141 mg of the adduct **18a**. The use of 1 equiv of Br_2 also afforded the same adduct. Anal. Calcd for $C_{20}H_{32}Br_2O_2$: C, 51.74; H, 6.95. Found: C, 53.64; H, 7.76. Keeping 27.0 mg (0.058 mmol) of the adduct under vacuum for 2 days affords 16.7 mg (0.055 mmol) of **15a**. A 0.1 M CCl_4 solution (0.5 mL) of tetramethylethylene and 23.9 mg of the adduct was mixed in an NMR tube. Analysis of the mixture by ^1H NMR showed the formation of a 1:1 mixture of **15a** and 2,3-dibromo-2,3-dimethylbutane. ^1H and ^{13}C NMR spectra of the adduct in $CDCl_3$ gave essentially the same spectra as those of **15a**. The mass spectrum also showed only peaks derived from **15a**. IR (KBr) 2912, 1472, 1389, 1359, 1268, 1194, 1104, 1012, 878, 706, 643, 597, 385 cm^{-1}.

Reaction of 15b with Br_2. A solution of 121 mg (0.76 mmol) of Br_2 in 2.4 mL of CCl_4 was added to a stirred and ice-cooled solution of 92 mg (0.3 mmol) of **15b** in 0.6 mL of CCl_4. The mixture was kept at room temperature in the dark without stirring, and the resulting yellow fine needles were collected by filtration and washed with a small amount of CCl_4 to give 82 mg of the adduct: mp 105-111 °C; IR (KBr) 2942, 2868, 1466, 1392, 1362, 1248, 1193, 1093, 1044, 953, 882, 721, 652, 585, 497, 419 cm^{-1}. Anal. Calcd for $C_{20}H_{32}Br_2O_2$: C, 51.74; H, 6.95. Found: C, 48.48; H, 7.00. Mixing a 0.1 M solution (0.5 mL) of tetramethylethylene in CCl_4 and 23.9 mg of the adduct in an NMR tube afforded a 1:1 mixture of **15b** and 2,3-dibromo-2,3-dimethylbutane. Keeping the adduct under vacuum at room temperature for several days afforded **15b** quantitatively.

Asymmetric Induction in the Ene Reactions of *N*-Sulfinylcarbamates

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Abstract: Ene reactions of *N*-sulfinylcarbamates derived from the chiral alcohols 8-phenylmenthol and *trans*-2-phenylcyclohexanol proceed with high levels (95+% de) of asymmetric induction. Where regioisomeric products are possible (with unsymmetrical alkenes), generally only that adduct with the more stable double bond is formed. In general, the reaction displays the characteristics of a concerted process with simultaneous carbon-sulfur bond formation and carbon-hydrogen bond cleavage at the transition state. The sulfinamide adducts can be transformed by 2,3 sigmatropic rearrangement of a derived sulfoxide into optically active allylic alcohols. Thus, the overall transformation effects allylic hydroxylation with high levels of regio- and absolute stereochemical control.

Since the late 1960s, there has been a serious effort by many research groups to develop synthetically viable transformations that proceed with absolute stereochemical control. Many of these efforts have been successful, resulting in practical methods for asymmetric induction, especially in carbon-carbon bond formation.[1] Special attention to this specific class of synthetic reactions is certainly justified by the central role that this bond plays in organic chemistry. In sharp contrast, there are relatively few techniques that result in absolute stereochemical control concomitant with the formation at a carbon-heteroatom linkage, with the contributions from Brown's laboratories in controlling hydroboration processes[2] and Sharpless epoxidation of allylic alcohols[3] representing notable exceptions. There are other techniques for absolute stereochemical control that result in heteroatom-substituted carbon stereocenters exemplified by Midland's reduction of alkinyl ketones,[4] but these processes do not result in an increase in molecular complexity from either the standpoint of the carbon framework or functional groups that are present.

A number of years ago we began a broad range of study of reactions that would transform simple alkenes into more complex arrays suitable for further synthetic manipulation.

Our first activities in this area involved ene reactions of alkenes with glyoxylate esters and were eminently successful, resulting in homoallylic alcohols through carbon-carbon bond formation with levels of stereochemical control in excess of 1000:1.[5] More recently, we have turned our attention to reactions that functionalize simple alkenes through the formation of new carbon-heteroatom bonds. We have already communicated initial findings relating to ene-like reactions of chiral *N*-sulfinylcarbamates with alkenes that result in allylic sulfinimides with high levels of stereochemical control at the carbon bearing the sulfur as well as the sulfur atom itself.[6] Further transformation of these adducts via 2,3 sigmatropic rearrangement of derived aryl sulfoxides afforded allylic alcohols. These ultimate products represent net allylic oxidation of the original alkene with retention of the position of the double bond and with high levels of regiocontrol at the two competing allylic sites as well as high levels of asymmetric induction. It is these studies that we describe here in some detail, providing significant new findings that relate to the mechanism for the ene reaction of *N*-sulfinylcarbamates in the presence of Lewis acids as well as to the synthetic scope of the overall process.

The thermal ene reactions of *N*-sulfinylsulfonamides have been study in great detail by Kresze.[7] Because we had previously observed a dramatic effect of Lewis acids on the level of absolute stereochemical control in the cycloaddition reactions of *N*-sulfinylcarbamates with dienes,[8] we restricted our study of the ene reactions of these species to similar conditions. Indeed, in the presence of an equivalent of $SnCl_4$, the reactions of alkenes with the *N*-sulfinylcarbamate **2** derived from our chiral auxiliary[9] *trans*-2-phenylcyclohexanol (**1**) provide adducts with excellent levels of stereochemical control (>95:5).

We have provided the stereo- and regiochemical outcomes from the reaction of the *N*-sulfinylcarbamate **2** with a number of simple, representative achiral alkenes in Table I and chiral alkenes in Table

(1) For reviews, see: Morrison, J. D., Ed. *Asymmetric Synthesis*; Wiley: New York, 1983-5; Vols. 1-5.
(2) For reviews, see: Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.
(3) Pfenninger, A. *Synthesis* **1986**, 89.
(4) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553.
(5) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.
(6) Whitesell, J. K.; Carpenter, J. *J. Am. Chem. Soc.* **1987**, *109*, 2839.
(7) For leading references, see: Muensterer, H.; Kresze, G.; Lamm, V.; Gieren, A. *J. Org. Chem.* **1983**, *48*, 2833. Schwobel, A.; Kresze, G. *Synthesis* **1984**, 945.
(8) Whitesell, J. K.; Carpenter, J. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1449.
(9) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1986**, *51*, 551.

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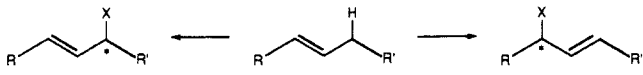


Figure 1.

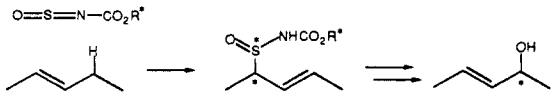


Figure 2.

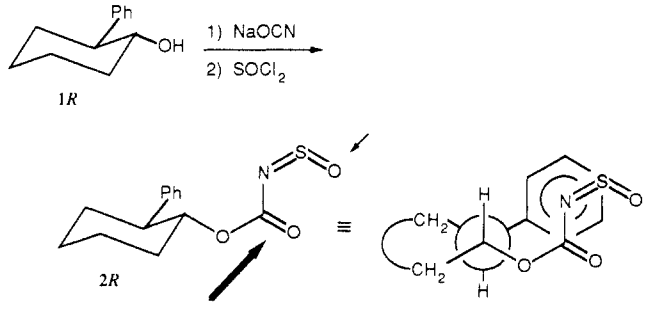


Figure 3.

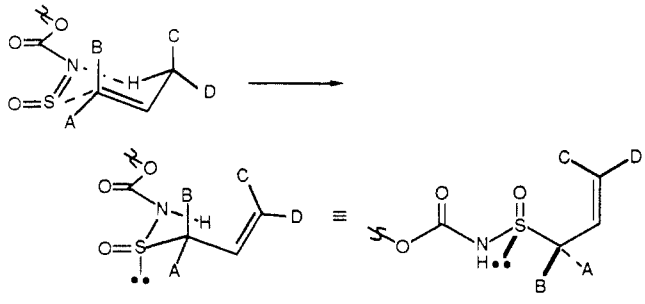


Figure 4.

II. The stereochemistry of the new centers of chirality in the adduct from *trans*-butene was established unambiguously by single-crystal, X-ray analysis using the auxiliary still present to assign absolute relationships through internal comparison. Reaction with *cis*-butene provided a diastereomerically different adduct and no crossover of diastereomers in the two reactions could be detected. Since the sign of rotation for both adducts was the same, we have assigned the stereochemistry to be the same at sulfur but differing at the newly formed carbon chiral center. Further conformation of the sense of stereochemical induction at sulfur and at the carbon center in adducts from *cis*-alkenes was obtained by single-crystal X-ray analysis of the adduct formed from racemic bicyclo[3.3.0]octene (Table II). Additional aspects of this reaction will be addressed below.

Provided in Figure 3 is a representation of the geometric arrangement of the *N*-sulfinyl unit relative to the chiral auxiliary *trans*-2-phenylcyclohexanol, which can be used to rationalize the absolute stereochemistry obtained at sulfur. It should be noted that evidence for this arrangement derives primarily from the observed absolute stereochemical bias in this transformation rather than from our own or previously established data relating to the three-dimensional arrangement and bonding in these species. We have, however, chosen to represent a geometric arrangement in which the oxygen on sulfur and that of the carbonyl group are so disposed as to be capable of forming a bidentate chelate with the Lewis acid.

These results, and indeed all of our observations, are consistent with a concerted reaction process, as shown in Figure 4 from which it would be predicted that isomeric alkenes would produce diastereomers differing in configuration at carbon but with the same configuration at sulfur. With unsymmetrical alkenes, such as *cis*-2-octene and *trans*-2-octene, two regioisomerically different sets of products are possible. However, we found no evidence for the products that would have resulted from hydrogen abstraction

Table I.

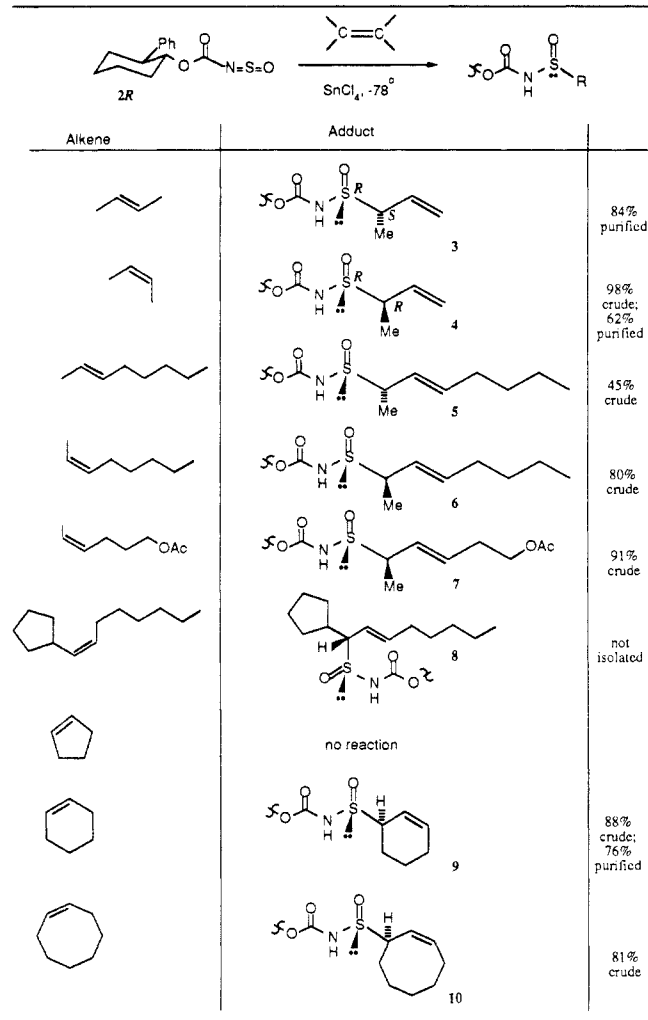
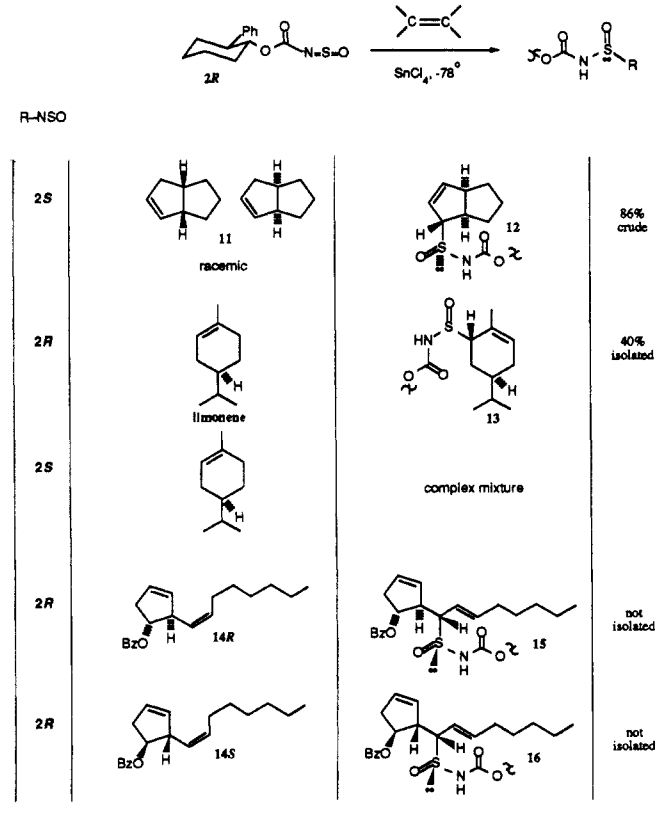


Table II



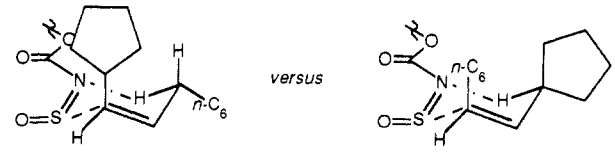


Figure 5.

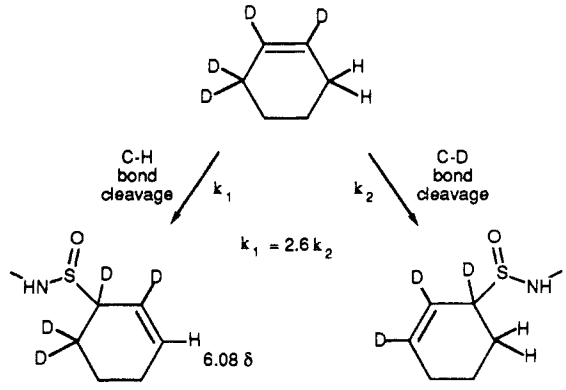


Figure 6.

from the terminal methyl carbon with simultaneous carbon–sulfur bond formation at C3. In addition, the observed regiochemistry provides a disubstituted alkene that could be formed, a priori, as either geometric isomer. Indeed, from *trans*-2-octene, two diastereomers differing in double-bond geometry were obtained, as a 3.3:1 ratio of trans to cis isomers. In addition, a third product was detected in the crude reaction mixture, presumably a diastereomer differing in configuration at carbon.[10] On the other hand, the reaction of *cis*-2-octene afforded only product of trans geometry where, the major diastereomer (13:1)[10] was different from that obtained from reaction of the trans alkene. In these reactions, the competing transition states leading to cis and trans products differ in the positioning of a hydrogen atom and an alkyl group at C and D in Figure 4. Substituents at C (leading to cis product) would be disfavored by steric interactions and these effects would be greater when the B position is occupied by an alkyl group (cis starting material geometry). Reaction of the cyclopentyl octene also occurred with a single sense of regiochemistry, that involving abstraction of a hydrogen from the methylene group rather than the methyne. The product was a single diastereomer, homogeneous at the double bond, the carbon, and sulfur stereocenters. The regiochemistry of this reaction is also consistent with the transition-state model proposed above, as reaction with the opposite regiochemistry would result in substituents at B, C, and D and substantial steric interactions, as depicted in Figure 5.

The most compelling evidence relating to the concertedness of the transition state involved in this reaction was obtained through competition between C–H and C–D bond cleavage in both intra- and intermolecular senses. In the reaction of 1,2,3,3-tetradeuteriocyclohexene illustrated in Figure 6, the rate preference for abstraction of a vinylic hydrogen as compared to a vinylic deuterium corresponded to a kinetic deuterium isotope effect of 2.6. Clearly then, cleavage of the carbon–hydrogen (deuterium) bond is involved in the rate-determining step for the reaction. In general, it would be possible to have a sizable D/H isotope effect in a two-step reaction if rate-determining formation of a complex was followed by a faster, but product-determining, second step. This is not possible in the present case, as the two faces of the π-bond are enantiotopic and complexation would establish stereochemistry and thereby fix whether hydrogen or deuterium must be removed to arrive at the single, observed absolute stereochemistry. Further, such a scenario can be rigorously excluded from our results on competitive *bi*molecular competitions. In

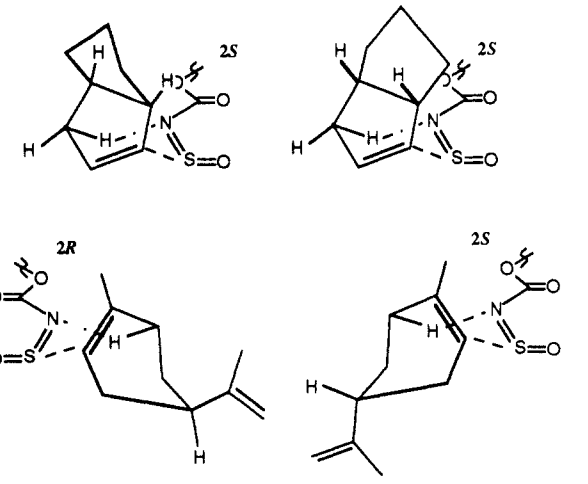


Figure 7.

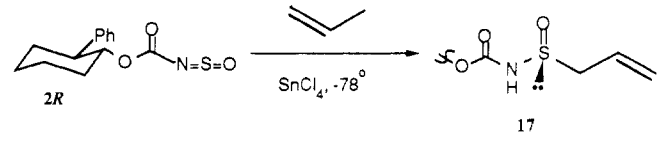


Figure 8.

reactions with a 1:1 mixture of tetradeuteriocyclohexene and undeuterated cyclohexene, the selectivity is the same (within experimental error) in the competition between deuterated and undeuterated starting materials as that observed in the intermolecular competition. Since complex formation would only secondarily involve the C–H(D) bond(s), the isotope effect would be expected to be substantially smaller than that observed. It is still possible that a complex is involved in the reaction but, if so, it must be formed rapidly and reversibly and its formation cannot be either a rate-limiting or product-determining step.

We have also determined the relative reactivity of cis versus trans alkenes, mono- versus disubstituted, and di- versus trisubstituted alkenes. In bimolecular competition reactions between *trans*- and *cis*-2-butene, and between *trans*-2-butene and 1-butene, the trans isomer was found to react twice as fast.

The entries in Table II represent examples where chirality was present in the starting alkene. The reaction of the racemic bicyclic alkene **11** represents a case of kinetic resolution, with selectivity arising from matched versus mismatched pairing of the chirality inherent in the reagent *N*-sulfinylcarbamate and that of the substrate alkene. Similarly, we have found (+)-limonine reacts with much greater facility with the *N*-sulfinylcarbamate derived from (−)-*trans*-2-phenylcyclohexanol than with that derived from the enantiomer. Depictions for both pairs of competing transition states are provided in Figure 7, with the favored arrangement on the left. Note that these results, while fully self-consistent, were derived from different types of experiments. For the simple bicyclic alkene, the racemic starting material was used and the transition-state preferences can be derived directly from the kinetic resolution that occurred. On the other hand, separate reactions between each enantiomer of the reagent and a single enantiomer of limonene were conducted. Note that in both cases it was possible a priori that reagent-based stereochemical control would override substrate bias resulting in endo addition to the bicyclic alkene and addition trans to the isopropyl group in limonene. Unfortunately, it appears that the transition-state energy for the mismatched pairing was raised above those for competing side reactions as these dominated the reaction.

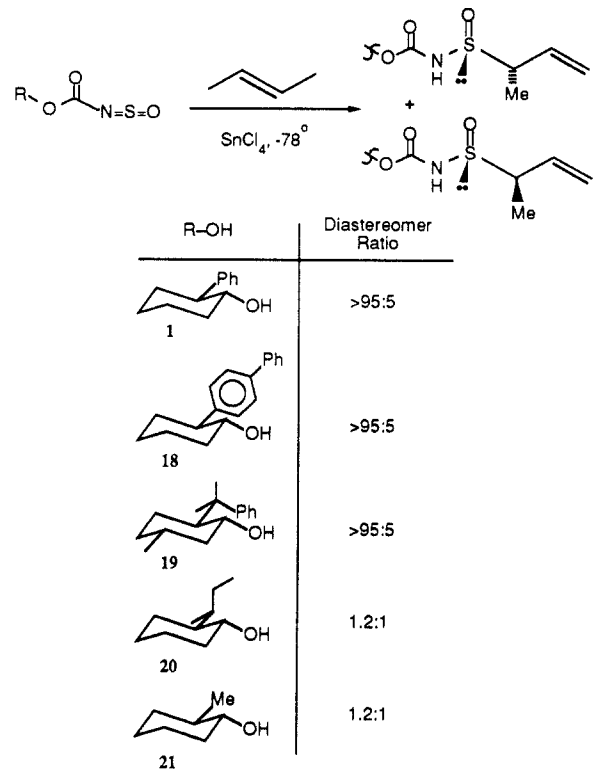
Both enantiomers of the prostaglandin precursor[11] dienes (*R*)-**14** and (*S*)-**14** were prepared by enzymatic resolution.[12] In this case, the site of reactivity (the side-chain alkene) is sufficiently remote

(10) The analysis of diastereomeric purity of the adducts is complicated by the fact that most of these are not configurationally stable in the solution or liquid (but not crystalline) state.

(11) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

(12) We have not assigned absolute stereochemistry to the enantiomers of **14**.

Table III



from the existing stereochemical features that both enantiomers react with the same facility with a single enantiomer of the reagent and diastereomers differing at the carbon stereocenter were produced.

The reaction of the chiral *N*-sulfinylcarbamate with terminal alkenes was also examined. With propene, a single stereoisomer (**17**, Figure 8) was obtained, as would be expected based upon the arguments advanced above. Also, as would be predicted, 1-hexene afforded a mixture of geometric isomers (5:1). Lacking chirality at carbon, such adducts will not undergo 2,3-rearrangements with high levels of stereocontrol based solely on the sulfur center. On the other hand, there are several additional applications of chiral sulfoxide species,[13] and this sequence provides access to them with high levels of stereochemical control at sulfur.

A number of other alcohols were prepared and tested as chiral auxiliaries in the ene reaction of the corresponding *N*-sulfinylcarbamate and these results are summarized in Table III. The best of these was the auxiliary that we introduced several years ago, *trans*-2-phenylcyclohexanol, from all pertinent aspects including ease of preparation (and resolution[14]), availability of both enantiomers, and chemical yield as well as stereochemical direction in the ene reactions of the *N*-sulfinylcarbamate. Some auxiliaries, in particular Corey's 8-phenylmenthol,[15,16] are sufficiently bulky that removal (by hydrolysis of the carbamate) becomes difficult.

Conversion of the Adducts to Allylic Alcohols. A 2,3 sigmatropic rearrangement of the sulfinyl moiety completes the sequence of allylic oxidation, providing an allylic alcohol where the double bond is in the same regiochemical position as in the starting alkene. However, little if any allylic alcohol could be obtained directly from the adducts, despite extensive experimentation under a variety of conditions in the presence of a range of thiophiles. It appears that temperatures necessary to effect rearrangement are near or exceed those required for a noncatalyzed, retro ene reaction of

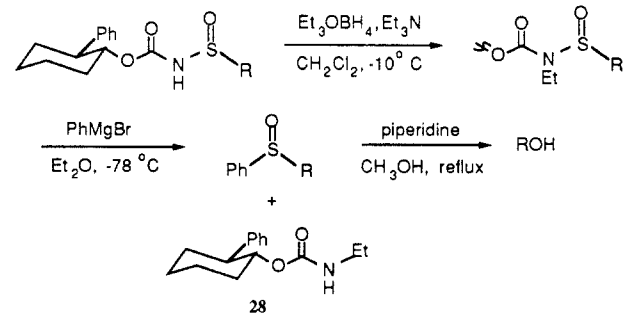
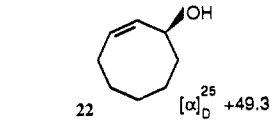
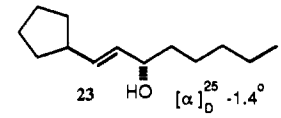
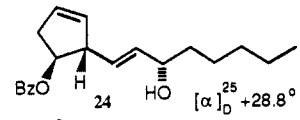
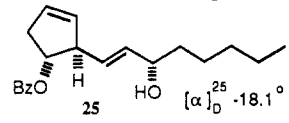
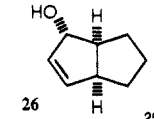
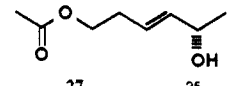


Figure 9.

Table IV

ROH	chemical yield	enantiomeric purity (e.e.)
 22 $[\alpha]_D^{25}$ +49.3	38	100 (b)
 23 $[\alpha]_D^{25}$ -1.4°	56%	91% (a)
 24 $[\alpha]_D^{25}$ +28.8°	62%	91% (a,c)
 25 $[\alpha]_D^{25}$ -18.1°	59%	92% (a,c)
 26 $[\alpha]_D^{25}$ -171°	62	96 (a)
 27 $[\alpha]_D^{25}$ - 3.6	64	84 (b)

the adducts. The *N*-sulfinylcarbamate regenerated by the process would be expected to suffer rapid reaction with the thiophile. Alternatively, we have been able to develop the practical sequence illustrated in Figure 9 involving N-alkylation followed by reaction with phenylmagnesium bromide. The aryl, allylic sulfoxides thus produced undergo smooth 2,3-rearrangement in the presence of piperidine as thiophile to afford the desired allylic alcohols in good overall yield. Representative examples are provided in Table IV.

The level of stereochemical purity of the allylic alcohols is a function of control at three stages: (1) the initial ene reaction of the *N*-sulfinylcarbamate, (2) preservation of stereochemistry before and during rearrangement, and (3) the 2,3 sigmatropic rearrangement. The stereochemical purity of the ene adducts indicate a high level of control at stage 1, and the high levels of transmission of stereochemistry in 2,3-rearrangements of allylic sulfoxides has been amply demonstrated (stage 3).[17] However, the ene adducts are somewhat unstable in regard to both chemical and stereochemical integrity, possibly as the result of some combination of thermal retro ene reaction and 2,3-rearrangement (stage 2). It is thus important that the adducts be taken im-

(13) Nudelmann, A. *The Chemistry of Optically Active Sulfur Compounds*; 1980; Part IV, p 9. Solladie, G. *Synthesis* **1981**, 185. Mikołajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333.
(14) Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318.
(15) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(16) Whitesell, J. K.; Liu, C.-L.; Buchanan, C. M.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551, and references cited therein.

(17) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

mediately through both the N-alkylation and rearrangement steps for the highest possible levels of enantiomeric purity and chemical yield to obtain at the final allylic alcohol. We have also found that it is possible to transform the *N*-sulfinyl adducts to allylic amines by treatment with hexamethyldisilazane.[18] We will report separately the details of this highly useful process that effects allylic amination.[19]

Conclusion

In summary, we have developed a practical method that effects the regioselective, heteroatom functionalization of an alkene by an ene reaction of chiral *N*-sulfinylcarbamates. The process occurs with concomitant control of absolute stereochemistry at two new chiral centers, one at carbon and the other at a sulfinamide sulfur. One of many possible applications of these intermediates was demonstrated by their conversion to allylic alcohols by a process that proceeds in good chemical yield and with excellent transmission of the stereochemical integrity at carbon imparted in the original ene reaction. One additional use for these intermediates, the conversion to allylic amines, has already been demonstrated.[19] Other possible applications of these ene adducts are being actively pursed.

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution resulting from benzopenone and sodium. Benzene and methanol were stored over molecular sieves. Methylene chloride, pyridine, triethylamine, diisopropylamine, piperidine, and trimethyl phosphite were distilled from calcium hydride and stored over molecular sieves. Skelly B was stirred first with concentrated sulfuric acid and then with solid sodium carbonate, filtered through alumina, and distilled before use. All other solvents and reagents were used as obtained from commercial sources unless stated otherwise.

Procedure. Reactions were routinely carried out under dry nitrogen or argon atmospheres with magnetic stirring. Preparative chromatography was carried out using recycling techniques with either a Waters Prep-500 system with two normal-phase silica gel cartidges or a Waters 600A HPLC with two 7.8 mm × 60 cm Porasil A silica gel semipreparative columns with a refractive index detector.

Spectra. ^{13}C NMR spectra were obtained with a Nicolet NT-360 spectrometer at 90 MHz, a General Electric QE-300 at 75 MHz, or a Varian FT-80A at 20 MHz. ^1H NMR spectra were obtained with a Nicolet NT-360 at 361 MHz or a General Electric QE-300 at 300 MHz. Both carbon and proton NMR spectra were obtained in chloroform-*d*, and chemical shift values are reported in ppm downfield shift from TMS as an internal standard. For the thiazine and sulfinamide adducts, only those carbons derived from the diene or alkene were assigned, as the rest were similar to that characteristic of the carbamate of the respective chiral auxiliary. Compounds described as "clean by ^{13}C NMR spectroscopy" exhibited no impurities greater than 5%. IR spectra were obtained on dilute (5%) CH_2Cl_2 solutions with a Beckman Acculab 8 or a Perkin-Elmer 298 infrared spectrophotometer, using polystyrene's absorption at 1601.4 cm^{-1} as a reference. Low-resolution mass spectra in EI mode were recorded with a Bell and Howell Model 21-491 spectrometer at 70 eV and those in CI mode with a Finnegan-MAT 4023 GC/MS with methane. High-resolution mass spectra were recorded with a CEC 21-110B instrument in EI mode. Only *m/z* values greater than or equal to 40% of the base peak and of *m/z* greater than or equal to 90 amu are reported. Optical rotations were measured with a Perkin-Elmer 141 polarimeter using the sodium D line. X-ray structures were determined by use of a Syntex $P2_1$ autodiffractometer with a grahite monochromator. Gas chromatography was performed by using a Varian Series 1440 gas chromatograph with a 5% Carbowax column.

***trans*-2-Phenylcyclohexyl Carbamate.** To 17.6 g (0.10 mol) of (*S*)-(+)-*trans*-2-phenylcyclohexanol [(*S*)-**1**] in 140 mL of dry benzene was added 13.0 g (0.20 mol) of NaOCN followed by the dropwise addition of 15.4 mL (0.20 mol) of trifluoroacetic acid, resulting in an emulsion. After 40 h, 70 mL of water was introduced followed by 70 mL of ethyl ether and stirring was continued for 15 min. The layers were seprarated and the aqueous layer was washed three times with ether. The combined organic layers were washed with a standard aqueous NaCl solution and then filtered through cotton and concentrated. Recrystallization from 4:1 EtOAc–pentane afforded 21.2 g (97%) of carbamate: mp 128–130 °C; $[\alpha]_D^{25}$ +35.8° (*c* = 5.0, EtOH) derived from (*S*)-**1**; ^{13}C NMR (20 MHz) δ 156.7 (C11), 143.4 (C7), 128.3 (C9), 127.5 (C8), 126.3 (C10), 76.5 (C1), 49.9 (C2), 34.4 (C6), 32.7 (C3), 25.9 (C4), 24.8 (C5); ^1H NMR (361 MHz) δ 7.14–7.30 (m, 5 H), 4.86 (ddd, *J* = 4.5, 10.8, 10.8 Hz, 1 H), 4.33 (s, 2 H), 2.64 (dt, *J* = 4.5, 11.2 Hz, 1 H), 2.22 (m, 1 H), 1.30–1.95 (m, 7 H); IR, 3535, 3420, 2940, 1727, 1583, 1380, 1062 cm^{-1}; MS, *m/e* 176, 159, 158 (base), 143, 130, 129, 117, 115, 104. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.51; H, 7.84; N, 6.30.

General Procedure for the Preparation of *N*-Sulfinylcarbamates: *trans*-2-Phenylcyclohexyl *N*-Sulfinylcarbamate [(*S*)-2]. To 1.0 g (4.6 mmol) of dried *trans*-2-phenylcyclohexyl carbamate in 50 mL of dry benzene at room temperature under nitrogen with rapid stirring were stimultaneously injected over a 15-min period 0.53 mL (6.8 mmol) of freshly distilled $SOCl_2$ and 0.74 mL (9.5 mmol) of pyridine. Stirring was continued for 15 min, after which the reaction was allowed to stand for 14 h. Moisture-free workup involved an initial Schlenk filtration under Ar to remove pyridinium salts followed by solvent and reagent removal under high vacuum, leaving a yellow oil. The *N*-sulfinylcarbamate was then used directly without further purification. Note: Due to the high moisture sensitivity of the *N*-sulfinylcarbamate, in vacuo solvent removal using a water aspirator leads to some hydrolysis, resulting in recovery of the carbamate after the ene reaction, and is not recommended: ^{13}C NMR (90 MHz) δ 151.0 (s), 142.0 (s), 128.5 (d), 127.4 (d), 126.7 (d), 81.4 (d), 49.4 (d), 33.8 (t), 32.0 (t), 25.5 (t), 24.6 (t).

General Procedure for the Ene Reactions of *N*-Sulfinylcarbamates. To the *N*-sulfinylcarbamate (*S*)-**2**, prepared by standard procedure from 1.0 g (4.6 mmol) of carbamate, in 8 mL of CH_2Cl_2, was added 5.4 mL (1.2 equiv) of a 1.0 M soln of $SnCl_4$ in CH_2Cl_2 at −78 °C under nitrogen. To this stirring mixture was added a soln of excess (>2 equiv) alkene precooled in 2 mL of CH_2Cl_2. After being stirred at −78 °C for 20 min, the reaction was quenched by pouring into an Et_2O–H_2O mixture. The aqueous layer was extracted three times with 50-mL portions of EtOAc and the combined organics were washed twice with saturated aqueous NaCl and dried over Na_2SO_4. Solvent removal in vacuo yielded the sulfinamide product. Note: A solution of $SnCl_4$ in CH_2Cl_2 proved to be less moisture sensitive and consequently gave consistently better results than neat $SnCl_4$.

***N*-[[*trans*-(2-Phenylcyclohexyl)oxy]carbonyl]-3-but-2-enesulfinamide [(*S*)-3] (from *trans*-2-Butene).** The *N*-sulfinylcarbamate (*S*)-**2**, prepared from 899 mg (4.11 mmol) of (*S*)-*trans*-2-phenylcyclohexyl carbamate, was reacted in the presence of 0.53 mL (4.5 mmol) of $SnCl_4$ with an excess (4 mL) of precondensed *trans*-2-butene at −78 °C in 4 mL of CH_2Cl_2. Standard isolation followed by recrystallization from EtOAc afforded 1.11 g (84% yield) of a white crystalline solid: mp 128–129 °C; $[\alpha]_D^{25}$ +97.7° (*c* = 3.6, EtOH); ^{13}C NMR (90 MHz) δ 153.1 (s), 142.8 (s), 130.1 (d, C3), 128.4 (d), 127.5 (d), 126.6 (d), 121.6 (t, C4), 79.4 (d), 61.7 (d, C2), 49.8 (d), 34.0 (t), 32.3 (t), 25.8 (t), 24.7 (t), 11.6 (q, C1); ^1H NMR (361 MHz) δ 7.14–7.32 (m, 5 H), 6.20 (s, 1 H), 5.84 (ddd, *J* = 6.5, 10.6, 16.8, Hz, 1 H), 5.44 (d, *J* = 10.6 Hz, 1 H), 5.28 (d, *J* = 16.8 Hz, 1 H), 4.93 (ddd, *J* = 4.2, 10.5, 10.5 Hz, 1 H), 3.48 (dq, *J* = 6.5, 6.5 Hz, 1 H), 2.72 (ddd, *J* = 2.7, 10.5, 10.5 H, 1 H), 2.24 (m, 1 H), 1.73–2.00 (m, 3 H), 1.26–1.63 (m, 4 H), 1.07 (d, *J* = 6.5 Hz, 3 H); IR, 3330, 2935, 2855, 1726, 1394, 1097 cm^{-1}; MS-CI *m/z* 322 (MH^+), 164, 159 (base); MS-EI, *m/z* 177, 176 (base), 159, 158, 143, 133, 132, 131, 130, 129, 128, 118, 117, 116, 115, 105, 104, 103, 98, 92, 91. Anal. Calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36; S, 9.97. Found: C, 63.21; H, 7.34; N, 4.42; S, 9.87.

***N*-[[*trans*-(2-Phenylcyclohexyl)oxy]carbonyl]-3-but-2-enesulfinamide [(*S*)-4] (from *cis*-2-Butene).** The *N*-sulfinylcarbamate (*S*)-**2**, prepared by standard procedure from 262 mg (1.19 mmol) of carbamate, was reacted in the presence of 0.15 mL (1.3 mmol) of $SnCl_4$ with an excess (4 mL) of precondensed *cis*-2-butene, affording 375 mg (98%) of a yellow oil: $[\alpha]^{25}_D$ +52.7° (*c* = 2.1, EtOH); ^{13}C NMR (90 MHz) δ 152.8, 142.8, 130.9 (C3), 128.4, 127.5, 126.6, 122.2 (C4), 79.5, 62.2 (C2), 49.8, 34.0, 32.3, 25.7, 24.7, 13.4 (C1); ^1H NMR (361 MHz) δ 7.13–7.33 (m, 5 H), 6.40 (s, 1 H), 5.72 (ddd, *J* = 9.6, 10.5, 16.6, Hz, 1 H), 5.43 (dd, *J* = 1.6, 10.5 Hz, 1 Hz, 1 H), 5.24 (d, *J* = 16.6 Hz, 1 H), 4.93 (ddd, *J* = 4.3, 10.1, 10.1 Hz, 1 H), 3.02 (br m, 1 H), 2.71 (ddd, *J* = 3.6, 10.1, 10.1 Hz, 1 H), 1.23–1.99 (br m, 8 H), 1.33 (*d*, *J* = Hz, 3 H); IR, 3330, 2925, 2855, 1727, 1399, 1097 cm^{-1}; MS, *m/e* 177, 176, 159, 158 (base), 143, 132, 131, 130, 129, 128, 117, 116, 115, 105, 104, 103, 98, 92, 91, 90.

***N*-[[*trans*-(2-Phenylcyclohexyl)oxy]carbonyl]-3-oct-2-enesulfinamide [(*S*)-5] (from *trans*-2-Octene).** The *N*-sulfinylcarbamate (*S*)-**2**, prepared by standard procedure from 297 mg (1.36 mmol) of carbamate, was reacted in the presence of 0.19 mL (1.6 mmol) of $SnCl_4$ with 0.46 mL (2.7 mmol of precooled *trans*-2-octene to afford 500 mg of a yellow oil consisting of a mixture of ene adducts to carbamate starting material with 78% and 19% yield, respectively (^{13}C NMR analysis). Three ene adducts were observed, two diastereomeric adducts in a 7:1 ratio and a *Z* isomer,

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the E/Z ratio was 3.3:1. Because these adducts readily isomerized at room temperature, further purification was not attempted.

For the E isomer: ^{13}C NMR (90 MHz) δ 153.4 (s), 142.8 (s), 138.5 (d, C4), 128.3 (d), 127.5 (d), 126.5 (d), 122.2 (d, C3), 79.1 (d), 61.5 (d, C2), 49.6 (d), 33.9 (t), 32.3, 32.2, (t, C6), 31.2 (t, C5), 25.7 (t), 24.7 (t), 22.2 (t, C7), 13.8 (q, C8), 12.7 (q, C1); ^1H NMR (361 MHz) δ 7.03–7.23 (m, 5 H), 6.57 (s, 1 H), 5.60 (m, 1 H) 5.23 (dd, J = 6.3, 15.5 Hz, 1 H), 4.82 (ddd, J = 4.7, 10.3, 10.3 Hz, 1 H), 3.30 (m, 1 H), 2.61 (m, 1 H), 1.12–2.24 (m, 14 H), 0.99 (d, J = 6.3 Hz, 3 H), 0.82 (t, J = 6.0 Hz, 3 H); IR, 3330, 2930, 2855, 1727, 1397, 1095 cm^{-1}; MS, m/e 158, 130, 129, 115, 104, 91 (base).

For the Z isomer: ^{13}C NMR (90 MHz) δ 153.4 (s), 142.8 (s), 137.9 (d, C4), 128.3 (d), 127.5 (d), 126.5 (d), 122.1 (d, C3), 79.1 (d), 58.1 (d, C2), 49.6 (d), 33.9 (t), 32.3 (t), 32.3 (t, C6), 27.8 (t, C5), 25.7 (t), 24.7 (t), 22.2 (t, C7), 13.8 (q, C8), 12.7 (q, C1).

***N*-[[*trans*-(2-Phenylcyclohexyl)oxy]carbonyl]-3-oct-2-enesulfinamide [(*S*)-6] (from *cis*-2-Octene).** The *N*-sulfinylcarbamate (*S*)-**2** prepared by standard procedure from 840 mg (3.84 mmol) of carbamate was reacted in the presence of 0.54 mL (4.6 mmol) of $SnCl_4$ with 1.3 mL (7.7 mmol) of precooled *cis*-2-octene to afford 1.45 g of a yellow oil consisting of a 13:1 mixture of diastereomeric adducts in a 91% yield plus 8% of recovered carbamate starting material (^{13}C NMR analysis). Because noncrystalline adducts readily isomerized at room temperature, further purification was not attempted: ^{13}C NMR (20 MHz) δ 153.2 (s), 142.8 (s), 139.0 (d, C4), 128.3 (d), 127.5 (d), 126.6 (d), 122.7 (d, C3), 79.1 (d), 61.5 (d, C2), 49.7 (d), 33.9 (t), 32.3 (t, C6), 32.3 (t), 31.2 (t, C5), 25.7 (t), 24.7 (t), 22.2 (t, C7), 13.9 (q, C8), 13.7 (q, C1); ^1H NMR (361 MHz) δ 7.14–7.30 (m, 5 H), 6.64 (s, 1 H), 5.60 (dt, J = 6.8, 14.8 Hz, 1 H), 5.35 (dd, J = 8.8, 14.8 Hz, 1 H), 4.91 (ddd, J = 4.7, 10.6, 10.6 Hz, 1 H), 2.97 (m, 1 H), 2.70 (ddd, J = 3.4, 10.6, 10.6 Hz, 1 H), 1.30–2.30 (m, 14 H), 1.28 (d, J = 6.8 Hz, 3 H), 0.89 (t, J = 7.2 Hz, 3 H); IR, 3325, 2925, 1727, 1392, 1097 cm^{-1}; MS, m/e 176, 158 (base), 130, 129, 117, 111, 104, 92, 91.

***N*-[[*trans*-2-(Phenylcyclohexyl)oxy]carbonyl]-*cis*-bicyclo[3.3.0]-3-oct-*endo*-2-enesulfinamide [(*S*)-12] (from Racemic *cis*-Bicyclo[3.3.0]-oct-2-ene).** The *N*-sulfinylcarbamate (*S*)-**2**, prepared by standard procedure from 260 mg (1.2 mmol) of carbamate, was reacted in the presence of 0.17 mL (1.4 mmol) of $SnCl_4$ with a greater than 2 equiv excess (510 mg, 4.8 mmol) of *cis*-bicyclo[3.3.0]oct-2-ene to afford 380 mg (86%) of semicrystalline material, which by ^{13}C analysis was a 7.3:1 mixture of diastereomers. The major diastereomer could be isolated by recrystallization from EtOAc:mp 151–152 °C; ^{13}C NMR (90 MHz) δ 153.6 (s), 143.2 (d, C4), 142.9 (s), 128.3 (d), 127.5 (d), 126.4 (d), 123.6 (d, C3), 79.1 (d), 79.0 (d, C2), 50.6 (d, C5), 49.8 (d), 41.2 (d, C1), 34.1 (t), 33.8 (t, C8), 32.3 (t), 31.2 (t, C6), 25.7 (t), 24.8 (t), 24.7 (t, C7); ^1H NMR (361 MHz) δ 7.13–7.28 (m, 5 H), 6.85 (br s, 1 H), 5.93 (d, J = 6.0 Hz, 1 H), 5.50 (m, 1 H), 4.94 (m, 1 H), 3.54 (s, 1 H), 3.12 (m, 1 H), 2.70 (m, 1 H), 2.12–2.27 (br m, 2 H), 1.23–1.97 (br m, 13 H); IR, 3360, 2950, 2870, 1725, 1390, 1095 cm^{-1}; MS, m/e 177, 176 (base), 159, 158, 143, 133, 132, 131, 130, 129, 128, 118, 117, 116, 115, 108, 107, 106, 105, 104, 103, 98, 92, 91, 90. Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75; S, 8.58. Found: C, 67.19; H, 7.48; N, 3.58; S, 8.71.

Deuterium Isotope Effect Studies. The *N*-sulfinylcarbamate (*S*)-**2**, prepared from 485 mg (2.2 mmol) of carbamate, was reacted by standard procedure with a precooled solution of 500 mg (5.8 mmol) of 1,2,3,3-tetradeuteriocyclohexene in 2 mL of CH_2Cl_2. The crude product was purified by preparative chromatography: ^1H NMR (300 MHz) δ 6.08 (0.79 H), 5.67 (0.077 H), 4.92 (1 H). Note: The integration at δ 5.67 indicates a 7.7% H contamination of the alkene. This was taken into account in the calculation of the isotope effect.

The *N*-sulfinylcarbamate (*S*)-**2**, prepared from 486 mg (2.2 mmol) of carbamate, was reacted by standard procedure with a precooled mixture of 275 mg (3.2 mmol) of 1,2,3,3-tetradeuteriocyclohexene and 262 mg (3.2 mg (3.2 mmol) of cyclohexene in 2 mL of CH_2Cl_2. the crude product was purified by preparative chroamtography: ^1H NMR (300 MHz) δ 6.08 (0.89 H), 5.67 (0.59 H), 4.92 (1 H).

(+)-(*S*)-2-Cycloocten-1-ol (22). The *N*-sulfinylcarbamate (*R*)-**2** prepared from 451 mg (2.06 mmol) of carbamate, 0.33 mL (4.1 mmol) of pyridine, and 0.24 mL (3.1 mmol) of thionyl chloride was reacted in the presence of 0.29 mL (2.5 mmol) of $SnCl_4$ with 1 equiv (0.27 mL, 2.1 mmol) of cyclooctene, affording sulfinamide adduct **10**. To this material in 7 mL of CH_2Cl_2 in a −10 °C bath was added 0.54 mL (3.1 mmol of Huenig's base followed by 783 mg (4.12 mmol) of triethyloxonium tetrafluoroborate. After the solution was stirred for 30 min, the solvent was removed and the mixture partitioned between 0.1 N aqueous HCl and EtOAc. The organic layer was washed with 0.1 N NaOH and then with saturated NaCl solution. Concentration afforded a light yellow oil. Without further purification, the *N*-ethylsulfinamide was reacted in 7 mL of ether at −30 °C with 1.0 mL of 3.1 N (3.2 mmol) phenylmagnesium bromide for 40 min. The reaction was allowed to warm to 0 °C and then quenched with saturated aqueous ammonium sulfate. Enough water was added to dissolve the precipitated salts. The aqueous layer was washed with CH_2Cl_2, and the combined organic layers were filtered through cotton. Semipreparative chromatography with 4:1 Skelly B–EtOAc afforded baseline separation of crystalline (−)-phenyl-2-octen-1-yl sulfoxide and *N*-ethylcarbamate *28* (344 mg, 68% recovery). To the (−)-sulfoxide in 7 mL of EtOH were added 331 mg (6.18 mmol) of NH_4Cl and 1.4 mL (14 mmol) of piperidine, and the resulting solution was heated at reflux for 40 h. The solvent was removed, and the residue was filtered through silica gel with 2:1 Skelly B–EtOAc. Semipreparative chromatography in 4:1 Skelly B–EtOAc yielded 98 mg (38% yield) of the alcohol **22**.

For the sulfinamide **10**: ^{13}C NMR (90 MHz) δ 153.3 (s), 142.8 (s), 135.8 (d, C3), 128.3 (d), 127.5 (d), 126.5 (d), 121.3 (d, C2), 79.2 (d), 61.3 (d, C1), 49.7 (d), 33.9 (t), 32.3 (t), 29.2 (t, C4), 28.9 (t, C5–7), 26.8 (t, C5–7), 26.3 (t, C5–7), 25.7 (t), 25.1 (t, C8), 24.7 (t); ^1H NMR (361 MHz) δ 7.16 (m, 5 H), 6.67 (s, 1 H), 6.00 (q, J = 8.3 Hz, 1 H), 5.56 (t, J = 8.3 Hz, 1 H), 4.56 (dt, J = 3.2, 10.3 Hz, 1 H), 3.38 (br t, 1 H), 2.60 (dt, J = 3.2, 9.9 Hz, 1 H), 2.2–1.15 (br m, 18 H); IR, 3340, 2935, 2865, 1732, 1400, 1105 cm^{-1}; MS, m/e 158 (base), 130, 91.

For sulfoxide: $[\alpha]^{25}_D$ −208° (c = 0.56, CH_2Cl_2); ^{13}C NMR (90 MHz) δ 142.7 (C1′), 134.1 (C3), 131.0 (C4′), 128.9 (C3′), 125.0 (C2′), 123.6 (C2), 63.6 (C1), 28.8 (C4), 28.4 (C5–7), 26.6 (C5–7), 26.3 (C5–7), 25.1 (C8); ^1H NMR (361 MHz) δ 7.64 (m, 2 H), 7.48 (m, 3 H), 5.83 (q, J = 8.8 Hz, 1 H), 5.48 (t, J = 8.8 Hz, 1 H), 3.67 (m, 1 H), 2.03 (m, 2 H), 1.7–1.2 (br m, 8 H).

For alcohol **22**: $[\alpha]^{25}_D$ =51.2° (c = 6.52, CH_2Cl_2); ^{13}C NMR (90 MHz) δ 135.3 (d, C2), 128.4 (d, C3), 69.4 (d, C1), 38.7 (t, C8), 29.2 (t, C4), 26.4 (t, C5), 26.1 (t, C6), 23.8 (t, C7); ^1H NMR (361 MHz) δ 5.55 (m, 2 H), 4.64 (m, 1 H), 2.13 (m, 2 H), 1.95–1.30 (m, 9 H); IR, 3605, 3445, 2920, 2855, 1445, 1042 cm^{-1}; MS, m/e 83 (base), 70, 67.

(−)-*trans*-1-Cyclopentyl-1-octen-3-ol (23). The *N*-sulfinylcarbamate (*R*)-**2**, prepared by standard procedure from 235 mg (1.07 mmol) of carbamate, 0.17 mL (2.1 mmol) of pyridine, and 0.13 mL (1.6 mmol) of thionyl chloride was reacted in the presence of 0.15 mL (1.3 mmol) of $SnCl_4$ with 1 equiv (0.19 mg, 1.1 mmol) of *cis*-1-cyclopentyl-1-octene to afford a yellow oil, the sulfinamide adduct. To this in 8 mL of CH_2Cl_2 at −10 °C were added 0.28 mL (1.6 mmol) of Huenig's base and then 0.610 g (3.21 mmol) of triethyloxonium tetrafluoroborate. After stirring for 30 min, standard workup afforded a light yellow oil. This *N*-ethylsulfinamide was reacted in 8 mL of ether at −30 °C with 1.1 mL of 3.1 N (3.2 mmol) phenylmagnesium bromide for 1 h with rapid stirring. The reaction was allowed to warm to 0 °C and was then quenched with NH_4Cl. To this were added 8 mL of methanol and then 0.74 mL (7.5 mmol) of piperidine. The solution was stirred at room temperature for 40 h, and then the solvent was removed. The mixture was filtered through silica gel column eluting with 2:1 Skelly B–EtOAc. Semipreparative chromatography with 7:1 Skelly B–EtOAc yielded 118 mg (56% recovery) of alcohol **23**, plus recovered *N*-ethylcarbamate **28** (178 mg, 68%).

For *N*-[[*trans*-(2-phenylcyclohexyl)oxy]carbonyl]-1-cyclopentyl-2-oct-1-enesulfinamide (**8**): ^{13}C NMR (90 MHz) δ 152.2 (s), 142.4 (s), 140.4 (d, C3), 128.0 (d), 127.1 (d), 126.1 (d), 120.0 (d, C2), 78.8 (d), 72.5 (d, C1), 49.4 (d), 39.4 (d, C1′), 33.6 (t), 32.2 (t, C2′), 32.1 (t, C6), 32.0 (t), 31.0 (t, C4), 28.5 (t, C5), 25.4 (t), 24.5 (t), 24.4 (t, C3′), 22.0 (t, C7), 13.7 (q, C8).

For **23**: $[\alpha]^{25}_D$ −1.4° (c = 5.9, CH_2Cl_2); ^{13}C NMR (90 MHz) δ 136.5 (d, C1), 131.3 (d, C2), 73.7 (d, C3), 42.8 (d, C1′), 37.5 (t, C4), 33.1 (t, C2′), 31.8 (t, C6), 25.2 (t, C3′,C5), 22.6 (t, C7), 14.0 (q, C8); ^1H NMR (361 MHz) δ 5.62 (dd, J = 7.2, 15.5 Hz, 1 H), 5.43 (dd, J = 6.5, 15.5 Hz, 1 H), 4.03 (dt, J = 6.5, 6.5 Hz, 1 H), 2.43 (hx, J = 7.3 Hz, 1 H), 1.11–2.00 (m, 17 H), 0.88 (m, 3 H); IR, 3385, 2940, 2860, 1665, 1453, 1378 cm^{-1}; MS, m/e 120 (base), 95, 69, 67.

***trans*-1-Cyclopentyl-1-octen-3-yl *O*-Acetylmandelate.** To 53.6 mg (0.273 mmol) of alcohol **23** in 1 mL of CH_2Cl_2 with stirring and chilled in a salted ice bath were added 64.0 mg (0.330 mmol) of (*R*)-*O*-acetylmandelic acid and then 3.3 mg (0.027 mmol) of DMAP. A solution of DCC (79.0 mg, 0.382 mmol) in 1 mL of CH_2Cl_2 was then slowly added via syringe over a 10 min. The cooling bath was removed and the reaction mixture was stirred for a further 14 h. The solution was again chilled in an ice bath an then filtered through cotton. The solvent was removed, and the mixture was taken up in EtOAc and washed sequentially with 0.1 N HCl, 1.0 N NaOH, and saturated aqueous NaCl. The solution was filtered through cotton and the solvent was removed, yielding 91.9 mg (90% recovery) of a yellow-brown oil containing traces of dicyclohexylurea (NMR). A diastereotopic purity of 82% for the (*R*)-*O*-acetylmandelate of (−)-alcohol **23** was calculated via proton integration of the allylic protons appearing at δ 2.42 and 2.30 for the two diastereomers. This value corresponds to an induction of 91% ee in the overall allylic oxidation when corrected for the 95:5 ratio of Z to E starting

alkene: ^{13}C NMR (90 MHz) δ 170.0 (s, C15), 168.1 (s, C9), 139.2 (d, C1), 134.5 (s, C11), 129.0 (d, C14), 128.6 (d, C13), 127.7 (d, C12), 125.8 (d, C2), 76.4 (d, C3), 74.8 (d, C10), 42.8 (d, C1'), 34.4 (t, C4), 32.8 (t, C2'), 31.4 (t, C6), 25.1 (t, C3'), 24.4 (t, C5), 22.4 (t, C7), 20.7 (q, C16), 13.8 (q, C8); ^{1}H NMR (361 MHz, acetone-d_6) δ 7.46 (m, 5 H), (s, 1 H), 5.68 (dd, J = 7.6, 15.5 Hz, 1 H), 5.41 (ddd, J = 1.4, 6.1, 15.5 Hz, 1 H), 5.20 (q, J = 6.1 Hz, 1 H), 2.42 (hx, J = 7.6 Hz, 1 H), 2.12 (s, 3 H), 2.08–0.94 (m, 16 H), 0.78 (t, J = 6.8 Hz, 3 H); IR, 2925, 2850, 1738, 1660, 1208, 1050 cm^{-1}.

The *O*-acetylmandelic acid esters were also prepared from racemic **23**, providing both the above as well as a second diastereomer: ^{13}C NMR (90 MHz) δ 170.0 (s, C15), 168.2 (s, C9), 139.0 (d, C1), 134.3 (s, C11), 129.0 (d, C14), 128.7 (d, C13), 127.8 (d, C12), 125.6 (d, C2), 76.3 (d, C3), 74.8 (d, C10), 42.6 (d, C1'), 34.5 (t, C4), 32.8 (t, C2'), 31.6 (t, C6), 25.1 (t, C3'), 24.8 (t, C5), 22.5 (t, C7), 20.7 (q, C16), 13.9 (q, C8); ^{1}H NMR (361 MHz, acetone-d_6) δ 7.46 (m, 5 H), 5.86 (s, 1 H), 5.68 (dd, J = 7.6, 15.5 Hz, 1 H), 5.37 (dd, J = 6.1, 15.5 Hz, 1 H), 5.25 (m, 1 H), 2.30 (hx, J = 7.6 Hz, 1 H), 2.12 (s, 3 H), 2.08–0.94 (m, 16 H), 0.78 (t, J = 6.8 Hz, 3 H).

***exo-cis*-Bicyclo[3.3.0]oct-3-en-2-ol (26).** To 1.41 g (3.78 mmol) of sulfinamide (*S*)-**12** in 30 mL of CH_2Cl_2 in a −10 °C bath were added 0.99 mL (5.7 mmol) of Huenig's base and then 1.44 g (7.56 mmol) of triethyloxonium tetrafluoroborate. After the solution was stirred for 30 min, the solvent was removed and the mixture was partitioned between 0.1 N HCl and EtOAc. The organic layer was washed with 0.1 N NaOH and then a saturated NaCl solution. After the solution was filtered through cotton, the solvent was removed, yielding a light yellow oil. This *N*-ethylsulfinamide was reacted in 30 mL of ether at −78 °C with a 3.8-mL solution of 3.0 N (11 mmol) phenylmagnesium bromide, stirring for 40 min. Then the reaction was quenched with a solution of 0.60 g (11 mmol) of NH_4Cl in 30 mL of MeOH followed immediately by 5.2 mL (20 mmol) of piperidine. This mixture was allowed to warm to room temperature and was then heated at reflux for 40 h. The solvent was removed, and the resulting oil was filtered through a chromatography-grade silica gel, eluting with a 2:1 mixture of Skelly B–EtOAc. Preparative chromatography yielded 0.28 g (62%) of the exo alcohol as well as 0.67 g (71%) of *trans*-2-phenylcyclohexyl *N*-ethylcarbamate (**28**).

For *N*-ethyl-*N*-[[*trans*-(2-phenylcyclohexyl)oxy]carbonyl]bicyclo-[3.3.0]-3-oct-2-enesulfinamide: ^{13} NMR (90 MHz) δ 153.8, 143.3, 143.2 (C4), 128.5, 127.2, 126.4 123.8 (C3), 78.4 (C2), 78.1, 50.7 (C5), 49.8, 40.6 (C1), 35.3 (C1'), 34.4, 33.7 (C8), 32.5, 31.1 (C6), 25.9, 24.8, 24.8 (C7), 15.3 (C2').

For exo alcohol: $[\alpha]^{25}_D$ +171.4° (c = 1.4, EtOH) derived from (*S*)-**1**; ^{13}C NMR (90 MHz) δ 139.8 (C4), 132.2 (C3), 85.5 (C2), 51.8 (C5), 49.4 (C1), 32.4 (C6), 30.7 (C8), 24.8 (C7); ^{1}H NMR (361 MHz) δ 5.80 (dd, J = 2.7, 6.8 Hz), 5.74 (ddd, J = 2.2, 2.2, 6.8 Hz, 1 H), 4.45 (d, J = 2.2 Hz, 1 H), 3.34 (m, 1 H), 2.44 (m, 1 H), 0.75–1.80 (m, 7 H); IR, 3590, 2940, 2830, 1250, 895, 730 cm^{-1}; MS, m/e 123, 96, 95, 91.

For the *N*-ethylcarbamate **28**: ^{13}C (90 MHz) δ 156.1 (s), 143.6 (s), 128.2 (d), 127.6 (d), 126.2 (d), 76.1 (d), 50.2 (d), 35.7 (t, C1), 34.4 (t), 32.9 (t), 26.0 (t), 24.8 (t), 15.1 (q, C2); ^{1}H NMR (361 MHz) δ 7.07–7.42 (m, 5 H), 4.86 (dt, J = 4.2, 10.8 Hz, 1 H), 4.36 (brs, 1 H), 2.98 (brs, 2 H), 2.62 (m, 1 H), 2.22 (brd, J = 10.8 Hz, 1 H), 1.95–1.65 (m, 3 H), 1.10–1.60 (m, 4 H), 1.00–0.70 (brs, 3 H); IR, 3445, 3043, 2980, 2935, 1714, 1422, 1265, 897 cm^{-1}; MS, m/e 176, 159, 158, 157, 143, 132, 131, 130, 129, 128, 117, 116, 115, 105, 104, 103, 98, 92, 91.

Recovery of Chiral Auxiliary *trans*-2-phenylcyclohexanol [(*R*)-1]. To 435 mg (1.76 mmol) of *trans*-2-phenylcyclohexyl *N*-ethylcarbamate (**28**) in 14 mL of THF at 0 °C was added 201 mg (5.28 mmol) of $LiAlH_4$. The mixture was stirred for 15 min, allowed to warm to room temperature, and then heated at reflux for 14 h. Saturated aqueous Na_2SO_4 was added until no more H_2 gas evolution could be detected, and then excess Na_2SO_4 was added to adsorb the water. The salts were removed by vacuum filtration and washed with EtOAc. Concentration of the filtrate afforded 288 mg (93%) of a crystalline material (mp 62–63 °C) that was clean alcohol (*R*)-**1** by ^{13}C NMR analysis [$[\alpha]^{25}_D$ −58.3° (c = 23.5, MeOH)].

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Supplementary Material Available: Full experimental details for the synthesis of all compounds listed in Tables I–IV not otherwise provided (19 pages). Ordering information is given on any current masthead page.

Total Synthesis and Structural Investigations of Didemnins A, B, and C

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Abstract: Didemnins A, B, and C, cyclodepsipeptides isolated from a marine tunicate of the family *Didemnidae*, were efficiently prepared in a stereocontrolled manner, producing the common macrocycle and, in a separate step, introducing the substituents on the amino group of L-threonine as optically pure units. We envisaged that disconnections between L-leucine and the HIP group (2*S*,4*S*) and between L-threonine and isostatine (3*S*,4*R*,5*S*) would afford two units: a HIP-isostatine unit (I) and a tetrapeptide unit (II). The HIP-isostatine unit was synthesized stereoselectively, and a convergent strategy was used to construct the tetrapeptide. The two units were coupled to afford a linear precursor which was cyclized after appropriate functionalization. Macrocyclization was accomplished at the carboxylic acid of the HIP unit and the free amino group of leucine by using diphenylphosphoryl azide (DPPA). After selective deprotection of the hydroxyl and amino groups of the macrocycle, the substituents attached to the amino group of L-threonine were introduced by using benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP).

Introduction

In 1981, a new class of cyclodepsipeptides, the didemnins (**1**), were isolated from a Caribbean tunicate of the family *Didemnidae* (*Tridemnum genus*).[1] These marine invertebrates have been found in waters off the coasts of Colombia, Honduras, Mexico, Belize, and Panama. *Tridemnum solidum* and *Tridemnum cyanophorum* both have been reported to contain didemnins.[2,3] Originally, five active components were isolated, didemnins A–E. Lower homologs, the nordidemnins, were also found. More re-

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