotonaldehyde to give the crude imine **29** in better than 93% yield. Treatment of **29** with TsOH afforded two Mannich products (+)-**30** and (+)-**31** in 18% and 58% yields, respectively (Scheme 5). Allyl bromide and (+)-**31** gave diene **32** which when subject to ring-closing metathesis using 5% of Grubbs first generation catalyst, followed by hydrogen gave indolizidine (+)-**33** in 72% yield. To remove the 7-oxo group the only method found to be successful was a radical deoxygenation protocol wherein the oxo group was reduced and the alcohol (+)-**34** was transformed into the phenylthionocarbonate **35**. On reaction with tri-

n-butyltin hydride and AIBN **35** afforded indolizidine alkaloid (-)-223A (**24**) in 74% yield. Our synthesis of (-)-**24**, the most concise to date was accomplished in nine steps (9.3% overall yield) from sulfinimines (-)-**26**.

5. Asymmetric Synthesis of (-)-Agelastatin A

(-)-Agelastatin A (**36**) is an architecturally unique cytotoxic tetracyclic alkaloid first isolated from a marine sponge *Agelas dedromorpha* in 1993 (Scheme 6).[12] At low concentrations this alkaloid exhibits potent cytotoxicity against L1210 in mice and human KB nasopharyngeal tumor cell lines.[13] To date the mechanism of antitumor activity has not been elucidated. Three syntheses of this alkaloid have reported. A racemic synthesis was first reported by Weinreb and co-workers and employed a hetero Diels-Alder cycloaddition reaction.[14] The Feldman and Saunders enantioselective synthesis of (-)-**36**, a vinylcarbene C-H insertion sequence was used for the preparation of the C-ring core,[15] and a chiral bicyclic cyclopentene oxazolidinone intermediate was exploited by Hale and co-workers in their synthesis of this alkaloid.[16]

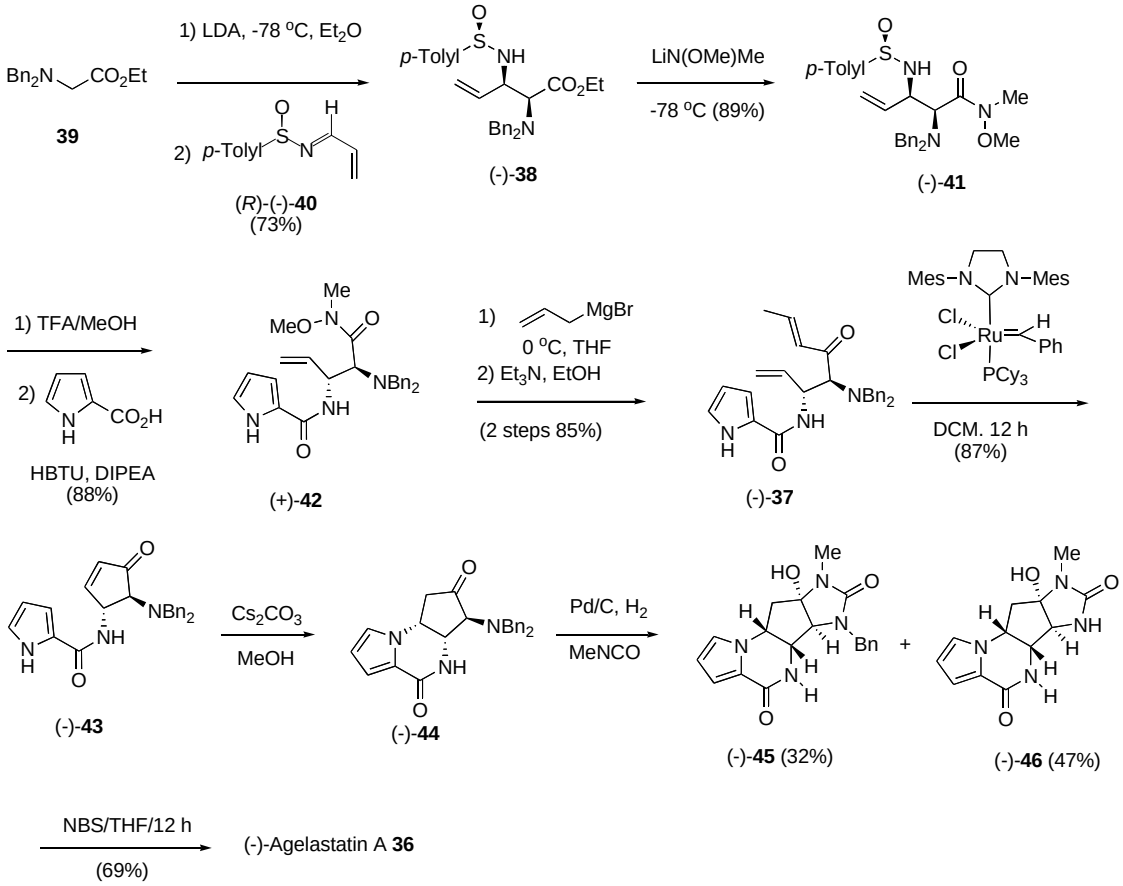


(-)-Agelastatin A **36** (-)-**37** (-)-**38**

Scheme 6

Our synthesis of (-)-**36**, which draws on the Weinreb,[14] Feldman[15] and Hale[16] syntheses, utilizes *syn*-1,2-diamino ester (-)-**38**, formed from diene (-)-**37**, and a ring-closing metathesis strategy to generate our key C-ring intermediate (Scheme 6). To prepare the 2,3-diamino ester (-)-**38** we treated the acrolein-derived sulfinimine (*R*)-(-)-**40** with the lithium enolate of (dibenzylamino)acetate (**39**),[18] which was then converted into the Weinreb amide (-)-**41** (Scheme 7). Selective deprotection of the sulfinyl group and coupling of the free amine with pyrrole-2-carboxylic acid gave (+)-**42** in excellent yield. Diene (-)-**37** was prepared by reacting Weinreb amide (+)-**42** with allyl magnesium bromide. Ring-closing metathesis with Grubb's second-generation catalyst afforded our key C-ring intermediate (-)-**43**. The intramolecular Michael addition of (-)-**43** to (-)-**44** was effected using Cs_2CO_3, as described by Weinreb.[14] Initial attempts to remove the *N*,*N*-dibenzyl with 10% Pd-C/H_2 resulted in decomposition. However, when the hydrogenation deprotection step was carried out in the presence of methyl isocyanate two products (-)-**45** and (-)-**46** were isolated in 32% and 47% yield, respectively (Scheme 7). Twelve hour bromination of (-)-**46** with NBS, according to the Feldman protocol,[15] afforded (-)-

agelastatin A (**36**) in 69% isolated yield. Our synthesis of (-)-agelastatin A (**36**) is the most efficient to date and was accomplished in approximately 11 steps with eight operations (9% overall yield) from sulfinimine (-)-**40**.



Scheme 7

6. Summary and Conclusions

Sulfinimine-derived chiral building blocks including δ-amino-β-ketoesters, β-amino Weinreb amides, β-amino ketones, and *syn*-2,3-diamino esters provide efficient access to enantiopure nitrogen heterocycles. Asymmetric syntheses using these polyfunctionalized building blocks are concise and require a minimum of protecting group chemistry. The examples given here illustrate new and general methodology for the asymmetric syntheses of complex nitrogen heterocycles in a highly stereocontrolled manner.

Acknowledgements

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7. References

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