Diastereoselective Synthesis of Unsaturated Vicinal Amino Alcohols via Diels–Alder Reactions of *N*-Sulfinyl Dienophiles

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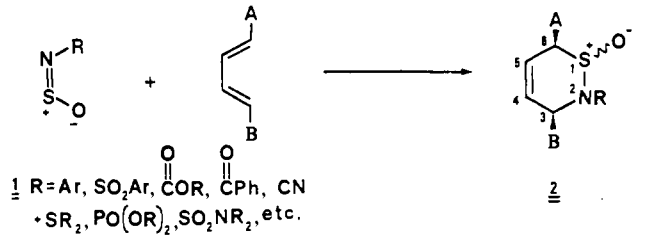
Abstract: A novel diastereoselective route for the synthesis of α-hydroxy-β,γ-unsaturated amine derivatives is described. The protocol starts with a 3,6-dihydrothiazine 1-oxide, which is obtained stereoselectively by a Diels–Alder [4 + 2] cycloaddition of a *N*-sulfinyl dienophile and a 1,3-diene of known geometry. Fission of the S–N bond of the adduct with a Grignard reagent leads to an allylic sulfoxide which is converted stereoselectively to an allyl alcohol via an allylic sulfoxide/sulfenate ester [2,3]-sigmatropic rearrangement. (*E*,*E*)-2,4-Hexadiene (**4**) and (*E*,*Z*)-2,4-hexadiene (**7**) were stereoselectively transformed to threo amino alcohol (**9**) and erythro amino alcohol (**11**), respectively. Intermediates in these transformations have been investigated by ^{1}H NMR experiments. The configuration and conformation of Diels–Alder adduct **5a** have been determined by X-ray crystallography and ^{1}H NMR lanthanide induced shift experiments. A variation of this strategy incorporating intramolecular *N*-sulfinyl Diels–Alder reactions has been used in total synthesis of the sphingolipid bases *erythro*- and *threo*-sphingosine. (*E*,*E*)-Diene carbamate **31** was converted to *threo*-sphingosine (**25**) in four steps in 52% overall yield. Similarly, (*E*,*Z*)-diene carbamate **46** was transformed to *erythro*-sphingosine (**27**) in 55% overall yield. Interestingly, the *N*-sulfinyl compound obtained from (*E*,*Z*)-diene carbamate **39** did not cyclize, probably for conformational reasons.

In 1953 Wichterle and Rocek[1] reported the first example of a Diels–Alder cycloaddition of a *N*-sulfinyl dienophile **1** (R = Ph) with a 1,3-diene to afford a 3,6-dihydrothiazine 1-oxide (**2**) (Scheme I). The same workers also investigated a few simple transformations of these interesting heterocyclic adducts. During the past 30 years relatively little additional research has been reported in this area other than a number of observations that various *N*-sulfinyl compounds bearing electron-withdrawing groups will undergo the cycloaddition at temperatures generally well below those usually required for "all carbon" Diels–Alder reactions.[2] Interestingly, *N*-sulfinyl compounds derived from alkylamines do not react at all as dienophiles.

More recently, Mock and Nugent[3] investigated the mechanism of the reaction of *N*-sulfinyl toluenesulfonamide with the three geometric isomers of 2,4-hexadiene. Based upon an analysis of the relative configurations of the various adducts obtained, it was concluded that these cycloadditions actually proceed stepwise via dipolar intermediates. Configuration at sulfur in the dihydrothiazine oxides was established by ^{1}H NMR lanthanide induced shift experiments and was the first (and to date only) time sulfur stereochemistry had been elucidated in any *N*-sulfinyl Diels–Alder adduct.[2] At present virtually nothing is known concerning the factors which control sulfur stereochemistry in this cycloaddition process.[4]

As part of our ongoing interest in synthetic applications of hetero Diels–Alder reactions[2a,5,6] we have recently begun to investigate the synthetic potential of cycloadditions with *N*-sulfinyl dienophiles.[4,7] A primary goal of this research program is to develop methodology for stereoselectively generating acyclic nitrogen-containing molecules.[8] Although there has been considerable activity recently in the general area of acyclic diastereoselectivity,[9,10] relatively little work has been reported on stereocontrolled synthesis of acyclic amines and related functionality.[11] As outlined in this paper, we have developed a strategy for predictably transforming double bond geometry of a 1,3-diene into relative stereochemistry in an unsaturated vicinal amino alcohol derivative via the intermediacy of a *N*-sulfinyl Diels–Alder adduct like **2**.[8]

Scheme I



We initially decided to test the methodology by using (*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene. We also chose to first utilize the previously unknown benzyl *N*-sulfinylcarbamate (**3**)[12] as dienophile since it seemed advisable to develop the procedure using a readily removable nitrogen protecting group. This sulfinyl compound was prepared from benzyl carbamate with thionyl chloride and pyridine and could be distilled before use or employed without purification with essentially identical results.

Addition of **3** to (*E*,*E*)-2,4-hexadiene (**4**) in toluene at room temperature gave a 15/1 mixture of chromatographically separable adducts **5a** and **6a** in 95% combined yield. The stereochemistry

(1) Wichterle, O.; Rocek, J. *Chem. Listy* **1953**, *47*, 1768. Wichterle, O.; Rocek, J. *Collect. Czech. Chem. Commun.* **1954**, *19*, 282.
(2) For reviews see: (a) Kresze, G.; Wucherpfennig, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 49. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(3) Mock, W. L.; Nugent, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 6521, 6526.
(4) Weinreb, S. M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1983**, *21*, 309.
(5) Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1397.
(6) (a) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. (b) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. (c) Khatri, N. A.; Schmitthenner, H. F.; Shringapure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6397. (d) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065. (e) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 261. (f) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.
(7) Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 987.
(8) For a preliminary account of a portion of this work, see: Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499.
(9) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1.
(10) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
(11) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101. Wang, Y. F.; Izawa, T.; Kobayashi, Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. Parker, K. A.; O'Fee, R. *Ibid.* **1983**, *105*, 654. Kohn, H.; Jung, S.-H. *Ibid.* **1983**, *105*, 4106. Cardillo, G.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1489.
(12) For preparation and Diels–Alder cycloadditions of related *N*-sulfinyl carbamates, see: Sommer, S. *Synthesis* **1977**, 305. Horhold, H. H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 357. Wucherpfenning, W. *Tetrahedron Lett.* **1967**, 3255. Levchenko, E. S.; Balon, Y. G.; Kirsanov, A. V. *Zh. Org. Khim.* **1967**, *3*, 1883. Ichimura, K.; Ichikawa, S.; Imamura, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1157.

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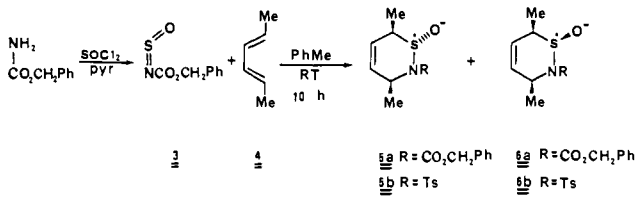
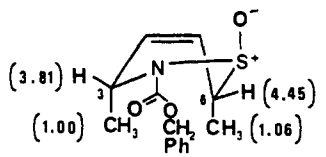


of the major adduct **5a** was unambiguously proven by a single-crystal X-ray structure determination.

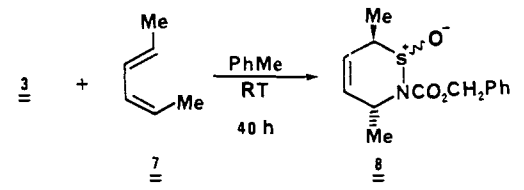
The stereochemical result of this cycloaddition is reversed relative to a similar one reported by Mock and Nugent,[3] who found that reaction of *N*-sulfinyl-*p*-toluenesulfonamide with diene **4** gave approximately a 30/1 mixture of adducts **6b**/**5b**, respectively. It should be noted that **5a** and **6a** do not interconvert under the reaction conditions or thermally, as do **5b** and **6b**.[3]

As can be seen from conformational drawing **5a**′, our major Diels–Alder adduct approximates a twist boat in the crystal. The



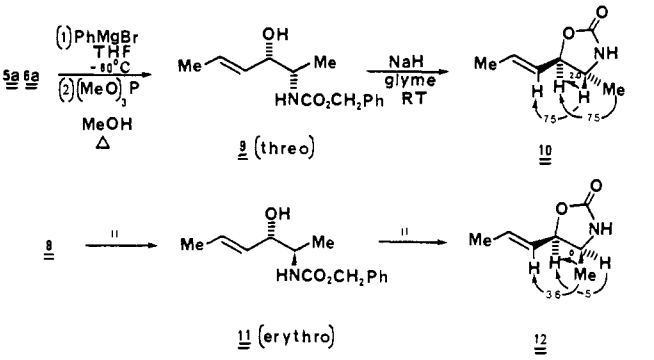
S–O bond in this adduct is quasi-axial, probably due to an anomeric effect.[13] The molecule exists as a half-twist boat, rather than as a half-chair, in order to minimize $A^{1,3}$ strain[14] between the C-3 methyl and the carbamate group. This boat conformation is probably also favored in solution as indicated by Eu(fod)$_3$ NMR shift experiments. The relative magnitudes of the downfield shifts observed for various protons are shown in parentheses. Assuming that lanthanide complexation occurs primarily at the sulfinyl oxygen, these shifts seem quite reasonable, although certainly not unambiguous, for the conformation shown in **5a**′. Mock and Nugent[3,15] found very similar europium-induced shifts for their minor adduct **5b**. However, these workers assigned a boatlike conformation to **5b** in which the sulfinyl oxygen and the two methyl groups are quasi-equatorial. We believe that **5b** probably exists in the same conformation as **5a** so as to satisfy the anomeric effect and to minimize nonbonded interactions. On the basis of X-ray crystal structures and LIS experiments on several other *N*-sulfinyl[16] and bis(*N*-sulfinyl)[17] dienophile Diels–Alder adducts, we believe that these systems probably all assume conformations in which the sulfur–heteroatom bond is quasi-axial. Thus, we feel that the solution conformations suggested by Mock and Nugent[3] for the adducts of *N*-sulfinyl-*p*-toluenesulfonamide and the isomeric 2,4-hexadienes might need revision, although their configurational assignments are correct. In the case of minor adduct **6a**, it was not possible to establish ring conformation using NMR methods since lanthanide-induced shifts were negligible.

Cycloaddition of *N*-sulfinyl carbamate **3** with (*E*,*Z*)-2,4-hexadiene (**7**) was relatively slow, but after 40 h at room temperature it was possible to isolate a *single* Diels–Alder adduct **8** in 57%

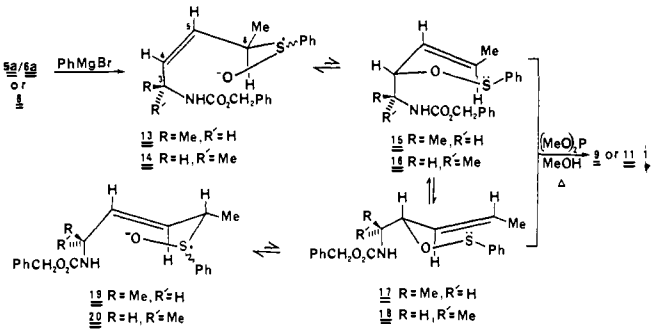


(13) Kirby, A. J. "The Anomeric Effect and Related Stereochemical Effects at Oxygen"; Springer-Verlag: New York, 1983.
(14) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(15) It appears that the resonances of the C-3 and C-6 hydrogen substituents of **5b** have been assigned incorrectly[3] and should be reversed.
(16) Remiszewski, S. W.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 3243.
(17) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.*, following paper in this issue.

Scheme II



Scheme III



yield. However, the configuration of **8** at sulfur could not be established by LIS NMR techniques, and at present the full stereochemistry of this compound is not known.

Addition of 1.1 equiv of phenylmagnesium bromide at −60 °C to the mixture of adducts **5a** and **6a**, followed by refluxing the crude product with trimethyl phosphite in methanol, afforded an 85% yield of (*E*)-*threo*-hydroxy carbamate **9** as the only detectable stereoisomer (Scheme II). Identical results were obtained with purified samples of both adducts **5a** and **6a**. The *E* double bond configuration of **9** was determined from ^{1}H NMR coupling constants (J = 15 Hz). Cyclization of **9** to oxazolone **10** was effected in high yield with sodium hydride, and the threo configuration was proved by ^{1}H nuclear Overhauser effect difference spectroscopy (NOEDS). Some of the more significant observed percent enhancements are indicated in the drawing (Scheme II).

Similar treatment of adduct **8**, derived from (*E*,*Z*)-hexadiene, with phenylmagnesium bromide followed by trimethyl phosphite stereospecifically afforded (*E*)-*erythro*-hydroxy carbamate **11** (85%). As in the above example, the double bond geometry of **11** was found to be *E* by ^{1}H NMR (J = 16 Hz). Analysis of the derived oxazolone **12** by NOEDS gave the enhancement shown, which clearly indicated that **11** had the erythro configuration.

We have examined the transformations of **5a**/**6a** and **8** to **9** and **11**, respectively, by ^{1}H NMR spectroscopy. Addition of phenylmagnesium bromide to pure major adduct **5a** produced a single allylic sulfoxide **13** possessing the expected cis double bond. Although 3,6-dihydrothiazine oxides have been opened with alkoxides and thiophenoxide, no examples of ring cleavages with carbon nucleophiles have previously been described for these systems.[18] Allylic sulfoxides are known to undergo rapid, reversible [2,3]-sigmatropic rearrangement via an envelope-like transition state to produce sulfenate esters (i.e., **15**), which upon treatment with a thiophile afford allylic alcohols.[19] Thus, if sulfoxide **13** rearranges through an envelope transition state having the methyl substituent at C-6 in a quasi-equatorial position, sulfenate ester **15** results which has the observed *E* double bond and threo configuration of the final product (Scheme III). Such

(18) Wucherpfennig, W. *Liebigs Ann. Chem.* **1971**, *761*, 16.
(19) Evans, D. A.; Andrews, G. C. *Acc. Chem. Ref.* **1974**, *7*, 147. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

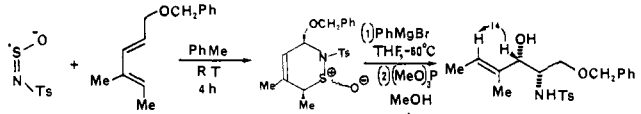
a conformation would minimize unfavorable nonbonded interactions in the transition state.[19]

When cis-allylic sulfoxide **13** was heated in $CDCl_3$ at 50 °C in an NMR tube, the compound slowly disappared ($t_{1/2} \sim 90$ min) and a mixture of trans-allylic sulfoxides **19** epimeric at sulfur was formed. Refluxing **19** in methanol containing trimethyl phosphite for several hours cleanly produced allylic alcohol **9**. The transformation of **13** to the thermodynamically more stable trans isomer **19** is precedented[20] and likely involves conformational inversion of sulfenate ester **15** to **17**, which undergoes reverse [2,3]-sigmatropic rearrangement to **19**. Not surprisingly, allylic sulfoxide **19** is a mixture of sulfur epimers since the stereochemistry of **13** is lost in **15**/**17**.

Similar results were obtained with the minor Diels–Alder adduct **6a**. One interesting difference was that the initial cis-allylic sulfoxide **13** formed from this adduct was *different* from the compound derived from the major adduct **5a**. We assume that the dihydrothiazine rings of these cycloadducts are opened stereospecifically by the Grignard reagent (probably with inversion[21]) to afford cis-allylic sulfoxides which are epimeric at sulfur. Unfortunately, the configurations of these intermediates are not easily determined. Upon warming in the absence of phosphite, the *cis*-sulfoxide **13** from the minor Diels–Alder adduct **6a** gave the same mixture of trans-allylic sulfoxides **19** as observed in the case of adduct **5a**. Thus, it seems from approximate relative rates of reaction that allylic alcohol **9** is probably derived from both sulfoxides **13** and **19**. Clearly, allylic sulfoxide **19** rearranges stereospecifically to **17** via a transition state in which the methyl group on the sulfur-bearing carbon is quasi-equatorial.

In the case of adduct **8** derived from (*E*,*Z*)-hexadiene, the initial cis-allylic sulfoxide **14** rearranged more rapidly to the trans isomer **20** ($t_{1/2} \sim 30$ min, $CDCl_3$, 50 °C) than in the above cases. Once again, reaction of pure **20** with trimethyl phosphite in refluxing methanol cleanly afforded allylic alcohol **11**. Thus, a similar sequence of [2,3]-sigmatropic rearrangements involving sulfenate ester conformers **16** and **18** must occur in this system.

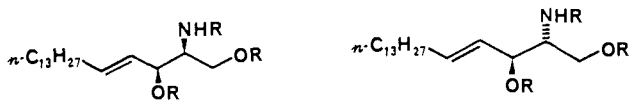
To further test this methodology, *N*-sulfinyltoluenesulfonamide (**21**)[22] was added to diene **22**[23] to afford dihydrothiazine oxide **23** as a single sulfur stereoisomer (91%). Treatment of **23** with



21 **22** **23** **24**

phenylmagnesium bromide followed by methanolic trimethyl phosphite gave exclusively the (*E*)-threo allylic alcohol sulfonamide **24** (85%). The double bond geometry of **24** was proven by ^1H NOEDS, which inter alia gave the percent enhancement shown in the drawing. This stereochemistry and double bond configuration are fully consistent with the rearrangement mechanism shown in Scheme III.

We next turned out attention to *threo*-sphingosine (**25**) and *erythro*-sphingosine (**27**) as seemingly ideal targets for the above

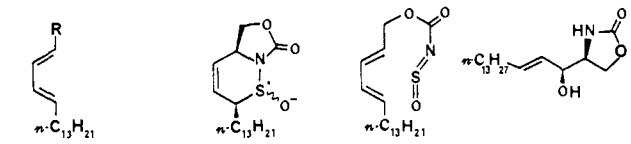


25 R=H
26 R=$COCH_3$

27 R=H
28 R=$COCH_3$

synthetic methodology. These components of sphingolipids have been synthesized several times,[24] but many of the routes to **25** and **27** do not show outstanding stereochemical control. In planning syntheses of the sphingosines, it was apparent that we would have to utilize unsymmetrical 1,4-disubstituted dienes which would probably not show significant regioselectivity in the initial Diels–Alder step. Thus, we investigated the use of intramolecular cycloaddition processes for controlling regiochemistry. No examples of intramolecular *N*-sulfinyl dienophile Diels–Alder reactions existed previously, but as outlined below, such a strategy can be easily and efficiently executed.

For preparation of *threo*-sphingosine (**25**) an (*E*,*E*)-diene was required. Accordingly, diene ester **29** was prepared from 1-tetradecanal and trimethyl phosphonocrotonate in 60% yield as a single stereoisomer having the desired configuration. This ester was reduced with lithium aluminum hydride to alcohol **30** ((85%),



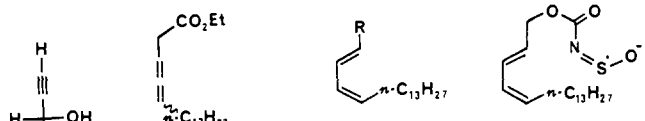
29 R=CO_2Me
30 R=CH_2OH
31 R=CH_2OCNH_2 (O)

32 **33** **34**

which on treatment with sodium cyanate/TFA[25] gave carbamate **31** (88%). Reaction of this carbamate with thionyl chloride/pyridine (−15 °C to room temperature) afforded the expected dihydrothiazine oxide **32** as one stereoisomer (85%). Although not isolated, *N*-sulfinyl carbamate **33** is undoubtedly an intermediate in this transformation. The usual sequence involving phenylmagnesium bromide, followed by trimethyl phosphite in methanol, served to convert adduct **32** stereospecifically to (*E*)-threo carbamate **34** in 85% yield. As in the above cases, no other stereoisomer was detected here. Saponification of **34** with barium hydroxide yielded racemic *threo*-sphingosine (**25**) which was most easily characterized as its triacetyl derivative **26**.[26]

Synthesis of *erythro*-sphigosine (**27**) by this methodology required using a 1,4-disubstituted diene having an *E*,*Z* configuration. Two possible diene systems can, in principle, suffice, and we have investigated both. Once again, intramolecular Diels–Alder chemistry was used to control regiochemistry.

The first diene system explored was prepared by using a sequence reported by Takeda and co-workers.[27] Addition of ethynyl Grignard reagent to 1-tetradecanal gave ethynyl alcohol **35** (70%) which underwen the Johnson ortho ester Claisen rearrangement to afford a mixture of allenic esters **36** (60%). This mixture could



35 **36**

37 R=CO_2Et
38 R=CH_2OH
39 R=CH_2OCNH_2 (O)

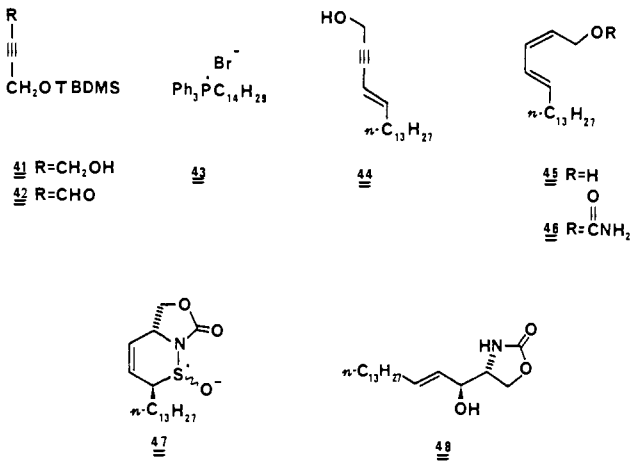
40

be rearranged by using basic alumina as catalyst[27] to give (*E*,*Z*)-diene ester **37** in 60% yield. Reduction of ester **37** with lithium aluminum hydride to diene alcohol **38** and carbamate formation with NaOCN/TFA gave **39** in excellent yield. When this car-

(20) Cf: Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 6774.
(21) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: New York, 1976; pp 194–203.
(22) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.
(23) Kim, M. Y.; Starrett, J. E.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383.
(24) For other syntheses, see: (a) Shapiro, D. "Chemistry of Sphingolipids"; Hermann: Paris, France, 1969. (b) Newman, H. *J. Am. Chem. Soc.* **1973**, *95*, 4098. (c) Tkaczak, P.; Thorton, E. R. *J. Org. Chem.* **1981**, *46*, 4393. (d) Schmidt, R. R.; Klager, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 210. (e) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491.
(25) Loev, B.; Kormendy, M. R. *J. Org. Chem.* **1963**, *28*, 3421.
(26) Grob, C. A.; Gadient, F. *Helv. Chim. Acta* **1957**, *40*, 1145.
(27) Tsuboi, S.; Masuda, T.; Takeda, A. *J. Org. Chem.* **1982**, *47*, 4478.

bamate was treated with thionyl chloride/pyridine, *N*-sulfinyl carbamate **40** was in fact produced, as evidenced by IR spectroscopy and its rapid hydrolysis back to **39**. However, this compound could not be induced to cyclize at any temperature. It is probable that for steric reasons **40** cannot assume the s-cis conformation necessary for cycloaddition.

The alternative (*E*,*Z*)-diene was prepared by starting with acetylenic alcohol **41**[28] which upon oxidation with barium manganate[29] gave aldehyde **42** in 95% yield. Reaction of this aldehyde with the ylide derived from phosphonium salt **43**, followed by acidic workup, afforded the (*E*)-enyne alcohol **44** (75%).[30] Lindlar



reduction of **44** yielded the desired (*E*,*Z*)-diene alcohol **45** (83%), which was transformed to carbamate **46** (NaOCN/TFA,[25] 85%). Treatment of **46** with thionyl chloride/pyridine gave an intermediate *N*-sulfinyl carbamate which slowly cyclized at room temperature (90 h) to give adduct **47** as a single stereoisomer (86%). Ring cleavage of dihydrothiazine oxide **47** with phenylmagnesium bromide followed by heating the intermediate allylic sulfoxide with trimethyl phosphite in methanol cleanly produced allylic alcohol **48** in 86% yield. Hydrolysis of **48** with barium hydroxide afforded racemic *erythro*-sphigosine (**27**) which was directly compared with naturally derived material[31] and was further characterized as its triacetyl derivative **28**.[26]

Thus, we have demonstrated that 1,3-dienes can be efficiently and predictably transformed to acyclic unsaturated amino alcohol derivatives with complete stereocontrol. This and related methodology[17] are currently being applied to the synthesis of some complex natural products.

Experimental Section

***N*-Sulfinylbenzyl Carbamate (3).** To a suspension of 5.138 g (0.034 mol) of benzyl carbamate in 80 mL of dry ether at 0 °C was added 2.5 mL (0.034 mol) of distilled thionyl chloride. To the reaction mixture was added 5.4 mL of dry pyridine via a syringe pump over a period of 1.5 h. The reaction mixture was stirred at 0 °C for an additional 2 h. The precipitated pyridinium hydrochloride was removed by filtration, and the salt was washed with dry ether. Excess thionyl chloride, pyridine, and solvent were removed in vacuo. The resulting yellow oil was purified by bulb-to-bulb distillation, yielding 4.83 g (72%) of the pale yellow, air-sensitive sulfinyl carbamate **3**: bp 75–85 °C (0.03 torr); IR (film) 1740 (br), 1260, 1220, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.25 (2 H, s), 7.33 (5 H, s).

Phenylmethyl (∓)-(1α,3β,6β)-3,6-Dihydro-3,6-dimethyl-2*H*-1,2-thiazine-2-carboxylate 1-Oxide (5a) and Phenylmethyl (∓)-(1β,3β,6β)-3,6-Dihydro-3,6-dimethyl-2*H*-1,2-thiazine-2-carboxylate 1-Oxide (6a). To a solution of *N*-sulfinylbenzyl carbamate (**3**, 0.500 g, 2.67 mmol) in anhydrous toluene (3 mL) was added (*E*,*E*)-2,4-hexadiene (**4**, 0.27 mL, 2.43 mmol), and the mixture was stirred at room temperature for 4 h. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (1/1 ethyl acetate/hexane) to afford 0.607 g (89%) of thiazine oxide **5a** and 0.038 g (6%) of epimeric thiazine oxide **6a**.

An analytical sample of **5a** recrystallized from ether/hexane had a melting point of 50–52 °C: IR (film) 3040, 2975, 2925, 1720, 1450, 1380, 1270, 1240, 1200, 1100, 1060, 780, 740, 700 640 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.34 (d, J = 7.0 Hz, 3 H), 1.48 (d, J = 6.4 Hz, 3 H), 3.23 (m, 1 H), 3.44 (m, 1 H), 5.26 (s, 2 H), 5.84 (dd, J = 7.0, 10.7 Hz, 1 H), 6.07 (dd, J = 4.27, 10.7, 1 H), 7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.28, 21.90, 48.94, 53.82, 68.67, 118.93, 127.80, 128.45, 131.89, 135.07, 155.59; mass spectrum m/z (relative intensity) 280 (0.2), 279 (0.9), 91 (100), 82 (19.5), 67 (12.3); exact mass calcd for $C_{14}H_{17}NO_3S$, 279.0929, found, 279.0924.

Adduct **6a**: oil; IR (film) 3040, 2980, 2930, 1720, 1520, 1450, 1380, 1300, 1210, 1100, 1050, 1000, 750, 720, 620 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.47 (d, J = 7.1 Hz, 6 H), 3.35 (m, 1 H), 4.54 (m, 1 H), 5.28 (s, 2 H), 5.40 (m, 1 H), 5.95 (m, 1 H), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) 15.54, 22.04, 49.33, 51.82, 68.45, 119.06, 128.06, 128.37, 128.49, 129.88, 135.10, 153.32; mass spectrum m/z (relative intensity) 280 (0.5), 279 (2.7), 91 (100), 82 (12.6), 67 (8.5); exact mass calcd for $C_{14}H_{17}NO_3S$, 279.0929, found, 279.0922.

Preparation of Adduct 8. A mixture of (*E*,*Z*)-2,4-hexadiene (**7**, 0.35 mL, 3.04 mmol), *N*-sulfinylbenzyl carbamate (**3**, 0.50 g, 3.04 mmol), and 4 drops of toluene was stirred for 40 h at room temperature. The crude product was purified by flash chromatography (1/1 ethyl acetate/hexane) to afford 0.402 g (57%) of thiazine oxide **8** as an oil: IR (film) 3040, 2975, 2925, 1720, 1500, 1450, 1380, 1290, 1270, 1120, 1090, 1050, 750, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.36 (d, J = 6.4 Hz, 3 H), 1.52 (d, J = 7.3 Hz, 3 H), 3.42 (m, 1 H), 4.56 (m, 1 H), 5.27 (ABq, J = 12.5 Hz, 2 H), 5.50 (dd, J = 2.7, 10.0 Hz, 1 H), 6.90 (m, 1 H), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.48, 20.07, 49.72, 50.87, 68.74, 121.53, 127.79, 127.92, 128.29, 128.51, 129.03, 133.21, 135.10, 154.50; mass spectrum m/z (relative intensity) 280 (0.45), 279 (2.40), 91 (100), 82 (12.55) 65 (4.85); exact mass calcd for $C_{14}H_{17}NO_3S$, 279.0929, found, 279.0915.

Phenylmethyl (∓)-(1*S,2*S**,3*E*)-(2-Hydroxy-1-methyl-3-pentenyl)-carbamate (9).** A solution of 3 M phenylmagnesium bromide in ether (0.35 mL, 1.00 mmol) was added to a solution of thiazine oxide **5a** (0.255 g, 0.913 mmol) in anhydrous THF (6 mL) at −60 °C. The mixture was stirred for 10 min and was diluted with 15 mL of saturated NH_4Cl solution. The mixture was extracted with ether (3 × 10 mL), washed with brine (2 × 10 mL) and dried. Concentration of the organic phase in vacuo yielded *cis*-allylic sulfoxide **13**, which was used directly in the next step. A sample of **13** was purified by preparative TLC (1/3 ethyl acetate/hexane): IR (film) 3300, 3060, 3040, 2975, 2925, 1710, 1530, 1420, 1240, 1170, 1040, 1000, 740, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 3 H), 1.25 (d, J = 6.6 Hz, 3 H), 3.90 (m, 1 H), 4.32 (m, 1 H) 5.13 (ABq, J = 12.2 Hz, 2 H), 5.32 (m, 2 H), 5.60 (dd, J = 6.0, 11.8 Hz, 1 H), 7.40 (m, 5 H).

To a solution of crude allylic sulfoxide **13** (0.325 g, 1.00 mmol) in 15 mL of methanol was added trimethyl phosphite (0.16 mL, 1.36 mmol), and the mixture was heated at 50 °C for 5 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by preparative TLC (1/1 ethyl acetate/hexane) to yield 0.193 g of allylic alcohol **9** as a colorless oil (85% from **5a**): IR (film) 3375, 3050, 2975, 2925, 2875, 1700, 1520, 1450, 1340, 1240, 1100, 1050, 970, 930, 780, 740, 700, 610 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.15 (d, J = 6.7 Hz, 3 H), 1.68 (d, J = 6.9 Hz, 3 H), 2.63 (br s, 1 H), 3.72 (m, 1 H), 3.40 (m, 1 H), 5.08 (s, 2 H), 5.48 (qdd, J = 1.5, 7.1, 15.4 Hz, 1 H), 5.71 (qd, J = 6.1, 15.4 Hz, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.46, 17.62, 51.27, 66.58, 75.37, 127.87, 127.93, 128.36, 128.67, 130.59, 136.48, 156.43; CI MS ((M + 1)/z) 251, 250, 233.

Phenylmethyl (∓)-(1*R,2*S**,3*E*)-(2-Hydroxyl-1-methyl-3-pentenyl)-carbamate (11).** The allylic alcohol **11** was prepared from adduct **8** in 85% yield by the procedure described above for alcohol **9**. The crude product was purified by preparative TLC (1/1 ethyl acetate/hexane): oil; IR (film) 3425, 3325, 3075, 3050, 2980, 2940, 1700, 1520, 1450, 1320, 1240, 1100, 1050, 970, 780, 740, 700, 610 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.64 (d, J = 6.78 Hz, 3 H), 1.70 (dd, J = 1.5, 6.4 Hz, 3 H), 2.56 (br s, 1 H), 3.11 (m, 1 H), 4.12 (m, 1 H), 5.10 (s, 2 H), 5.45 (qdd, J = 1.5, 6.5, 16.2 Hz, 1 H), 5.75 (m, 1 H), 7.37 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.21, 17.77, 51.43, 66.75, 75.18, 128.07, 128.49, 128.69, 129.60, 136.41, 156.37; CI MS ((M + 1)/z) 251, 250, 233.

(∓)-[4α(*E*),5β]-5-Methyl-4-(1-propenyl)-2-oxazolidinone (10). To a solution of allylic alcohol **9** (0.292 g, 1.17 mmol) in dry glyme (6 mL) was added sodium hydride (0.073 g, 50% in mineral oil, 1.52 mmol), and the mixture was stirred for 2 h. The reaction mixture was carefully diluted with water, extracted with ethyl acetate (3 × 20 mL) and washed with brine (2 × 10 mL). The organic phase was dried and concentrated

(28) Motto, M. G.; Sheves, M.; Tsujimoto, K.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1980**, *102*, 7947. These workers converted **41** to **42** in 69% yield with MnO_2.
(29) Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839.
(30) Bosshardt, H.; Schlosser, M. *Helv. Chim. Acta* **1980**, *63*, 2393.
(31) D-*erythro*-Spingosine was obtained from Sigma Chemical Co.

in vacuo. Purification of the crude product by preparative TLC (1/1 ethyl acetate/hexane) yielded the oxazolone **10** (0.155 g, 94%). An analytical sample recrystallized from CH_2Cl_2/hexane had a melting point of 55–57 °C: IR (KBr) 3300, 2975, 2925, 1760, 1390, 1240, 1000 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.27 (d, J = 6.1 Hz, 3 H), 1.76 (dd, J = 1.39, 6.56 Hz, 3 H), 3.65 (m, 1 H), 4.43 (t, J = 7.6 Hz, 1 H), 5.51 (m, 1 H), 5.84 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.65, 19.22, 54.17, 85.03, 126.84, 132.31, 159.39; mass spectrum m/z (relative intensity) 141 (8.6), 101 (1.8), 86 (8.4), 84 (12.5), 71 (100), 49 (19.5). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.47; H, 7.87.

(∓)-[4α(*E*),5α]-5-Methyl-4-(1-propenyl)-2-oxazolidinone (12). Oxazolone **12** was prepared from allylic alcohol **11** in 88% yield by the procedure described above for oxazolone **10**. The crude product was purified by preparative TLC (1/1 ethyl acetate/hexane). An analytical sample recrystallized from CH_2Cl_2/hexane had a melting point of 79–80 °C: IR (film) 3300, 2975, 2925, 1760, 1560, 1410, 1380, 1290, 1230, 1110, 1000, 975, 940, 770 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3 H), 1.76 (dd, J = 1.5, 7.10 Hz, 3 H), 3.92 (quintet, J = 6.9 Hz, 1 H), 4.96 (t, J = 7.9 Hz, 1 H), 5.53 (qdd, J = 1.5, 8.1, 15.1 Hz, 1 H), 5.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.90, 17.80, 51.63, 80.96, 123.86, 132.91, 159.35; mass spectrum m/z (relative intensity) 141 (16.9), 128 (8.9), 127 (21.9), 101 (10.4), 98 (30.6), 92 (10.2), 91 (100). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.73; H, 7.87.

Diels–Alder Reaction of Diene 22. To an ice-cold solution of *N*-sulfinyl-*p*-toluenesulfonamide (**21**, 1.22 g, 5.63 mmol) in anhydrous toluene (20 mL) was added diene **22** in toluene (10 mL). The mixture was stirred for 4 h at room temperature, and the solvent was evaporated in vacuo. Purification of the crude product by flash chromatography yielded adduct **23** (1.94 g, 91%) as a colorless oil: IR (film) 3100, 3075, 3025, 2975, 2925, 2875, 1600, 1500, 1450, 1350, 1160, 1140, 1110, 1080, 990, 930, 890, 840, 810, 790, 710, 700, 680, 660, 620, 610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (d, J = 7.6 Hz, 3 H), 1.78 (d, J = 1.5 Hz, 3 H), 2.37 (s, 3 H), 3.24 (m, 1 H), 3.60 (d, J = 7.3 Hz, 2 H), 4.40 (ABq, J = 12.2 Hz, 2 H), 4.68 (m, 1 H), 5.89 (m, 1 H), 7.19–7.36 (m, 7 H), 7.73 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.09, 21.50, 21.62, 54.35, 55.39, 72.74, 72.86, 120.61, 125.38, 126.28, 127.04, 127.54, 128.23, 129.51, 129.84, 137.16, 137.81, 144.44; CI MS ((M + 1)/z) 421, 420.

Preparation of Alcohol 24. The allylic alcohol **24** was prepared from adduct **23** in 85% yield by the procedure described above for preparation of alcohol **9**. The product was purified by TLC (20% ethyl acetate/hexane): IR (film) 3500, 3375, 3300, 3075, 3050, 2925, 2850, 1600, 1500, 1460, 1410, 1330, 1210, 1160, 1100, 1030, 940, 820, 740, 700, 760 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.46 (d, J = 7.0 Hz, 3 H), 2.4 (s, 3 H), 2.92 (br s, 1 H), 3.30 (m, 1 H), 3.50 (m, 2 H), 4.15 (d, J = 4.0 Hz, 1 H), 4.42 (ABq, J = 11.2 Hz, 2 H), 5.16 (d, J = 7.6 Hz, 1 H), 5.48 (m, 1 H), 7.23–7.36 (m, 7 H), 7.68 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.10, 12.95, 21.38, 38.08, 54.73, 70.73, 73.48, 121.74, 127.09, 127.67, 127.80, 128.35, 129.37, 133.32, 137.37, 137.62, 143.14; CI MS ((M + 1)/z) 392, 391, 390, 373, 372, 338, 337. Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99. Found: C, 64.67; H, 7.05.

Methyl Octadeca-2(*E*),4(*E*)-dien-1-oate (29). To a solution of diisopropylamine (1.10 mL, 7.91 mmol) in anhydrous THF (2 mL) at −40 °C was added a soluton of 1.6 M *n*-butyllithium in hexane (4.35 mL, 7.25 mmol) and the mixture was stirred for 20 min. Trimethyl 4-phosphonocrotonate (1.37 g, 6.6 mmol) in anhydrous THF (8 mL) was added to the LDA solution at −40 °C, and the mixture was stirred for 2 h. To the orange mixture at −40 °C was added *n*-tetradecanal (1.00 g, 4.7 mmol) in anhydrous THF (10 mL) and the mixture was stirred at −40 °C for 2 h and at room temperature for 12 h. The reaction mixture was diluted with saturated NH_4Cl solution and was extracted with hexane (5 × 30 mL). The organic phase was dried and concentration in vacuo, and the crude product was purified by flash chromatography (5% ethyl acetate/hexane) to yield ester **29** (0.83 g, 60%) as a low melting solid: IR (film) 3075, 3025, 2925, 2860, 1730, 1640, 1620, 1460, 1430, 1330, 1310, 1280, 1270, 1140, 1040, 1000, 870, 720 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.25 (s, 20 H), 1.40 (q, J = 7.0 Hz, 2 H), 2.15 (m, 2 H), 3.73 (s, 3 H), 5.78 (d, J = 15.3 Hz, 1 H), 6.14 (m, 2 H) 7.26 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.34, 22.64, 28.66, 29.16, 29.37, 29.60, 31.53, 31.87, 32.96, 51.34, 118.61, 128.25, 144.92, 145.35, 167.67; mass spectrum m/z (relative intensity) 296 (1.2), 295 (7.4), 294 (27.9), 293 (0.5), 263 (15.0), 226 (6.4), 220 (18.3), 150 (12.5), 139 (10.6) 111 (100). Exact mass calcd for $C_{19}H_{34}O_2$: 294.2558. Found: 294.2531.

Octadeca-2(*E*),4(*E*)-dien-1-ol (30). To a suspension of $LiAlH_4$ (0.054 g, 1.41 mmol) in anhydrous ether (20 mL) was added ester **29** (0.500 g, 1.61 mmol) in ether (5 mL), adn the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with saturated NH_4Cl solution (1 mL) and 5% NaOH solution (3 mL). The mixture was filtered, and the filtrate was washed with brine (10 mL). The organic phase was dried and concentrated in vacuo. The crude product was purified by flash chromatography (15% ethyl acetate/hexane) to yield alcohol **30** (0.385 g, 85%). An analytical sample recrystallized from hexane had a melting point of 56 °C: IR ($CHCl_3$) 3625, 2930, 2860, 1450, 1380, 990, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 6.1 Hz, 3 H), 1.26 (s, 22 H), 2.06 (m, 2 H), 4.17 (d, J = 5.9 Hz, 2 H), 5.74 (m, 2 H), 6.12 (m, 1 H), 6.24 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.67, 29.21, 29.35, 29.48, 29.59, 29.65, 31.91, 32.61, 63.54, 129.29, 132.16, 135.86; CI MS ((M + 1/z) 250, 249.

Octadeca-2(*E*),4(*E*)-dienyl Carbamate (31). To a solution of octadeca-2*E*,4*E*)dien-1-ol (**30**, 0.380 g, 1.42 mmol) in ether (10 mL) in a pressure bottle was added sodium cyanate (0.195 g, 2.99 mmol) and TFA (0.22 mL, 2.85 mmol).[25] The bottle was sealed, and the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ether and was washed with water. The organic phase was dried and concentrated in vacuo. Purification of the crude product by flash chromatography (1/3 ethyl acetate/hexane) yielded carbamate **31** (0.390 g, 88%) as a white solid. An analytical sample recrystallized from CH_2Cl_2/hexane had a melting point of 90–91 °C: IR (KBr) 3425, 2825, 2750, 1690, 1330, 1230, 1000, 720 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 3 H), 1.23 (s, 22 H), 2.05 (q, J = 7.1 Hz, 2 H), 4.58 (m, 2 H), 4.84 (m, 2 H), 5.63 (m, 1 H), 5.74 (m, 1 H), 6.01 (m, 1 H), 6.21 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.66, 29.15, 29.33, 29.47, 29.63, 31.89, 32.62, 65.58, 124.12, 129.05, 134.80, 136.87, 156.69; mass spectrum m/z (relative intensity) 310 (2.5) 309 (10.3), 266 (4.4), 249 (7.9), 248 (15.9) 211 (8.2), 141 (4.5), 123 (13.5), 121 (10.1). Anal. Calcd for $C_{19}H_{35}NO_2$: C, 73.60; H, 11.06. Found: C, 73.74; H, 11.39.

Cycloaddition of Carbamate 31. To a solution of carbamate **31** (0.330 g, 1.06 mmol) and pyridine (0.52 mL, 6.4 mmol) in anhydrous toluene (5 mL) at −15 °C was added thionyl chloride (0.12 mL, 1.6 mmol) in toluene (5 mL) over 90 min. The mixture was stirred for 1 h at −15 °C and for 15 h at room temperature. Pyridinium hydrochloride was removed by filtration and the filtrate was evaporated in vacuo. Flash chromatography (1/1 ethyl acetate/hexane) of the crude product yielded the dihydrothiazine oxide **32** as a white crystalline solid (0.320 g, 85%). An analytical sample was recrystallized from CH_2Cl_2/hexane: mp 102–103 °C; IR (KBr) 2940, 2860, 1770, 1480, 1405, 1210, 1110, 1090, 1070, 1050, 790, 770, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3 H), 1.26 (s, 20 H), 2.05 (m, 2 H), 2.79 (m, 2 H), 3.01 (m, 1 H), 4.22 (dd, J = 8.10, 11.1 Hz, 1 H), 4.35 (m, 1 H) 4.76 (t, J = 8.0 Hz, 1 H), 5.87 (td, J = 3.2, 9.8 Hz, 1 H), 6.32 (td, J = 2.5, 9.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.66, 26.65, 28.90, 29.22, 29.30, 29.45, 29.60, 31.89, 52.68, 60.17, 69.27, 127.76, 129.23, 155.07; CI MS ((M + 1)/z) 357, 356. Anal. Calcd for $C_{19}H_{33}NSO_3$: C, 64.18; H, 9.35. Found: C, 63.87; H, 9.45.

(∓)-[*R,*S**-(*E*)]-4-(1-Hydroxy-2-hexadecenyl)-2-oxazolidinone (34).** A solution of 3 M phenylmagnesium bromide in ether (0.23 mL, 0.66 mmol) was added to a solution of dihydrothiazine oxide **32** (0.183 g, 0.513 mmol) in anhydrous THF (5 mL) at −60 °C, and the mixture was stirred for 15 min at −60 °C. The reaction mixture was diluted with saturated NH_4Cl (15 mL) and was extracted with ether (3 × 10 mL). The extract was washed with brine (2 × 10 mL), dried, and concentrated in vacuo. The crude sulfoxide was used directly in the next step. IR (film) 3275, 3050, 2925, 2850, 1760, 1470, 1440, 1400, 1320, 1090, 1040, 970, 930, 750, 690 cm^{-1}.

To a solution of the above crude sulfoxide (0.200 g, 0.46 mmol) in dry methanol (30 mL) was added trimethyl phosphite (0.2 mL, 0.92 mmol), and the mixture was heated at 50 °C for 18 h. The reaction mixture was evaporated in vacuo, and the crude product was purified by flash chromatography (1/1 ethyl acetate/hexane) to afford 0.142 g (85%) of **34** as a white solid. An analytical sample recrystallized from CH_2Cl_2/hexane had a melting point of 100–101 °C. IR (KBr) 3450, 3250, 2850, 1730, 1470, 1250, 1020, 970, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz), 1.26 (s, 22 H), 3.77 (m, 1 H), 4.01 (t, J = 7.3 Hz, 1 H), 4.13 (dd, J = 5.2, 8.8 Hz, 1 H), 4.37 (t, J = 8.8 Hz, 1 H), 5.35 (dd, J = 7.3, 15.2 Hz), 5.83 (m, 1 H), 5.95 (NH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.67, 28.95, 29.18, 29.33, 29.44, 29.59, 29.65, 31.91, 32.33, 56.79, 66.66, 75.01, 127.08, 136.83, 159.81; mass spectrum m/z (relative intensity) 326 [M^+ + 1] (0.3), 325 [M^+] (0.5), 309 (2.4), 296 (4.5), 279 (2.1), 264 (2.1), 254 (10.1), 253 (5.1), 252 (24.6), 251 (10.9), 250 (34.3), 239 (24.5), 222 (2.8) 210 (1.2). Exact mass calcd for $C_{19}H_{35}NO_3$: 325.2669. Found: 325.2643.

***dl-threo*-Triacetylsphingosine (25).** To a solution of 0.015 g (0.046 mmol) of oxazolone **34** in glyme (1.5 mL) and water (1 mL) was added (0.037 g, 0.115 mmol) of barium hydroxide octahydrate, and the mixture was refluxed under nitrogen for 36 h. The mixture was cooled to room temperature and was saturated with CO_2 gas to precipitate the barium salts. Filtration of the inorganic salts and concentration of the filtrate in vacuo afforded *dl-threo*-sphingosine (**25**). This material was dissolved

in 1 mL of acetic anhydride and 1 mL of pyridine, and the solution was stirred for 6 h at room temperature. Evaporation of the solvent in vacuo and purification of the residue by preparative TLC ($CHCl_3$/MeOH/9/1) gave *dl-threo*-triacetylsphingosine (**26**, 14.1 mg, 72%) as a white solid. A sample recrystallized from CH_2Cl_2/hexane had a melting point of 68 °C (lit.[26] mp 69–71 °C): IR (KBr) 3300, 2940, 2860, 1750, 1660, 1550, 1460, 1430, 1370, 1230, 1050, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (t, J = 6.2 Hz, 3 H), 1.25 (s, 22 H), 1.61 (m, 2 H), 2.00 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 3.64 (t, J = 6.4 Hz, 1 H), 4.10 (m, 2 H), 4.40 (m, 1 H), 5.38 (m, 1 H), 5.72 (m, 2 H).

Ethyl Octadeca-2(*E*),4(*Z*)-dien-1-oate (37). To a solution of ethynylmagnesium bromide (25 mmol) in THF (15 mL) at 0 °C was added freshly distilled *n*-tetradecanal (4.20 g, 19 mmol) under an atmosphere of acetylene. The mixture was stirred at room temperature overnight, poured into saturated NH_4Cl solution, and extracted with ether (3 × 40 mL). The organic phase was dried and concentrated in vacuo. The residue was distilled affording alcohol **35** (3.3 g, 70%) as a colorless oil: bp 135 °C (0.1 torr); IR (film) 3600–3100 (br), 2940, 2850, 2125, 1460, 1380, 1040, 720, 660, 630 cm^{-1}.

A mixture of alcohol **35** (3.0 g, 12 mmol), triethyl orthoacetate (15 mL, 83 mmol) and 6 drops of propionic acid was heated at 150 °C for 35 h while ethanol was removed by slow distillation. The reaction mixture was concentrated in vacuo, and the residue was distilled to afford allenes **36** (2.3 g, 60%) as a colorless oil: bp 160 °C (0.05 torr); IR (film) 2940, 2850, 1970, 1740, 1640, 1470, 1370, 1240, 1160, 1050, 950, 870, 720 cm^{-1}.

A solution of allenic esters **36** (2.0 g, 6.5 mmol) in benzene was refluxed in the presence of 200–300 mesh Woelm basic alumina (3 g) for 2.5 h.[26] The mixture was cooled and was filtered. Concentration of the filtrate in vacuo and purification of the residue by preparative TLC (5% ethyl acetate/hexane) afforded diene ester **37** (1.2 g, 60%) as a colorless oil: IR (film) 2940, 2850, 1720, 1640, 1600, 1460, 1410, 1370, 1300, 1270, 1180, 1140, 1100, 1040, 990, 960, 870, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.26 (s, 20 H), 1.29 (t, J = 5.9 Hz, 3 H), 1.39 (m, 2 H), 2.30 (br q, 2 H), 4.21 (q, J = 7.0 Hz, 2 H), 5.85 (m, 2 H), 6.10 (t, J = 10.9 Hz, 1 H), 7.64 (ddd, J = 1.1, 11.7, 15.2 Hz, 1 H).

Octadeca-2(*E*),4(*Z*)-dien-1-ol (38). To a suspension of $LiAlH_4$ (0.066 g, 1.74 mmol) in anhydrous ether (20 mL) was added ester **37** (0.700 g, 2.27 mmol) in ether (6 mL), and the mixture was stirred for 4 h at room temperature. The reaction mixture was carefully diluted with saturated NH_4Cl solution (1 mL) and 5% NaOH solution (3 mL). The mixture was filtered, and the filtrate was washed with brine (10 mL) and dried. Evaporation of the solvent in vacuo yielded alcohol **38** (0.507 g, 90%) as a colorless oil of sufficient purity for use in the next step. IR (film) 3320, 3010, 2950, 2925, 2850, 1460, 1280, 1050, 720, 610 cm^{-1}.

Octadeca-2(*E*),4(*Z*)-dienyl Carbamate (39). This compound was prepared from alcohol **38** in 90% yield by the procedure described above for **31**.[25] An analytical sample recrystallized from CH_2Cl_2/hexane had a melting point of 90–91 °C: IR (KBr) 3425, 2910, 2850, 1680, 1610, 1460, 1410, 1340, 1050, 990, 950, 780, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.27 (s, 20 H), 1.38 (br, 2 H), 2.18 (m, 2 H), 4.63 (br d, 4 H), 5.52 (m, 1 H), 5.74 (m, 1 H), 5.99 (t, J = 11.1 Hz, 1 H), 6.58 (ddd, J = 1.1, 11.0, 15.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.67, 27.82, 29.25, 29.34, 29.50, 29.59, 29.65, 31.91, 65.65, 126.36, 127.25, 129.66, 134.34, 156.60; mass spectrum m/z (relative intensity) 310 (1.77) [M^+ + 1], 309 (8.9) [M^+], 267 (1.3), 266 (7.0), 250 (5.8), 249 (3.8), 248 (8.9), 222 (7.8), 194 (3.3), 180 (2.9), 166 (2.1), 152 (2.3), 138 (3.1), 137 (3.9), 135 (5.7) 127 (3.9), 124 (5.3), 123 (7.5), 121 (9.2), 109 (14.6), 96 (38.2), 80 (67.2), 67 (62.0), 55 (64.9). Anal. Calcd for $C_{19}H_{35}NO_2$: C, 73.60; H, 11.06. Found: C, 73.56; H, 11.24.

4-[(1,1-Dimethylethyl)dimethylsilyloxy]but-2-yn-1-al (42). To a solution of alcohol **41**[28] (1.50 g, 7.48 mmol) in dry CH_2Cl_2 (100 mL) was added barium manganate (9.00 g, 37.4 mmol), and the mixture was stirred at room temperature for 3.5 h. Filtration of the mixture through a pad of Celite and evaporation of the filtrate in vacuo gave aldehyde **42** (1.40 g, 95%) as an oil. The unstable aldehyde was used in the next step without purification: IR (film) 2960, 2940, 2900, 2860, 2260, 2170, 1680, 1460, 1380, 1360, 1250, 1130, 1090, 1070, 1000, 950, 830, 780, 720, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.1 (s, 6 H), 0.8 (s, 9 H), 4.4 (s, 2 H), 9.1 (s, 1 H).

Tetradecyltriphenylphosphonium Bromide (43). A mixture of triphenylphosphine (8.51 g, 0.032 mmol) and 1-bromotetradecane (10.00 g, 0.036 mL) was heated at 140 °C for 7 h. The reaction mixture was cooled, and tetradecyltriphenylphosphonium bromide (**43**) was crystallized from acetone/ether (17.00 g, 92%): mp 96–98 °C; IR ($CHCl_3$) 3060, 2925, 2850, 1590, 1480, 1460, 1440, 1240–1200, 1110, 1000, 640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.19 (s, 11 H), 1.23 (s, 11 H), 1.62 (m, 2 H), 3.77 (m, 2 H), 7.29–7.91 (m, 15 H). Anal. Calcd for $C_{32}H_{44}BrP$: C, 71.23; H, 8.21. Found: C, 71.54; H, 8.11.

Octadeca-4(*E*)-en-2-yn-1-ol (44). To a solution of tetradecyltriphenylphosphonium bromide (**43**) (3.90 g, 7.21 mmol) in anhydrous THF (25 mL) at −78 °C was added 1.55 M *n*-butyllithium in hexane (5.1 mL, 7.95 mmol). The mixture was stirred for 1.5 h at −30 °C. The orange-red reaction mixture was cooled to −78 °C, and aldehyde **42** (1.1 g, 5.54 mmol) in anhydrous THF (25 mL) was added. The mixture was stirred for 2 h at −78 °C, and 1.55 M *n*-butyllithium in hexane (5.1 mL, 7.95 mmol) was added. The resulting dark red solution was stirred at −30 °C for 1 h and was diluted with ether (10 mL) and methanol (3 mL). The resulting solution was stirred for 3 h at room temperature; 3.5 N HCl was added until pH 4 was reached, and the mixture was stirred for 22 h. The reaction mixture was diluted with water and extracted with ether (3 × 40 mL). The organic phase was dried and concentrated in vacuo. Purification of the crude product by flash chromatography (20% ethyl acetate/hexane) yielded alcohol **44** (0.98 g, 75%) as a white solid. An analytical sample recrystallized from hexane had a melting point of 64–66 °C: IR ($CHCl_3$) 3620, 2940, 2860, 2220, 1460, 1380, 1160, 1010, 960 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.26 (s, 18 H), 1.37 (m, 2 H), 1.54 (q, J = 6.0 Hz, 2 H), 2.11 (m, 2 H), 4.38 (dd, J = 1.6, 5.9 Hz, 2 H), 5.49 (dd, J = 1.7 Hz, 15.0 Hz, 1 H), 6.17 (J = 7.0, 15.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.65, 28.63, 29.06, 29.32, 29.45, 29.54, 29.62, 31.90, 33.02, 51.60, 84.62, 85.57, 108.74, 145.80; CI MS ((M + 1)/z) 265, 264, 263, 247, 246. Anal. Calcd for $C_{18}H_{32}O$: C, 81.55; H, 12.19. Found: C, 81.75; H, 12.03.

Octadeca-2(*Z*),4(*E*)-dien-1-ol (45). A mixture of propargyl alcohol **44** (0.850 g, 3.21 mmol), dry toluene (25 mL), and Lindlar catalyst (0.100 g) was stirred at room temperature under an atmosphere of hydrogen until TLC indicated the disappearance of the starting material (~3 h). The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (20% ethyl acetate/hexane) to yield alcohol **45** (0.710 g, 83%) as a colorless oil: IR (film) 3350 (br), 3025, 2940, 2850, 1460, 1260, 1040, 740, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.26 (s, 22 H), 2.09 (m, 2 H), 4.31 (d, J = 6.8 Hz, 2 H), 5.58 (m, 1 H), 6.24 (m, 1 H), 6.31 (m, 1 H) 6.38 (m, 1 H); ^{13},c NMR ($CDCl_3$) δ 14.09, 22.67, 29.19, 29.23, 29.34, 29.49, 29.59, 29.66, 31.91, 32.85, 58.83, 124.73, 127.01, 131.34, 137.63.

Octadeca-2(*Z*),4(*E*)-dienyl Carbamate (46). This compound was prepared from alcohol **45** in 85% yield by the procedure described above for **31**. An analytical sample recrystallized from hexane had a melting point of 78–81 °C: IR (KBr) 3440, 3340, 3260, 3210, 3010, 2920, 2850, 1690, 1610, 1460, 1420, 1410, 1070, 960, 680, 620 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.85 (t, J = 6.0 Hz, 3 H), 1.27 (s, 20 H), 1.37 (m, 2 H), 2.12 (q, J = 6.9 Hz, 2 H), 4.59 (NH_2), 4.73 (dd, J = 1.2, 7.1 Hz, 2 H), 5.42 (m, 1 H), 5.80 (m, 1 H), 6.15 (t, J = 11.0 Hz, 1 H), 6.32 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.67, 29.12, 29.22, 29.34, 29.47, 29.58, 29.64, 31.90, 32.84, 61.11, 121.90, 124.55, 133.13, 138.46, 156.82; mass spectrum m/z (relative intensity) 310 [M^+ + 1] (0.4), 309 [M^+] (2.1), 260 (2.0), 250 (18.6), 222 (6.2), 211 (2.3), 194 (3.5), 180 (3.2), 166 (2.9), 152 (3.8), 138 (6.7), 137 (6.8), 124 (10.8), 123 (11.5), 109 (20.0), 96 (59.4). Anal. Calcd for $C_{19}H_{35}NO$: C, 73.60; H, 11.06. Found: C, 73.98; H, 11.34.

Cycloaddition of Carbamate 46. To a solution of carbamate **46** (0.257 g, 0.83 mmol) and pyridine (0.27 mL, 3.32 mmol) in anhydrous toluene (70 mL) at −5 °C was added thionyl chloride (0.10 mL, 1.25 mmol) in toluene (5 mL) over a period of 2.5 h. The mixture was stirred at −5 °C for 2 h and at room temperature for 90 h. Pyridinium hydrochloride was removed by filtration, and the filtrate was concentrated in vacuo. Flash chromatography of the crude product (1/1 ethyl acetate/hexane) yielded dihydrothiazine oxide **47** (0.250 g, 86%) as a white crystalline solid. An analytical sample recrystallized from CH_2Cl_2/hexane had a melting point of 84–86 °C: IR (KBr) 3075, 2960, 2940, 2850, 1780, 1460, 1380, 1330, 1230, 1210, 1150, 1090, 1050, 990, 820, 800, 740, 720 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.18–1.39 (s, 18 H), 1.54–1.64 (m, 4 H), 1.73 (m, 2 H), 3.89 (m, 1 H), 4.07 (m, 1 H), 4.75 (m, 1 H), 5.69 (td, J = 1.75, 11.1 Hz, 1 H), 5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.66, 26.25, 29.26, 29.33, 29.45, 29.57, 30.02, 30.89, 31.90, 46.95, 57.77, 69.18, 122.56, 124.44, 153.76; CI MS ((M + 1)/z) 358, 357, 356. Anal. Calcd for $C_{19}H_{33}NO_3S$: C, 64.47; H, 9.37. Found: C, 64.18; H, 9.35.

(∓)-[*R,*R**-(*E*)]-4-(1-Hydroxy-2-hexadecenyl)-2-oxazolidinone (34).** The allylic sulfoxide was prepared from thiazine oxide **47** by the usual procedure: IR (film) 3200, 3050, 2940, 2850, 1760, 1460, 1440, 1390, 1230, 1090, 1030, 740, 690 cm^{-1}.

Oxazolone **48** was prepared from the crude sulfoxide (86% overall yield from **47**) by the procedure described above for oxazolone **34**. The crude product was purified by preparative TLC (1/1 ethyl acetate/hexane). An analytical sample was recrystallized from CH_2Cl_2/hexane:

mp 86–88 °C; IR ($CHCl_3$) 3610, 3450, 2925, 2850, 1760, 1460, 1390, 1220, 1030, 970 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.26 (s, 22 H), 2.05 (m, 2 H), 3.85 (m, 1 H), 4.10 (t, J = 6.0 Hz, 1 H), 4.37 (m, 1 H), 5.40 (dd, J = 7.1, 15.4 Hz, 1 H), 5.62 (NH), 5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.67, 28.99, 29.20, 29.34, 29.45, 29.60, 29.66, 31.90, 32.36, 56.25, 66.37, 73.22, 126.51, 136.57, 160.23; CIMS ((M + 1)/z) 328, 327, 326, 325, 324. Anal. Calcd for $C_{19}H_{35}NO_3$: C, 70.54; H, 10.29. Found: C, 70.12; H, 10.79.

***dl-erythro*-Triacetylsphingosine (28).** To a solution of oxazolone **48** (0.007 g, 0.021 mmol) in glyme (3 mL) and water (1 mL) was added barium hydroxide octahydrate (0.017 g, 0.053 mmol). After refluxing for 30 h, the mixture was cooled to room temperature and gaseous CO_2 was bubbled through the solution to precipitate the barium salts. Filtration of the mixture and concentration of the filtrate in vacuo afforded crude *dl-erythro*-spingosine (**27**). This material was dissolved in acetic anhydride (1 mL) and pyridine (1 mL), and the solution was stirred at room temperature for 8 h. Concentration of the reaction mixture in vacuo and purification of the residue by preparative TLC ($CHCl_3$/MeOH/9/1) gave *dl-erythro*-triacetylsphingosine (**28**) which was identical (TLC, IR, ^1H NMR) with material prepared from naturally derived *erythro*-D-sphingosine.[31] A sample recrystallized from CH_2Cl_2/hexane had mp 90–92 °C (lit.[26] mp 91–92 °C).

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Supplementary Material Available: Complete X-ray data for compound **5a** (9 pages). Ordering information is given on any current masthead page.

Stereocontrolled Synthesis of Unsaturated Vicinal Diamines from Diels–Alder Adducts of Sulfur Dioxide Bis(imides)

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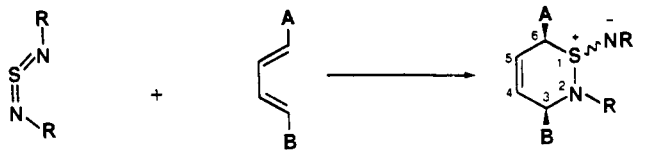
Abstract: As an extension of methodology previously developed for the synthesis of vicinal amino alcohols, stereocontrolled synthesis of unsaturated vicinal diamines from Diels–Alder adducts of sulfur dioxide bis(imides) (**1a**, **1b**) and various 1,3-dienes was investigated. The 3,6-dihydrothiazin-1-imine Diels–Alder adducts having a trans relationship of the sulfur and C-6 substituents stereospecifically afforded unsaturated vicinal diamines in high yields via ring opening with phenylmagnesium bromide to allylic sulfilimines which underwent [2,3]-sigmatropic rearrangement to sulfenamides. Desulfurization of the sulfenamide with trimethyl phosphite afforded (*E*)-threo diamines **11** and **12** from the Diels–Alder adducts of (*E*,*E*)-hexadiene **4** and **6**, respectively, and (*E*)-erythro diamines **18** and **19** from the adducts of (*E*,*Z*)-hexadiene **7** and **9**, respectively. In contrast, the epimeric thiazinimines **3** and **10**, having a cis relationship of the sulfur and C-6 substituents, were relatively unreactive toward carbon nucleophiles, affording the expected diamine derivatives in only fair to poor yields. However, the "unreactive" *cis*-thiazin-1-imines **3**, **5**, **8**, and **10** were found to undergo a facile thermal [2,3]-sigmatropic rearrangement to give thiadiazolidines **21**, **22**, **23**, and **24**, respectively, which were converted to the desired unsaturated diamine derivatives **11**, **12**, **18**, and **19** by sodium borohydride reduction in excellent yields. The reactivities of the Diels–Alder adducts are explained on the basis of the stereostructures of the Diels–Alder adducts, which were unambiguously determined by single-crystal X-ray analyses and ^1H NMR lanthanide induced shift studies. The Diels–Alder reaction of 1,3-cyclohexadiene and bis(imide) **1b** was investigated, leading to cis-vicinal carbamate **33** in a good yield along with the interesting amino diene derivative **32**.

Recent publications from these laboratories have described a diastereoselective approach to synthesis of unsaturated amino alcohol derivatives based upon Diels–Alder adducts of *N*-sulfinyl dienophiles.[1] We now report an extension of this general methodology to preparation of unsaturated vicinal diamines which allows total control of both relative and double bond configuration. The strategy outlined in this paper centers upon the propensity of readily available bis(imides) of sulfur dioxide **1a**,**b** to react with 1,3-dienes in Diels–Alder fashion[2] to produce 3,6-dihydrothiazin-1-imines (**2**) (Scheme I).[3] Although this type of cycloaddition has been known for a number of years, subsequent chemistry of adducts such as **2** has received scant attention.

Scheme I



1a R = Ts
1b R = CO_2Me

2

Since one of the primary objectives of this research program has been to develop diastereoselective routes to *acyclic* molecules, we have concentrated on developing the methodology with adducts of acyclic 1,3-dienes. Thus, bis(sulfonimide) **1a**, prepared in situ from disproportionation of *N*-sulfinyl-*p*-toluenesulfonamide as described by Kresze,[5] added to (*E*,*E*)-2,4-hexadiene at room temperature in benzene gives a chromatographically separable mixture of adducts **3** and **4** (91%) in a 1.1:1 ratio. Interestingly, Mock and Nugent[6] observed a very different ratio of **3** and **4** in

(1) (a) Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499. (b) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For reviews of this type of cycloaddition, see: Kresze, G.; Wucherpfennig, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 49. Weinreb, S. M.; Staib, R. R. *Tetrahedron*, **1982**, *38*, 3087.

(3) It should be noted that a conceptually similar approach to vicinal diamines has been briefly described (Sharpless, K. B.; Singer, S. P. *J. Org. Chem.* **1976**, *41*, 2504) based upon Diels–Alder chemistry of a bis(sulfonimide) of selenium. However, these authors did not investigate the stereochemistry of the process, and yields were not impressive in the examples reported.

(4) For other routes to vicinal diamines, see: Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703. Kohn, H.; Jung, S.-H. *J. Am. Chem. Soc.* **1983**, *105*, 4106 and references cited in these articles. See also: Fraenkel, G.; Pramanik, P. *J. Org. Chem.* **1984**, *49*, 1316. Jung, S.-H.; Kohn, H. *Tetrahedron Lett.* **1984**, *25*, 399.

(5) Wucherpfennig, W.; Kresze, G. *Tetrahedron Lett.* **1966**, 1671.

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