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ASYMMETRIC SYNTHESIS USING SULFINIMINES (THIOOXIME S-OXIDES)

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Abstract: The addition of diethylaluminum cyanide and the lithium enolate of methyl α -bromoacetate to sulfinimines (thiooxime S-oxides) is highly diastereoselective affording α -amino nitriles and N-sulfinylaziridines, respectively. Hydrolysis of the α -amino nitriles gives α -amino acids in high ee, while hydrolysis of N-sulfinylaziridine carboxylic acids give β -hydroxy- α -amino acids. The latter compounds were transformed into (+)-thiamphenicol, a broad spectrum antibiotic and sphingosine, an important component of the sphingolipids.

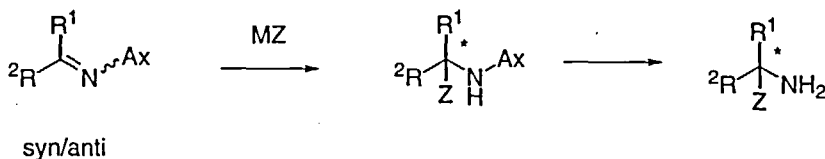
KEYWORDS: Sulfinimines, α -amino acids, N-sulfinylaziridine 2-carboxylic acids, β -hydroxy- α -amino acids.

INTRODUCTION

Chiral nonracemic amines containing nitrogen attached to a stereogenic carbon are ubiquitous in nature. Prominent examples include protein and nonprotein α - and β -amino acids.^{1,2} In addition, these compounds serve as important chiral building blocks for the asymmetric construction of many pharmacologically active materials. Although the diastereoselective addition of organometallic reagents (MZ) to the C-N double bond of chiral imines is an attractive approach for the asymmetric construction of amine derivatives, it is problematic for a number of reasons (Scheme 1).³ First, the poor electrophilicity of imines often results in either no reaction or competitive reduction and/or coupling. With enolizable, aliphatic imines α -deprotonation generates azaenolates which undergo undesirable reactions. Secondly, when the imine exists as a *syn/anti* mixture of isomers, selective addition of the

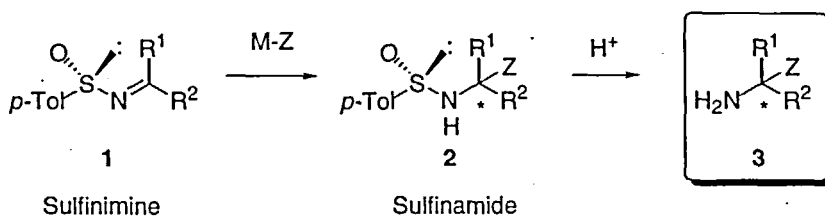
organometallic reagent is difficult and de's are low. Finally, if primary amines are the objective, the auxiliary needs to be removed without destroying or epimerizing the product.

Scheme 1



By using chiral nonracemic sulfinimines (thiooxime S-oxides **1**) these problems are avoided. Sulfinimines are chiral ammonia imine building blocks because nucleophilic addition across the C-N bond affords a sulfinamide **2** which on cleavage furnishes primary amine **3** containing a new stereogenic center (Scheme 2). The application of **1**, derived from aliphatic and aromatic aldehydes, in highly diastereoselective asymmetric syntheses of α -amino acids,^{4,5} N-sulfinyl *cis*-aziridine 2-carboxylic acids,⁶ β -amino acids,^{7,8,9,10} the taxol C-13 side chain⁸ and its fluorinated analog¹¹ has recently been described by us. In these additions the N-sulfinyl auxiliary activates the C-N bond to such an extent that most nucleophiles are readily added and competitive enolization with aliphatic substrates is avoided. Since the N-sulfinyl group is a powerful stereodirecting group, high diastereoselectivities result. Furthermore, because easily separable diastereoisomers are produced in this "chiral auxiliary" based asymmetric synthesis, mild acid catalyzed hydrolysis then affords the enantiomerically pure product **3**. Importantly, epimerization of the product is not detected in the hydrolysis process.

Scheme 2



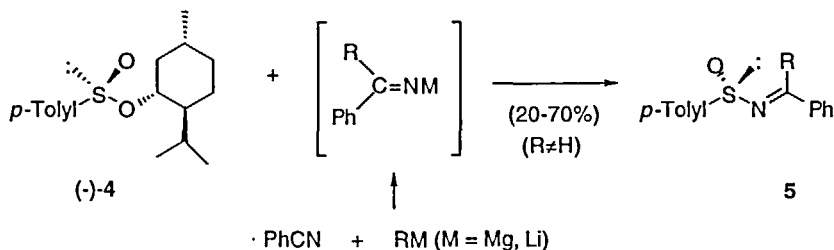
SYNTHESIS AND PROPERTIES OF SULFINIMINES

The first examples of sulfinimines **1** were reported by us in 1974 and prepared by oxidation of a sulfenimine (ArS-N=CR_2) with *m*-CPBA.^{12,13} C-Aryl

sulfinimines are solids, whereas the C-alkyl species tend to be oils. Although the barrier to nitrogen inversion in ketone derived **1** is low (17 kcal/mole), the corresponding aldehyde derivatives exist exclusively in the E geometry.¹⁴ On heating (80-100 °C, 24 h) N-alkylidenearene sulfinimines **1** ($R^1 = H$, $R^2 = Ar$) undergo syn elimination to furnish the valuable and elusive sulfenic acid ($ArSOH$).^{13,15}

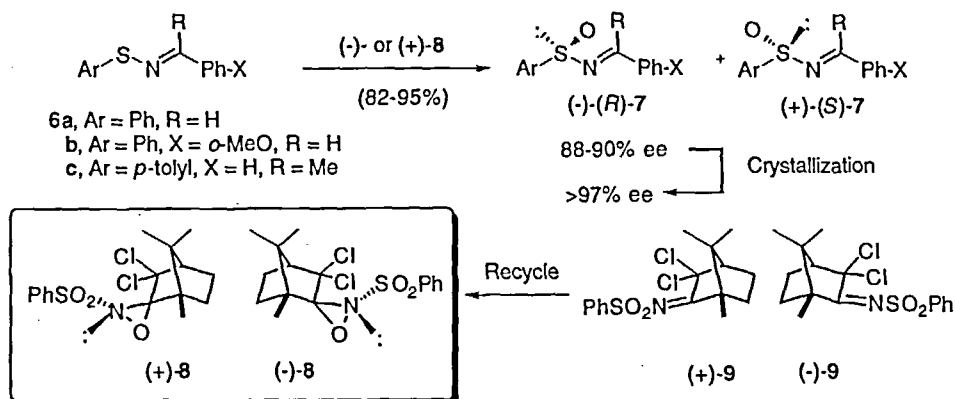
The first enantiomerically pure sulfinimines **5** were obtained by Cinquini et al., in modest yield, by reaction of metalloketimines with the "Andersen" reagent, (-)-L-menthyl (*S*)-*p*-toluenesulfinate (**4**) (Scheme 3).^{16,17} In a related method enantiopure sulfinimines were prepared from a metalloketimine and a sulfinamide.¹⁸ However, these Andersen-type syntheses are limited in scope because the metalloketimines are generated by reaction of organolithium or Grignard reagents with an aromatic benzonitrile. This means that the more versatile aliphatic and aromatic aldehyde derived derivatives, e.g. $R \neq H$ and $Ph \neq alkyl$, are unavailable by this methodology.¹⁶⁻¹⁸

Scheme 3



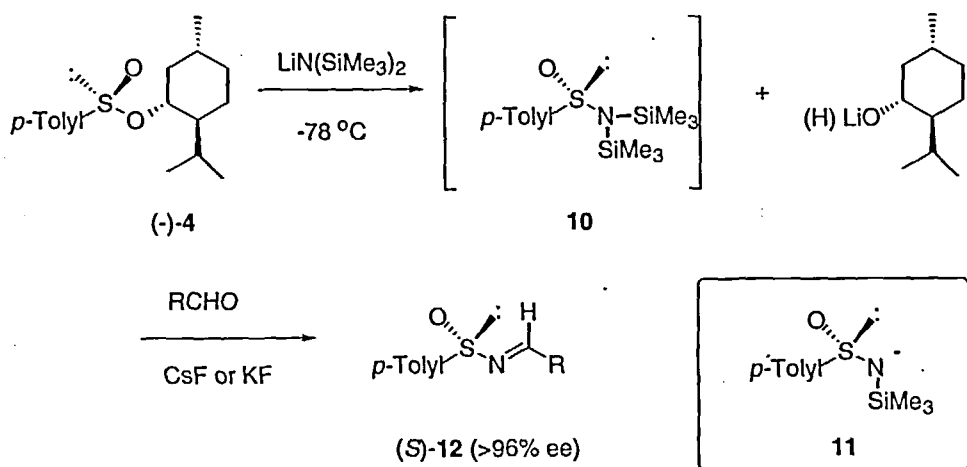
A more general route, which provides access to the previously unavailable aldehyde-derived sulfinimines **7a-b**, is the asymmetric oxidation of sulfenimines **6** (Scheme 4).¹⁹ We accomplished this with the N-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridines (+)- and (-)-**8**, asymmetric oxidizing reagents developed in our laboratory for the asymmetric oxidation of sulfides to sulfoxides.²⁰ A simple crystallization from *n*-hexane upgrades the ee's of **7** from 88-90% to greater than 97% ee.¹⁹ Because the relative and absolute configurations of the oxaziridine ring control the absolute stereochemistry of the product, either enantiomer can be generated by selection of the appropriate reagent; thus (-)-**8** gave (-)-(*R*)-**7** and (+)-**8** gave (+)-(*S*)-**7**. Furthermore, the sulfonimine by-product **9** can easily be isolated in high yield for recycling. However, this oxidation procedure is also limited, such that if the sulfinimine **7** is noncrystalline, as is true of most aliphatic examples, it cannot be up-graded to >95% ee by crystallization.

Scheme 4



Importantly, aliphatic and aromatic aldehyde derived sulfinimines **12** are available enantiomerically pure via a one-pot procedure directly from the aldehyde (Scheme 5). In this protocol we treat the Andersen reagent **4** with lithium bis(trimethylsilyl)amide (LiHMDS) to give an intermediate bis(trimethylsilyl)sulfonamide **10**, followed by reaction with the aldehyde and CsF or KF at -78°C .^{9,21} Some examples are given in Table 1. The reaction mechanism probably involves attack of a fluoride ion generated silylamide anion **11** at the carbonyl group of the aldehyde followed by a Peterson-type Olefination reaction. If



Scheme 5



the reaction mixture is warmed to room temperature prior to quenching, poor yields of **12** from aliphatic aldehydes result. Base catalyzed aldol-type reactions, caused by the lithium menthoxide by-product are probably responsible for these results. The menthyl auxiliary is isolated in good to excellent yield for recycling. Menthyl *p*-

toluenesulfinate (4), a widely used chiral sulfinyl building block,²² is commercially available in both enantiomeric forms or can be prepared on a large scale using Posner's *Organic Syntheses* procedure.^{23,24}

Table 1:
Asymmetric Synthesis of Sulfinimines **12** from Aldehydes.

Aldehyde (R =)	% Isolated Yield of Sulfinimine 12
Ph	78 ^a
<i>p</i> -F-Ph	84 ^b
	70 ^c
	77 ^a
CH ₃ CH ₂ CH ₂ -	64 ^a
(CH ₃) ₃ C-	68 ^d

a) Ref. 9, 21. b) Ref. 25. c) Ref. 10. d) Ref. 5.

APPLICATIONS OF SULFINIMINES

Asymmetric Synthesis of α -Amino Acids.

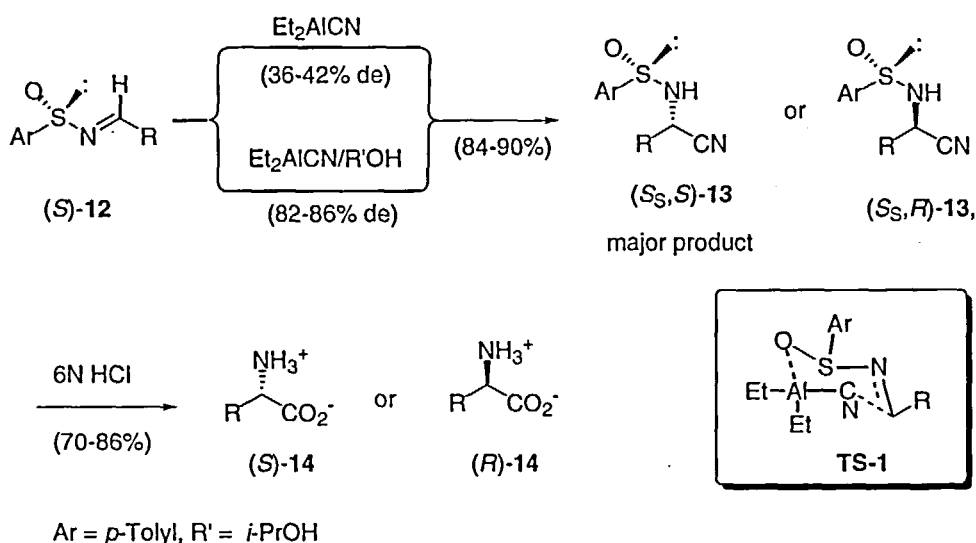
The occurrence of protein and non-protein α -amino acids in biological systems and their exceptional utility as chiral building blocks underlies the importance of improved methods for their synthesis in enantiopure form.¹ This is particularly true for nonproteinogenic or "unnatural" amino acids as their incorporation into peptides can lead to improved bioactivity and stability.

Of the many methods used to prepare α -amino acids the asymmetric Strecker synthesis should hold particular prominence because of its simplicity.²⁶ However, the auxiliary controlled nucleophilic addition of cyanide or its equivalent to optically active imines is problematic for several reasons. First, the diastereoselectivity, with rare exception, is mostly modest (22-60% de), although fractionation can often be used to give a diastereomerically pure product.²⁶ Second, removal of the chiral

auxiliary without destroying or epimerizing the α -amino acid is frequently a problem.

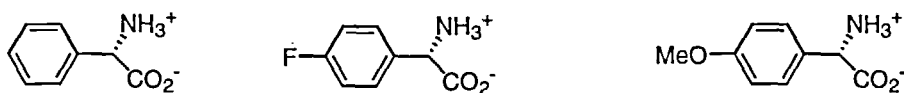
Initial attempts to add common cyanide sources (KCN, TMSCN, etc.) to sulfinimine (*S*)-12 were unsuccessful.⁴ However, diethylaluminum cyanide (Et_2AlCN), a commercially available reagent introduced by Nagata and co-workers,²⁷ adds to 12 to give α -amino nitriles (S_S,S)-13 and (S_S,R)-13 in good yield (Scheme 6). Unfortunately the diastereoselectivity, as observed in other asymmetric Strecker syntheses, is modest, never exceeding 40%. Formation of the major product, (S_S,S)-13, is consistent with complexation of Et_2AlCN with the sulfinyl oxygen activating the imine for intramolecular cyanide addition via chair-like transition state TS-1. The diastereoisomers 13 are readily separable by flash chromatography.

Scheme 6

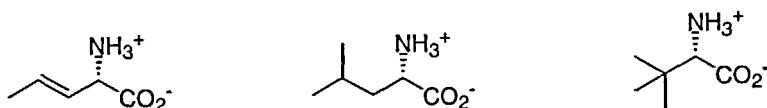


Significantly, addition of ethyl alkoxy aluminum cyanide [$\text{Et}(\text{R'O})\text{AlCN}$], prepared by treatment of Et_2AlCN with isopropyl alcohol (R'OH), to (*S*)-12 results in a dramatic improvement in the diastereoselectivity; e.g. from 36-42% to 82-86% (Scheme 6).⁵ Simple crystallization of the amino nitriles affords a diastereomerically pure product (>96% de) in good yield. The enhanced de's are attributed to the reduced Lewis acidity of $\text{Et}(\text{R'O})\text{AlCN}$ vs. Et_2AlCN which makes it more selective. Finally, acid catalyzed hydrolysis of the diastereomerically pure α -amino nitrile (S_S,S)-13 not only removes the sulfinyl auxiliary, but hydrolyzes the nitrile affording the enantiomerically pure (>95%) α -amino acids 14. Importantly, racemization of the sensitive aryl glycines was not detected. Some examples are given in Scheme 7.

Scheme 7



(*S*)-Phenylglycine (80%) (*S*)-*p*-Fluorophenylglycine (70%) (*S*)-*p*-Methoxyphenylglycine (86%);



(*S*)- α -Propenylglycine (75%)

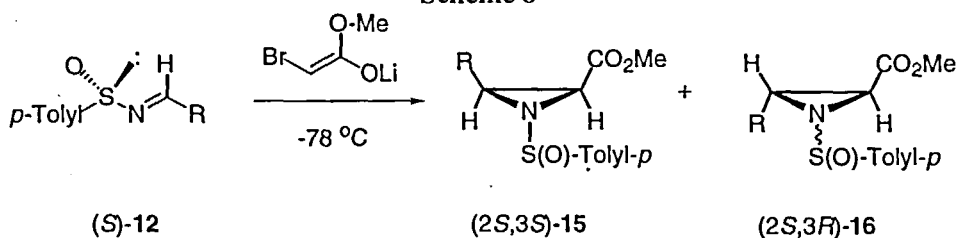
(*S*)-Leucine (82%)

(*S*)-*t*-Leucine (78%)

cis-N-Sulfinylaziridine-2-Carboxylic Acids.

Enantiomerically pure aziridines serve as versatile intermediates for the asymmetric synthesis of many biologically active materials (e.g., alkaloids, β -lactams, amino acids) because they undergo highly regio- and stereocontrolled ring opening reactions with nucleophiles.^{28,29} This is particularly true for aziridine-2-carboxylic acids, which, upon ring opening, afford β -substituted α -amino acids.³⁰ *cis*-Aziridine-2-carboxylic acids, precursors of the syn- β -hydroxy- α -amino acid structural unit found in many bioactive compounds, are difficult to prepare in enantiomerically pure form. In this regard we developed a Darzens-type

Scheme 8



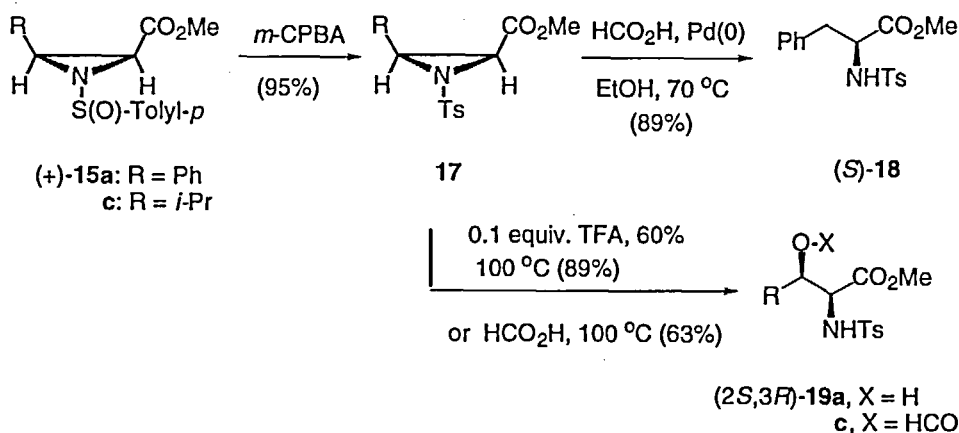
R = a) Ph, b) *p*-MeSPh, c) *i*-Pr-

R =	15/16	% Yield
Ph	97:3	65
<i>p</i> -MeSPh	99:1	60
Me ₂ CH	99:1	64

condensation involving addition of the lithium enolate of methyl bromoacetate to sulfinimines **12**, affording enantiopure *cis*-N-(*p*-toluenesulfinyl)-2-carbomethoxyaziridines **15** (Scheme 8).^{6a}

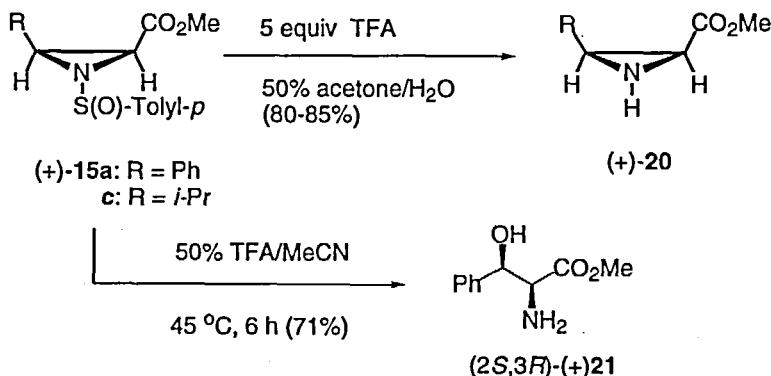
Aziridine ring opening requires activation at nitrogen, and many activating groups have been studied. N-Tosyl activation often affords superior reactivity and regioselectivity. However, attempts to tosylate 1*H* 3-arylaziridine-2-carboxylic esters, lead predominantly to ring opened products.³¹ In contrast, our approach installs this key activating group prior to ring opening by oxidation of **15a** and **15c** with *m*-CPBA affording **17** in excellent yield (Scheme 9).⁶ Transfer hydrogenation of **17a** afforded the (*S*)-phenylalanine derivative **18**, and acid-catalyzed hydrolysis at 100 °C (24 h) gave the phenylserine derivative **19** as an 84:16 mixture of diastereoisomers. Under similar conditions **17c** was unreactive but gave the formate ester **19** as a single isomer on heating with 98% formic acid.⁶

Scheme 9



Although Rapoport et. al. have developed methodologies for removal of the sulfonamide group in hydroxy amino acids the conditions are often harsh.³² One of the advantages of the N-sulfinyl auxiliary is that it can be removed under comparatively mild conditions. Thus treatment of **15a** and **15c** with 5 equiv. of TFA

Scheme 10

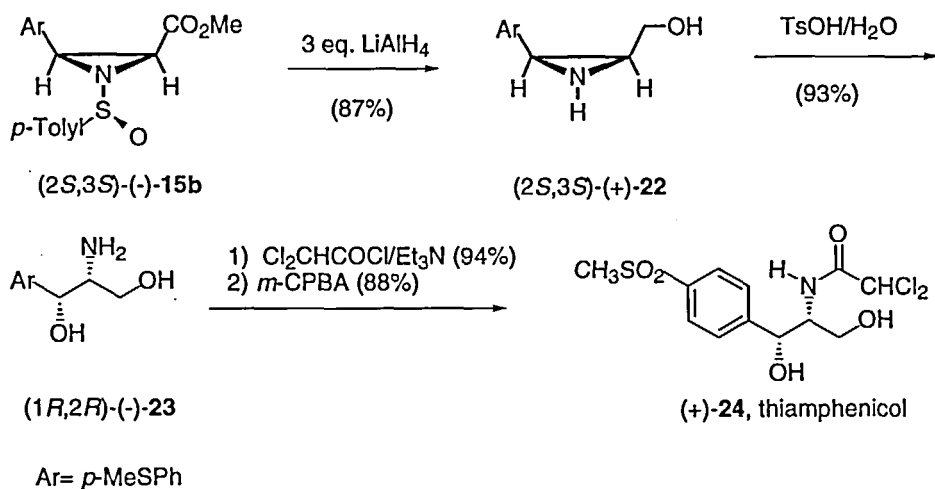


in aqueous acetone afforded 1H-aziridines **20a** and **20c** in 83 and 80 percent yield, respectively (Scheme 10). On the other hand heating **15a** at 45 °C in 50% aqueous TFA gives a 71% yield of *syn*-β-phenylserine derivative **21** as a 93:7 mixture of diastereoisomers.

Asymmetric Synthesis of (+)-Thiamphenicol.

(+)-Thiamphenicol (**24**) is a broad spectrum synthetic antibacterial agent used in the animal health industry (Scheme 11). The precursor of **24** is *threo*-(1*R*-2*R*)-(-)-1-[(4-methylthio)phenyl]-1,3-propanediol (**23**) whose manufacture involves a multi-step sequence ending with its resolution. As outlined in Scheme 11, key intermediate **23** is prepared in two steps in 81% overall yield from readily available N-sulfinylaziridine-2-carboxylic acid (-)-**15b**.³³ This protocol avoids the wasteful resolution of racemic **23** used in earlier procedures. Conversion of 2-amino-1,3-propanediol (-)-**23** into (+)-thiamphenicol (**24**) is straight forward involving treatment with dichloroacetyl chloride and oxidation with *m*-CPBA.

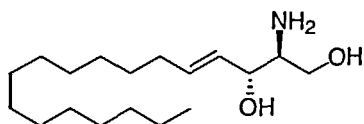
Scheme 11



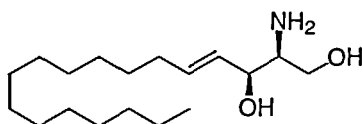
Asymmetric D-erythro- and L-threo-Sphingosine.

Sphingosine [*erythro*-(*-*)-2-amino-D-4(E)-octadecene-1,3-diol (**25a**)] is the major constituent of the lipid backbone of the sphingolipids (e.g. ceramides, cerebrosides, sphingomyelins, gangliosides and glycosphingolipids).³⁴ The sphingolipids are important membrane components that play crucial roles in cell recognition events such as growth, differentiation, the immune response³⁵ and as

receptors for HIV binding in cells lacking the CD4 receptor.³⁶ Furthermore, all of the sphingosine enantiomers; e.g. **25b**, are reported to be potent inhibitors of protein kinase C (PKC)³⁷ as well as stimulators of DNA synthesis and cell proliferation.³⁸



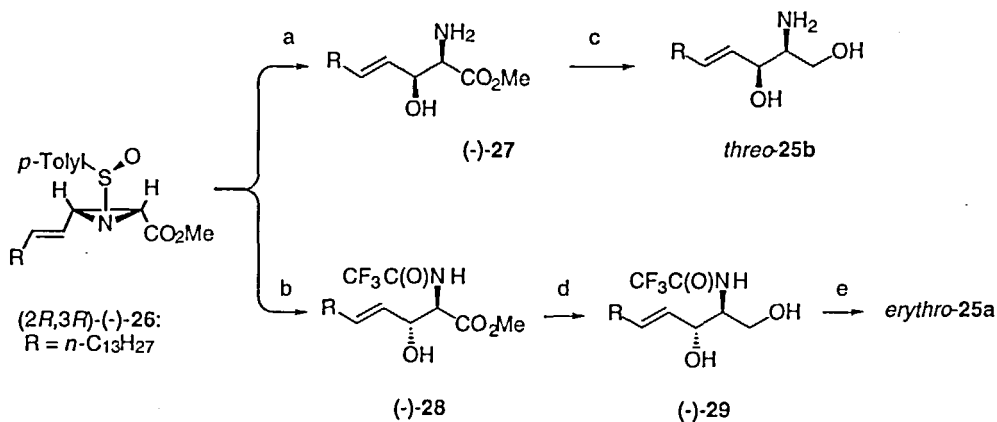
D-erythro-Sphingosine-25a



L-threo-Sphingosine-25b

Synthesis of the less common *L-threo* sphingosine **25b** by the protocol outlined in Scheme 12 requires aziridine (2*R*,3*R*)-(-)-**26**³⁹ and would appear to be straightforward. However, reduction with lithium aluminum hydride (LAH) and other reducing reagents gave the corresponding aziridine methanol in low yield (ca 30%) and hydrolysis (TsOH/H₂O) gave an inseparable mixture of stereo- and regioisomeric aminodiols. On the other hand, treatment of (-)-**26** in acetone/TFA/H₂O gave β-hydroxy-α-amino acid (-)-**27** as a single isomer in 72%

Scheme 12

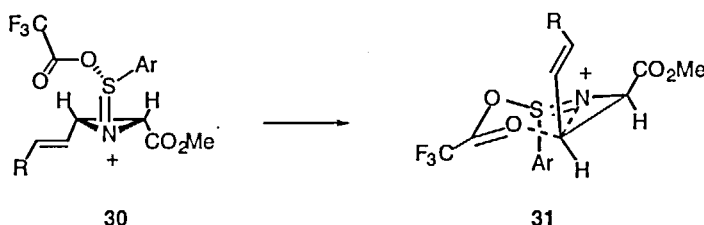


(a) 50% aqueous TFA/acetone, 72%; (b) TFAA/CH₂Cl₂, 59%; (c) LiBH₄/MeOH, 80%; (d) LiBH₄/MeOH, 71%; (e) K₂CO₃/EtOH, 75%; (f) Ac₂O/pyr., 100%.

yield. Reduction of (-)-**27** with LiBH₄ gave *L*-(-)-*threo* sphingosine (**25b**) in 80% yield.⁴⁰

Selectivity in aziridine ring-opening depends on the ring substituents, the activating group on nitrogen and the reaction conditions because competitive S_N1 and S_N2 processes are involved. Since anti-selectivity generally predominates, it would appear impossible to obtain the naturally occurring D-(-)-*erythro*-sphingosine **25a** as the major isomer from *cis*-aziridine (-)-**26**. Remarkably, treatment of (-)-**26**

with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at 35°C resulted in an 88:12 mixture of *erythro*- and *threo*-**28** which were separated by radial chromatography to give the major isomer in 59% yield.⁴⁰ Formation of *erythro*-**28** from *cis*-**26** requires the highly unusual attack of the nucleophile from the same side as the departing amino group. While details of this transformation are at present unclear, we suggest that activated sulfoxide complex **30**, well precedent in the Pummerer rearrangement of sulfoxides,⁴¹ undergoes a stereospecific [3,3]-sigmatropic rearrangement of the trifluoromethyl acetoxy group to a developing carbocation or ion pair **31**. The aziridine N-activating group which promotes this type of ring-opening is the amino-sulfonium salt.



Reduction of (-)-**28** with LiBH_4 to give (-)-**29** in 71% and hydrolysis with aqueous $\text{K}_2\text{CO}_3/\text{EtOH}$ afforded *erythro*-(-)-sphingosine **25a** in 75% yield and was identical in all respects with an authentic sample.

Acknowledgments

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REFERENCES

1. α -Amino Acids: (a) G. C. Barrett, Ed., "Chemistry and Biochemistry of the Amino Acids," Chapman and Hall: London 1985; (b) M. J. O'Donnell, Ed., *Tetrahedron Symposia-in-Print*, **44**, 5253 (1988); (c) R. M. Williams, *Organic Chemistry Series Volume 7: Synthesis of Optically Active α -Amino Acids*, J. E. Baldwin, P. D. Magnus, Eds., Pergamon Press: Oxford, 1989; (d) O. R. Duthaler, *Tetrahedron*, **50**, 1539, (1994); (e) H. Kunz, in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, Eds., *Houben-Weyl*, **E 21b**, 1931, 1995.
2. β -Amino acids: (a) E. Juaristi, D. Quintana, J. Escalante, *Aldrichchimica Acta*, **27**, 3, (1994); (b) D. C. Cole, *Tetrahedron*, **50**, 9517, (1994).
3. (a) N. Risch, M. Arend, in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, Eds., *Houben-Weyl*, **E 21b**, D.1.4, 1833, 1995; (b) R. A. Volkmann, in *Comprehensive Organic Synthesis*: S. L. Schreiber, Ed., Pergamon Press, Oxford, Vol 1, Chapter 4, p 893, 1991.
4. F. A. Davis, R. E. Reddy, P. S. Portonovo, *Tetrahedron Lett.*, **35**, 9351, (1994).

5. F. A. Davis, P. S. Portonovo, R. E. Reddy, Y.-H. Chiu, *J. Org. Chem.*, **61**, 440, (1996).
6. (a) F. A. Davis, P. Zhou, G. V. Reddy, *J. Org. Chem.*, **59**, 3243, (1994); (b) F. A. Davis, P. Zhou, C. H. Liang, R. E. Reddy, *Tetrahedron: Asymmetry*, **6**, 1511, (1995).
7. J. Jiang, K. K. Schumacher, M. M. Joullie, F. A. Davis, R. E. Reddy, *Tetrahedron Lett.*, **35**, 2121, (1994).
8. F. A. Davis, R. T. Reddy, R. E. Reddy, *J. Org. Chem.*, **57**, 6387, (1992).
9. F. A. Davis, R. E. Reddy, J. M. Szewczyk, *J. Org. Chem.*, **60**, 7037, (1995).
10. F. A. Davis, J. M. Szewczyk, R. E. Reddy, *J. Org. Chem.*, **61**, 2222, (1996).
11. F. A. Davis, R. E. Reddy, *Tetrahedron: Asymmetry*, **5**, 955, (1994).
12. F. A. Davis, A. J. Friedman, E. W. Kluger, *J. Am. Chem. Soc.*, **96**, 5000, (1974).
13. F. A. Davis, A. J. Friedman, U. K. Nadir, *J. Am. Chem. Soc.*, **100**, 2844, (1978).
14. F. A. Davis, E. W. Kluger, *J. Am. Chem. Soc.*, **98**, 302, (1976).
15. For leading references on the chemistry of sulfenic acids see: F. A. Davis, L. A. Jenkins, R. L. Billmers, *J. Org. Chem.*, **51**, 1033, (1986).
16. R. Annunziata, M. Cinquini, F. Cozzi, *J. Chem. Soc., Perkin I*, 339, (1982).
17. D. H. Hua, S. W. Miao, J. S. Chen, S. Iguchi, *J. Org. Chem.*, **56**, 4, (1991).
18. D. R. J. Hose, M. F. Hahon, K. C. Molloy, T. Raynham, M. Wills, *J. Chem. Soc. Perkin I*, 391, (1996).
19. F. A. Davis, T. R. Reddy, R. E. Reddy, *J. Org. Chem.*, **57**, 6387, (1992).
20. F. A. Davis, T. R. Reddy, W. Han, P. J. Carroll, *J. Am. Chem. Soc.*, **114**, 1428, (1992).
21. F. A. Davis, R. E. Reddy, J. M. Szewczyk, P. S. Portonovo, *Tetrahedron Lett.*, **34**, 6229, (1993).
22. G. Soilladie, in "Methods of Organic Chemistry (Houben-Weyl)," G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, Eds., Georg Thieme Verlag, Stuttgart, **E 21a**, Chapter 1.1.1.5.1, 1056, (1995); G. Soilladie, in "Methods of Organic Chemistry (Houben-Weyl)," G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, Eds., Georg Thieme Verlag, Stuttgart, **E 21b**, Chapter 1.3.6.1, 1793, 1995.
23. M. Hulse, J. P. Mallamo, L. L. Frye, T. P. Kogan, G. H. Posner *Org. Synth.*, **64**, 196, (1984).
24. G. Soilladie, *Synthesis*, 185, (1981).
25. H. Zhang, Unpublished results.
26. For excellent reviews on the asymmetric Strecker synthesis see references 1f-1h. See also T. K. Chakraborty, K. A. Hussain, G. V. Reddy, *Tetrahedron*, **51**, 9179, (1995).
27. (a) W. Nagata, M. Yoshioka, S. Hirai, *J. Am. Chem. Soc.*, **94**, 4635, (1972); (b) W. Nagata, M. Yoshioka, M. Murakami *J. Am. Chem. Soc.*, **94**, 4644, (1972).
28. For a review on the chemistry of aziridines see: J. A. Deyrup, In *Heterocyclic Compounds*; A. Hassner, Ed., John Wiley & Sons: New York, Chapter 1, p 2, 1983.
29. For a review on chiral nonracemic aziridines see: D. Tanner, *Angew. Chem., Int. Ed. Engl.*, **33**, 599, (1994).
30. For leading references on the application of aziridine 2-carboxylic acids to the synthesis of α -amino acids, see ref 6.
31. J. Legters, J. G. H. Willems, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas*, **111**, 59, (1992).
32. R. C. Roemmele, H. Rapoport, *J. Org. Chem.*, **53**, 2367, (1988).
33. F. A. Davis, P. Zhou, *Tetrahedron Lett.*, **35**, 7525, (1994).
34. J. N. Kanfer, S. Hakomori, *Sphingolipid Biochemistry*, Plenum Press: New York 1983; N. S. Radin, J. A. Shayman, J. Inokuchi, *Adv. Lipid Res.*, **26**, 183, (1993).

35. (a) T. A. Springer, L. A. Lasky, *Nature*, **349**, 196, (1991); (b) T. Feizi, *Trends Biochem. Sci.*, **16**, 84, (1991); (c) K.-A. Karlsson, *Trends Pharm. Sci.*, **12**, 265, (1991).
36. J. M. Harouse, S. Bhat, S. L. Spitalnik, M. Laughlin, K. Stefano, D. H. Silberberg, F. Gonzalez-Scarano, *Science*, **253**, 320, (1991).
37. A. H. Jr. Merrill, S. Nimkar, D. Menaldino, Y. A. Hannun, C. Loomis, R. M. Bell, S. R. Tyahi, J. D. Lambeth, V. L. Stevens, R. Hunter, D. C. Liotta, *Biochemistry*, **28**, 3138, (1989).
38. H. Zhang, N. E. Buckley, K. Gibson, S. Spiegel, *J. Biol. Chem.*, **265**, 39, (1990).
39. F. A. Davis, G. V. Reddy, H. Liu, *J. Am. Chem. Soc.*, **117**, 3651, (1995).
40. F. A. Davis, G. V. Reddy, *Tetrahedron Lett.*, **37**, 4349 (1996).
41. For a recent example of the Pummerer rearrangement using TFAA see: M. E. Jung, C. Kim, L. von dem Bussche, *J. Org. Chem.*, **59**, 3248, (1994).