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Asymmetric Synthesis of Alkaloids Using Polyfunctionalized Chiral Building Blocks

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ABSTRACT: *Enantiopure N-sulfinyl-δ-amino-β-ketoesters and isoquinolones, prepared from sulfinimines (N-sulfinyl imines) are a new class of polyfunctionalized chiral building blocks. These building blocks provide easy access to enantiomerically pure, functionalized piperidines and tetrahydroisoquinolines with a minimum of chemical manipulation and protecting-group chemistry.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:486–492, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10090

INTRODUCTION

Polyfunctionalized chiral building blocks, which we define as molecules having at least one stereogenic center and more than one chemically differentiated functional group, have played significant roles in asymmetric synthesis and the synthesis of biologically and pharmacologically active molecules [1]. Examples include carbohydrates, amino acids, hydroxy acids, and terpenes. Because they are derived from the "chiral pool" they usually require extensive manipulation and protecting-group chemistry to transform them into the desired target. Furthermore, access to both enantiomers is usually limited. More recently, designed polyfunctionalized chiral building blocks have been developed to avoid these limitations. Because they are designed for a specific purpose, these types of building blocks are generally easily prepared in both enantiomerically pure forms and require a minimum of manipulation and protecting-group chemistry.

Sulfinimines (*N*-sulfinyl imines **2**) developed in our laboratory are polyfunctionalized chiral building blocks that provide a general solution to the problem of addition of organometallic reagents to chiral imines (Scheme 1). Such additions are problematic because of the unreactivity of imines, the propensity of aliphatic examples to undergo α-deprotonation rather than addition, and the lack of suitable chiral examples. The chiral sulfinyl group in **2** is a superior auxiliary in that it activates the imine toward addition to such an extent that α-deprotonation is not an important issue. It is highly stereodirecting and easy to remove without epimerization of the product. Furthermore, sulfinimines are readily prepared from commercially available (*R*)-(−)- or (*S*)-(+)-*p*-toluenesulfinamide **1** and diverse aldehydes and ketones using $Ti(OEt)_4$ [2,3]. The utility of sulfinimines **2** in highly diastereoselective asymmetric syntheses of amine derivatives has been demonstrated and is the subject of several reviews [4].

A number of sulfinimine-derived polyfunctionalized chiral building blocks for the asymmetric synthesis of amine derivatives have recently been developed in our laboratory. These include aziridine 2-carboxylate esters [5] and aziridine 2-phosphonates [6], for amino acid and amino

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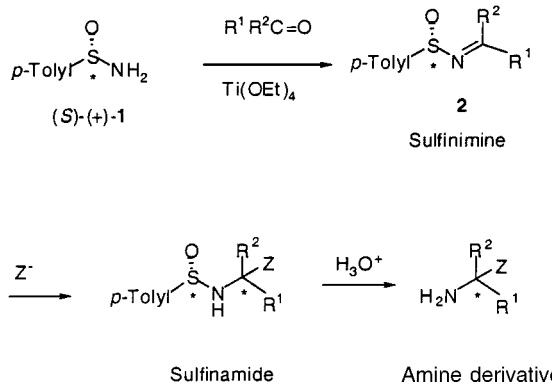


SCHEME 1 Asymmetric synthesis of amines from sulfinimines.

phosphonate synthesis and δ-amino β-ketoesters [1] and isoquinolones [7] for alkaloid synthesis. Recent applications of the latter two building blocks are presented here.

N-Sulfinyl δ-Amino β-Ketoesters

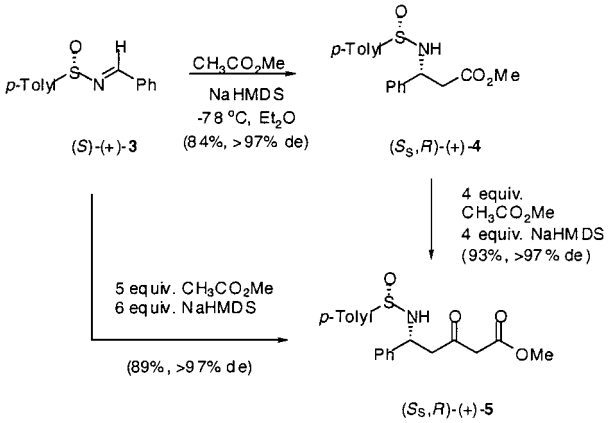
Earlier we reported that (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**3**) reacts with the sodium enolate of methyl acetate in ether at −78°C to give *N*-sulfinyl β-phenylalanine **4** in 84% yield and >97% de (Scheme 2) [8]. Subsequent treatment of **4** with an excess of this enolate afforded (S_S, *R*)-(+)-methyl-3-oxo-*N*-(*p*-toluenesulfinyl)-5-amino-5-phenyl pentanoate (**5**) in 93% yield [1]. The de was >97%. Importantly, (+)-**5** could be prepared in one pot, in 89% yield, by directly treating sulfinimine **3** with an excess of the sodium enolate. The de was the same, i.e., >97%. Although the one-pot method is more efficient, the two-pot procedure could be advantageous if the initial enolate addition were not highly diastereoselective; i.e., upgrading the diastereomeric purity of the β-amino ester could be performed prior to formation of the δ-amino β-ketoester.

Monosubstituted Piperidines

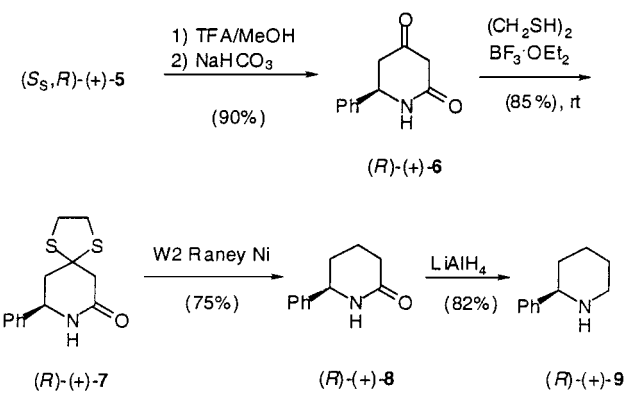
N-Sulfinyl δ-amino β-ketoesters are a new polyfunctionalized chiral building block for piperidine alkaloid synthesis. For example, a general enantioselective route to monosubstituted piperidines is illustrated in the synthesis of (*R*)-(+)-2-phenylpiperidine (**9**) (Scheme 3) [1]. Our synthesis began with (*R*)-(+)-6-phenylpiperidine-2,4-dione (**6**), obtained in >90% by treating (+)-**5** sequentially with TFA and $NaHCO_3$. Raney nickel desulfurization of the thioketal **7**, followed by reduction of **8** with $LiAlH_4$ furnished (+)-**9** in 62% yield for the two steps.

4-Hydroxypipecolic Acid

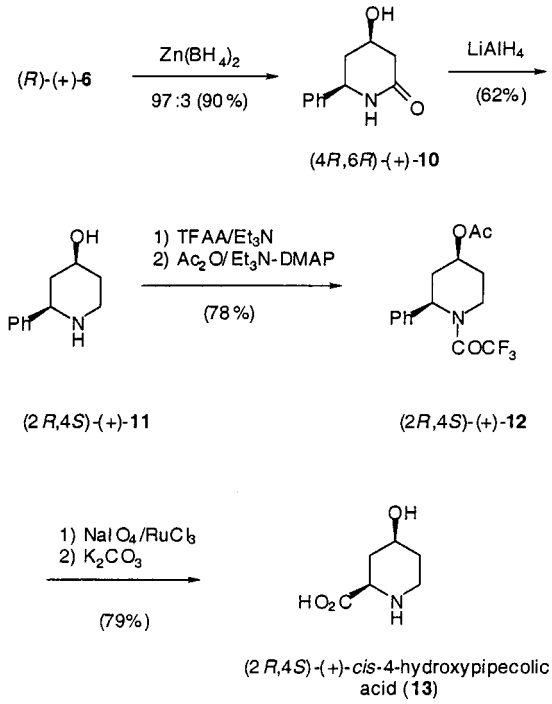
Currently, there is considerable interest in the synthesis of conformationally restricted, cyclic amino acids because of the effects these amino acid, once incorporated into peptides, have on biological activity [9]. In this regard we devised a simple method for the preparation of all four stereoisomers of 4-hydroxypipecolic acid **13**, an amino acid found in antibiotics such as virginiamycin S_2, and in Palinavir, a new class of HIV proteases inhibitors [10]. Stereoselective reduction of (*R*)-(+)-**6** with $Zn(BH_4)_2$ gave a 97:3 cis–trans mixture of (+)-**10** in 90% yield (Scheme 4). Reduction with $LiAlH_4$ gave (+)-**11**, and the amino and hydroxyl groups were differentially protected by sequential treatment with trifluoroacetic anhydride (TFAA) and acetic anhydride to furnish (+)-**12**. The phenyl group in **12** was oxidized to the carboxylic acid using $NaIO_4/RuCl_3$, which furnished *cis*-(2*R*,4*S*)-(+)-4-hydroxypipecolic acid (**13**) in 79% (Scheme 4).



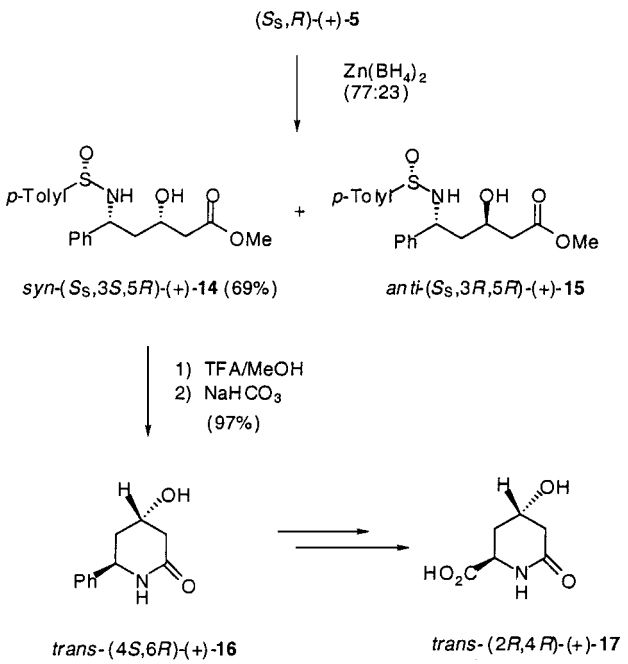
SCHEME 2 Asymmetric synthesis of δ-amino β-ketoesters.



SCHEME 3 Asymmetric synthesis of monosubstituted piperidines from δ-amino β-ketoesters.



SCHEME 4 Synthesis of (2*R*,4*S*)-(+)-4-hydroxypipecolic acid.



SCHEME 5 Stereoselective reduction of δ-amino β-ketoester (+)-5.

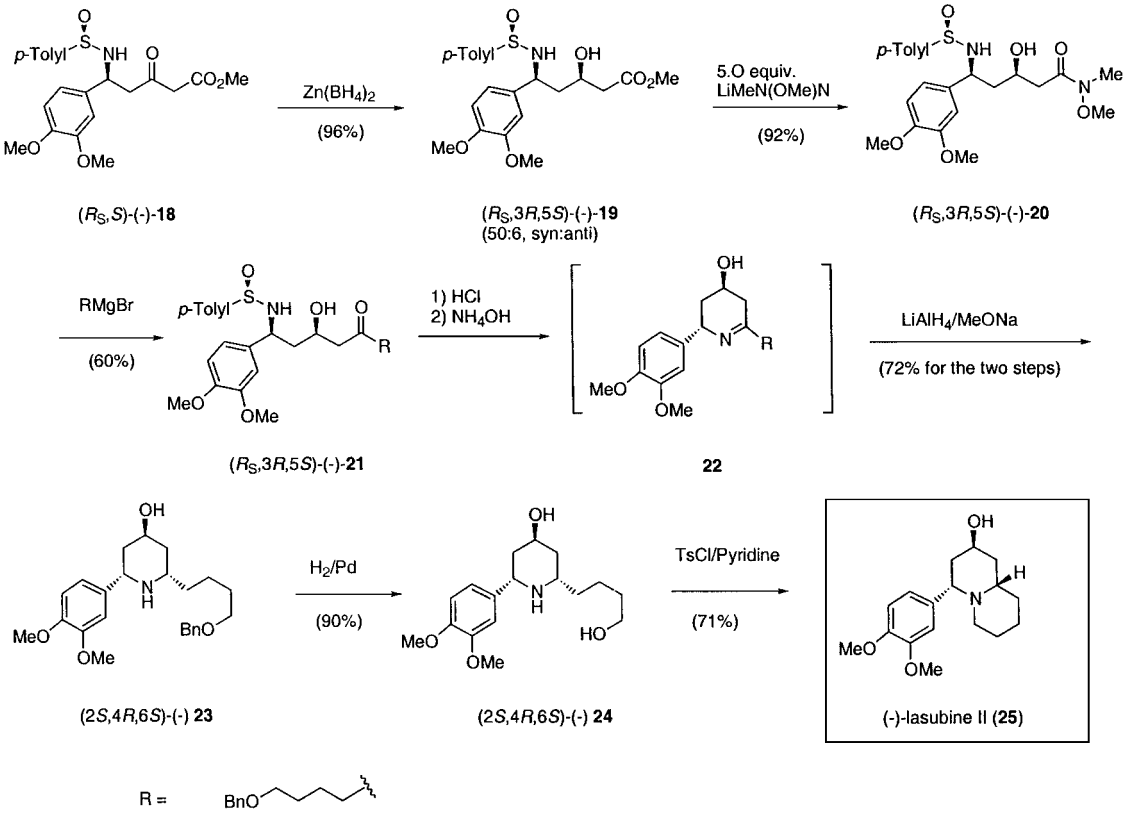
trans-(4*S*,6*R*)-4-Hydroxy-6-phenylpiperidin-2-one (**16**) is required for the synthesis of *trans*-(2*R*,4*R*)-(+)-4-hydroxypipecolic acid (**17**) (Scheme 5) [10]. However, all attempts to achieve synthetically useful ratios of the trans isomer by reduction of (*R*)-(+)-**6** were unsuccessful. Even a sterically hindered reducing agent such as L-Selectride only gave a cis/trans ratio of 1:1. We believe the reason for this is that axial attack is particularly favorable in **6**. Not only is torsional strain relieved in **6**, but also a bulky reducing reagent encounters a single 5-axial hydrogen on approach. Fortunately, reduction of *N*-sulfinyl-δ-amino-β-ketoester (+)-**5** with $Zn(BH_4)_2$ gave a satisfactory 77:23 syn/anti ratio of the δ-amino β-hydroxy acids **14** and **15** (Scheme 5). The major isomer was isolated in 69% yield. Cyclization gave **16** in 97% yield and (2*R*,4*R*)-(+)-4-hydroxypipecolic acid (**17**) was obtained as outlined in Scheme 4.

(−)-*Lasubine II*

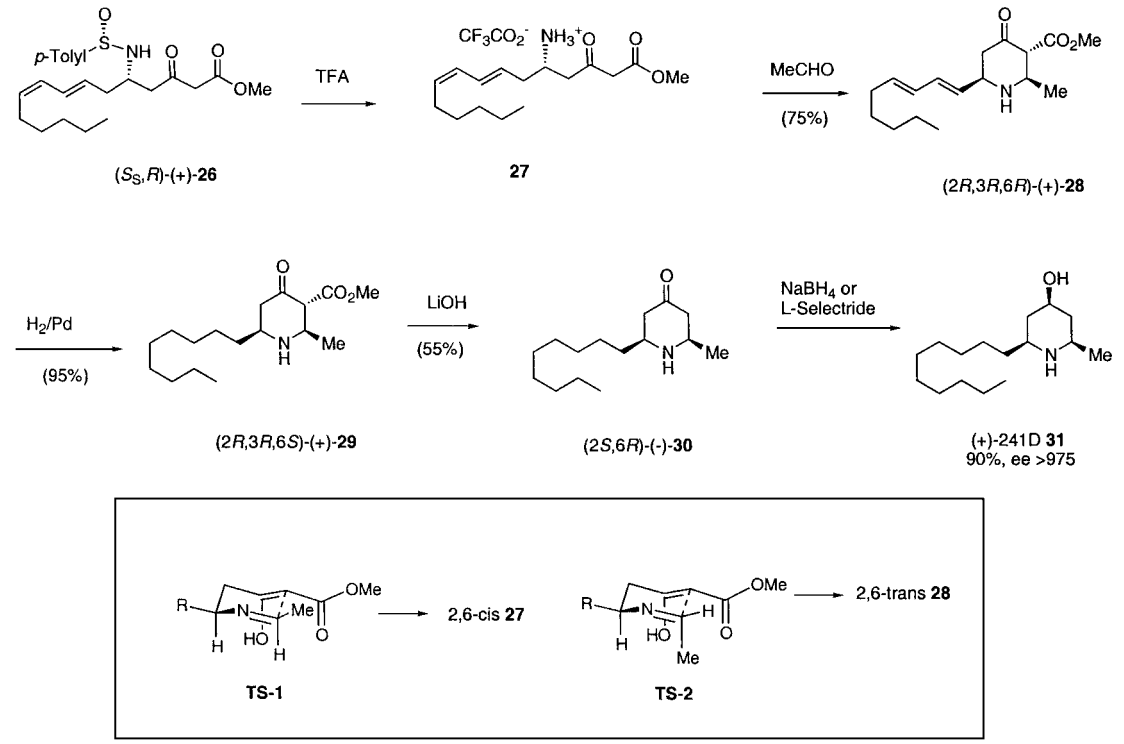
(−)-Lasubine II (**25**) is a member of the lythraceaes, a large family of naturally occurring alkaloids, a number of which contain the 4-arylquinolizidine substructure. The synthesis of **25** requires conversion of the carbomethoxy group in the *N*-sulfinyl δ-amino β-ketoester into a ketone having a substituent that can be used to form the quinolizidine skeleton. Thus stereoselective reduction of δ-amino β-ketoester, (R_S,*S*)-(−)-methyl-3-oxo-*N*-(*p*-toluenesulfinyl)-5-amino-5-[3,4-dimethoxy)phenyl]pentanoate (**18**), with $Zn(BH_4)_2$ gave a 50:6 syn/anti ratio of the β-amino alcohol (−)-**19** (Scheme 6) [11]. This reduction sets the trans arrangement of the 1-aryl and 3-hydroxy groups found in lasubine II (**25**). Treatment of **19** with excess lithium *N*,*O*-dimethylhydroxyl amine afforded the Weinreb amide (−)-**20** in excellent yield. The fact that the *N*-sulfinyl group remains intact during these reactions is undoubtedly due to formation of the lithium *N*-sulfinyl amide that protects it from further transformations. Reaction of (−)-**20** with **4**-(benzyloxy)-1-butyl magnesium bromide gave the desired ketone **21** in 60% yield, which cyclizes to the imine **22** on treatment with acid. Reduction of the crude imine furnished the cis hydroxy piperidine (−)-**22** exclusively, in 72% yield for the two steps. Deprotection of the benzyl group and reaction with pyridine and TsCl completes the synthesis of (−)-**25**. The asymmetric synthesis of **25** represents a new and concise entry into the quinolizidine skeleton [11].

(+)-*241D*

Alkaloid (+)-241D (**31**) was isolated from the skin of the dendrobate frogs and exhibits a range of potent biological activities [12]. Its asymmetric synthesis employs a new intramolecular Mannich reaction of *N*-sulfinyl δ-amino β-ketoesters and represents a new strategy for the synthesis of polysubstituted piperidines (Scheme 7) [13]. Removal of the



SCHEME 6 Asymmetric synthesis of (-)-lasubine II.



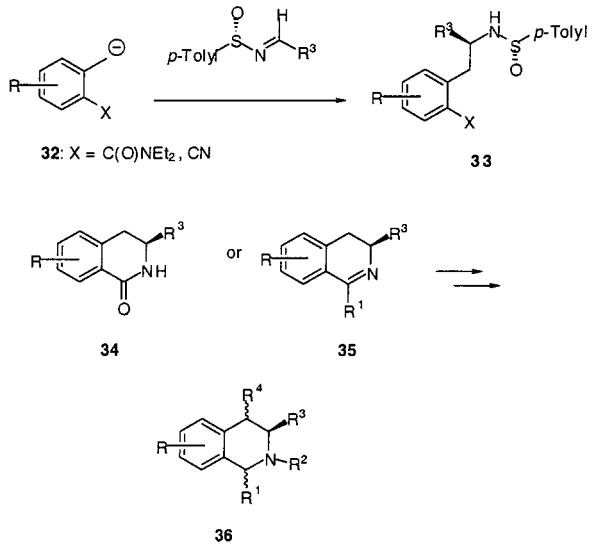
SCHEME 7 Asymmetric synthesis of (+)-241D.

N-sulfinyl auxiliary in (+)-**26** gave the salt **27**, which was isolated in crude form and treated with acetaldehyde to furnish the 4-oxopiperidine (+)-**28** as a single isomer, exclusively. The exclusive cis orientation of the piperidine 2,6-substitutents is consistent with transition state TS-1 because $A^{1,3}$ strain disfavors TS-2, which would lead to the trans isomer (Scheme 7). Next hydrogenation removed the double bonds and decarboxylation, using LiOH/MeOH, furnished 4-oxopiperidine **30**. Stereoselective reduction of **30** with $NaBH_4$ gave (+)-241D (**31**) in 90% yield and >97% ee.

Isoquinolines

The current interest in 3-substituted 1,2,3,4-tetrahydroisoquinolines stems from their unique structures and diverse biological properties. Typically these alkaloids are prepared by cyclization of β-arylethylamino derivatives using the Bischler–Napieralski and Pictet–Spengler protocols. Because nitrilium ion intermediates are involved, side reactions can occur and there are difficulties in controlling the regio- and stereoselective formation of the isoquinoline ring. In the asymmetric synthesis of isoquinolines, preparation of nonracemic β-arylethylamino derivatives is problematic.

As part of a program aimed at developing new strategies for the asymmetric synthesis of tetrahydroisoquinolines we have been examining the reactions of laterally lithiated species **32** with enantiopure sulfinimines (Scheme 8) [7,14]. Cyclization of the resulting sulfinamide **33** furnishes the isoquinolone **34** or cyclic imine **35**, which can be elaborated to the tetrahydroisoquinoline **36**. Importantly, this methodology has the potential for avoiding many of the limitations of the Bischler–Napieralski and Pictet–Spengler protocols as well as providing isoquinolines with substitution patterns not easily accessible by other means.



SCHEME 8 Synthesis of tetrahydroisoquinolines using laterally lithiated anions.

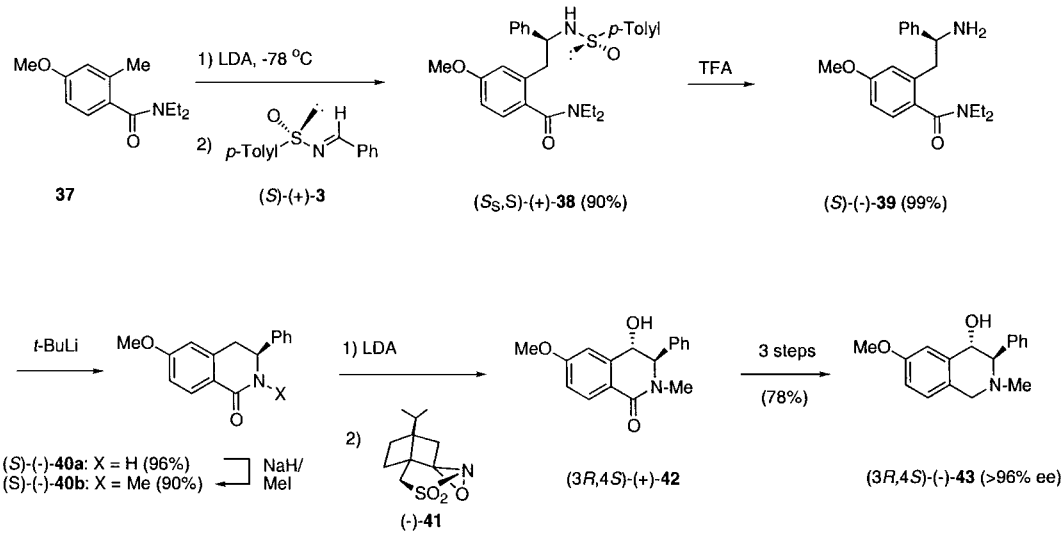
4-Hydroxy-3-phenyltetrahydroisoquinoline

Hydroxy isoquinolines are potential precursors of hydroxyprotoberberines, a class of alkaloids that exhibit diverse biological properties. A new route to these types of isoquinolines is illustrated in the asymmetric synthesis of 4-hydroxy-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**43**) (Scheme 9) [14]. The laterally lithiated amide anion of 5-methoxy *N*,*N*-diethyl-*o*-toluamide (**37**), prepared by reaction with LDA, was treated with sulfinimine (*S*)-(+)-**3** affording sulfinamide (S_SS)-(+)-**38** in 90% yield. Because atropodiastereoisomers are formed, it was not possible to accurately determine the diastereoselectivity of this material by NMR. By conversion into a known product, i.e. (−)-**43**, the de of (+)-**38** was determined to be >97%. Removal of the sulfinyl auxiliary in **38** and cyclization with *tert*-butyllithium afforded isoquinolone **40a**. To introduce the C-4 hydroxy group, we carried out an oxaziridine-mediated hydroxylation of the C-4 anion of **40b** using (camphorylsulfonyl)oxaziridine (−)-**41**. A single hydroxy diastereoisomer (+)-**42** having the trans orientation was obtained. Protection, reduction, and deprotection of (+)-**42** gave (3*R*,4*S*)-(−)-**43** in 78% yield for the three steps [14].

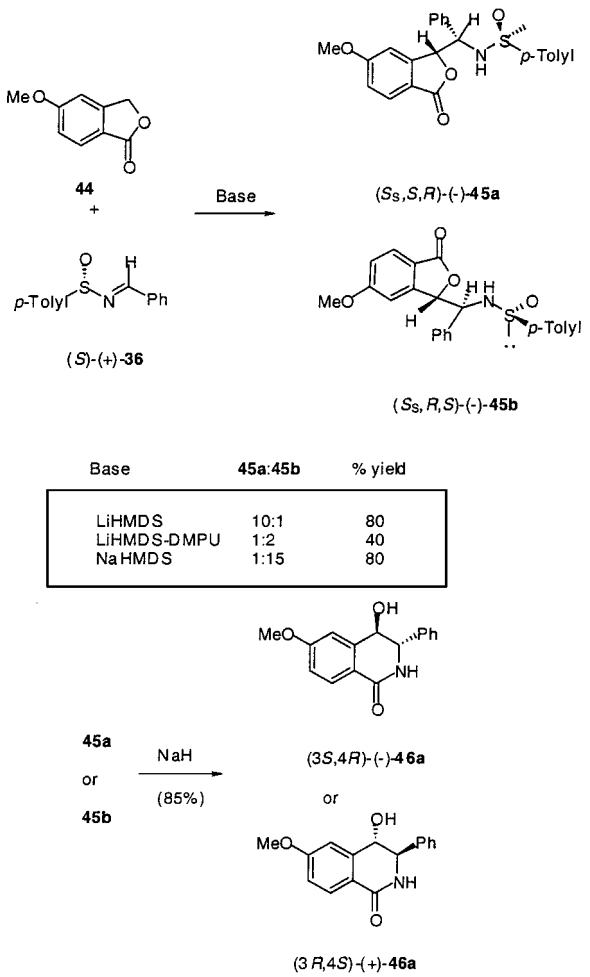
A more direct route to hydroxy isoquinolines is illustrated by the reaction of phthalide anions with sulfinimines (Scheme 10) [14]. When an equimolar mixture of 6-methoxyphthalide (**44**) and (*S*)-(+)-**36** were treated with base, pseudoenantiomers **45a** and **45b** were obtained in good yield (Scheme 10). Interestingly, the selectivity proved to be counterion dependent with LiHMDS affording a 10:1 ratio of **45a:45b** while NaHMDS gave a 1:15 ratio. Chelation and steric control arguments were suggested to explain the stereoselectivity and were supported by the fact that LiHMDS-DMPU, known to disrupt metal chelation, resulted in a 1:2 mixture of **45a:45b**. Treatment of these sulfinamides with NaH afforded isoquinolones **46a** and **46b**, which were elaborated in two steps to **42**.

1,3-Disubstituted Tetrahydroisoquinolines

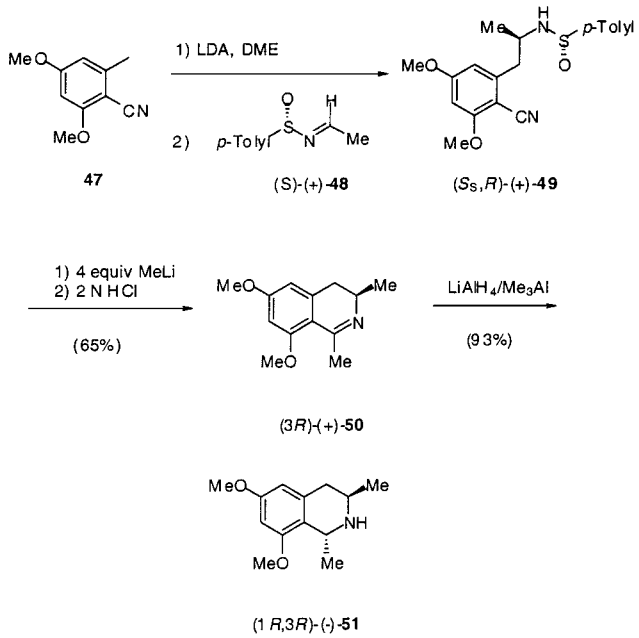
The formation of atropodiastereoisomers in the addition of lateral lithiated amides to sulfinimines (Scheme 9) makes it nearly impossible not only



SCHEME 9 Asymmetric synthesis of 4-hydroxy-3-phenyltetrahydroisoquinoline.



to determine the de but to obtain a diastereomerically pure product. To circumvent this problem an anionic species is required that does not produce atropodiastereoisomers on addition to the sulfinimine, while still retaining the necessary functionality for elaboration to the target. The laterally lithiated species generated from substituted *o*-tolunitriles more than meets these requirements and their utility is illustrated in the asymmetric synthesis of *trans*-6,8-dimethoxy-1-3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**51**) (Scheme 11). This alkaloid is the isoquinoline segment of the anti-HIV



SCHEME 10 Phthalide anion synthesis of 4-hydroxy-3-phenyltetrahydroisoquinoline.

SCHEME 11 Asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines.

michellamines [7]. The diastereoselectivity for sulfinamide (+)-**49**, formed on the addition of the laterally lithiated anion of **47** to the acetaldehyde derived sulfinimine (+)-**48**, was >97% and also easily determined by ^{1}H NMR. On treatment with excess MeLi, **49** was directly transformed into cyclic imine (+)-**50** on acidification. This method accomplishes three operations in one pot: (i) removal of the sulfinyl auxiliary, (ii) installation of the 1-methyl group, and (iii) cyclization to the imine. Reduction with $LiAlH_4/Me_3Al$ afforded exclusively the *trans*-1,3-dimethylisoquinoline **51** in 93% yield.

SUMMARY

The sulfinimine-derived polyfunctionalized chiral building blocks, *N*-sulfinyl-δ-amino-β-ketoesters and isoquinolones, provide convenient access to enantiopure, functionalized piperidines and tetrahydroisoquinolines with a minimum of chemical manipulation and protecting/deprotecting group chemistry.

REFERENCES

[1] Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. Org Lett 2000, 2, 1041.
[2] Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. J Org Chem 1999, 64, 1403.
[3] Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. W.; Burns, D. M.; Davis, F. A. Org Synth 2000, 77, 50.
[4] For reviews on the chemistry of sulfinimines see (a) Zhou, P.; Chen, B.-C.; Davis, F. A. In Advances in Sulfur Chemistry; Rayner, C. M. (Ed.), JAI Press: Stamford, CT, 2000, Vol. 2. pp. 249–282; (b) Hua, D. H.; Chen, Y.; Millward, G. S. Sulfur Reports 1999, 21, 211; (c) Davis, F. A.; Zhou, P.; Chen, B.-C. Chem Soc Rev 1998, 27, 13.
[5] (a) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. J Org Chem 1999, 64, 7559; (b) McCoull, W.; Davis, F. A. Synthesis 2000, 1347.
[6] (a) Davis, F. A.; McCoull, W. Tetrahedron Lett 1999, 40, 249; (b) Davis, F. A.; McCoull, W.; Titus, D. D. Org Lett 1999, 1, 1053.
[7] Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. Org Lett 2000, 2, 3901 and references cited therein.
[8] Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. J Org Chem 1995, 60, 7037.
[9] For a review see Hanessian, S.; McNaughton-Smith, G.; Lombaart, H.-G.; Lubell, W. D. Tetrahedron 1997, 53, 12789.
[10] Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. Synthesis 2000, 2106.
[11] Davis, F. A.; Chao, B. Org Lett 2000, 2, 2623.
[12] Edwards, M. W.; Daly, J. W. J Nat Prod 1988, 51, 1188.
[13] Davis, F. A.; Chao, B.; Rao, A. Org Lett 2001, 3, 3169.
[14] Davis, F. A.; Andemichael, Y. M. J Org Chem 1999, 64, 8627.