(under) nitrogen) washed twice with methylene chloride. The aqueous phase was acidified to pH 1 with 1 N hydrochloric acid and (still under nitrogen) extracted 3 times with chloroform. The combined chloroform extracts were dried over sodium sulfate and concentrated under reduced pressure to give 69.6 mg of a white solid (90.3%): NMR (C_6D_6, 79.5 mHz) δ 6.74 (s), 3.41 (s), 2.71 (s); NMR (C_6D_6/D_2O, 79.5 mHz) δ 6.74 (s), 2.72 (s), IR ($CHCl_3$) 2937, 2830, 1451, 1354, 1282 cm^{-1}; mass spectrum, *m/e* 168 (parent ion). This material was used without further purification or characterization.

2',3',4',5',6',7'-Hexahydrodispiro[cyclobuta[*f*]-1,3-benzodithiole-2,1'-anthracene-8',2''-cyclobuta[*f*]-1,3-benzodithiole] (2). A dry 10 mL two-nicked reacton flask was fitted with a nitrogen bubbler and a magnetic stirring bar. To this flask was added 1,2-dihydro-4,5-dimercaptobenzocyclobutene (**7**, 261 mg, 1.55 mmol), diketone **3** (111 mg, 0.518 mmol), chloroform (2.5 mL), and trimethylsilyl chloride (1.0 mL, 0.856 g, 7.88 mmol). This mixture was stirred at room temperature for 94 h and then diluted with chloroform and washed with 5% aqueous sodium carbonate. The chloroform phase was concentrated under reduced pressure to give a pink solid. This solid was dissolved in hot carbon tetrachloride, cooled to room temperature, and filtered. Storage in the freezer overnight gave 234 mg of white crystals (87.9%, based on **3**). The mother liquor was concentrated to dryness, dissolved in hot ethyl acetate, and filtered. The filtrate, after being concentrated under a stream of nitrogen, gave 29.1 mg of pale yellow crystals (10.9%) for a combined yield of 98.8%: mp > 250 °C; NMR ($CDCl_3$, 300 mHz) δ 9.70 (s, 1 H), 6.83 (s, 4 H), 6.78 (s, 1 H), 3.05 (d, J = 1.5 Hz, 8 H), 2.76 (t, J = 6.3, 4 H), 2.58 (m, 4 H), 1.97 (m, 4 H); IR ($CHCl_3$) 2943, 2876, 2844, 1489, 1448, 1272 cm^{-1}; mass spectrum, *m/e* 514 (parent ion); high-resolution mass spectrum calcd for $C_{30}H_{26}S_4$ 514.0917, found 514.0913.

Acknowledgment. This work was supported by the Office of Naval Research and the Center for Microelectronics and Information Science at the University of Minnesota. Dr. D. Britton performed the X-ray structure determination.

Registry No. **1**, 93304-13-3; **2**, 93304-14-4; **3**, 82817-90-1; **4**, 93304-15-5; **5**, 57297-31-1; **6**, 93304-16-6; **7**, 93304-17-7; 1,3-bis(4-pentenyl)benzene, 93304-18-8; *m*-xylene, 108-38-3; *m*-xylene dipotassium salt, 78831-97-7; 4-bromo-1-butene, 5162-44-7; 1,3-bis(4-carboxypropyl)benzene, 54698-75-8; 1,2-dimercaptobenzene, 17534-15-5; lead(II) thiocyanate, 592-87-0; thiocyanogen, 505-14-6; potassium *tert*-butoxide, 865-47-4.

Supplementary Material Available: X-ray data (11 pages). Ordering information is given on any current masthead page.

Enantioselective Processes. Reaction of Optically Active Amines with Photochemically Generated Ketenes

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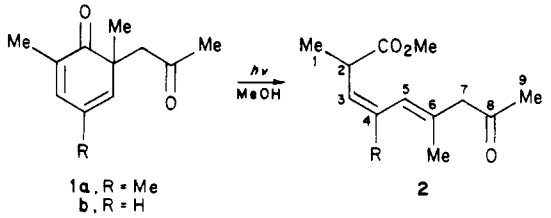
The diastereoselectivity of the reaction of *d*- and *l*-ephedrine with ketenes photochemically generated from 6-(2-oxopropyl)-2,4,6-trimethyl-2,4-cyclohexadien-1-one (**1a**), 6-(2-oxopropyl)-2,6-dimethyl-2,4-cyclohexadien-1-one (**1b**), and 6-acetoxy-2,4,6-trimethyl-2,4-cyclohexadien-1-one (**3a**) is described. Configurational assignments at C(2) in the major products **5a** and **6** resulting from irradiation of **1a** in the presence of *d*-ephedrine and *l*-ephedrine, respectively, were made by chemical degradation and correlation studies with (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**7a**).

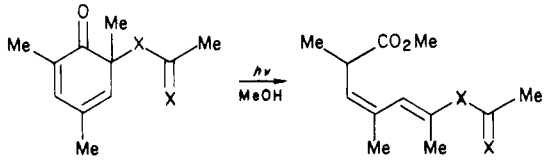
We recently reported[1] the near quantitative photoconversion of 6-(2-oxopropyl)-2,4,6-trimethyl-2,4-cyclohexadien-1-one (**1a**)[2] to 2-carbomethoxy-2,4-dimethyl-3,5-nonadien-8-one (**2a**). Remarkably, **2a** was isolated in 96% yield as a single geometric isomer. The conversion of **1b** to **2b** also occurs with similar stereoselectivity.



1a, R = Me
b, R = H

2

Diene carboxylic acid derivatives produced by photoreaction of 2,4-cyclohexadienones tend to be isomerically pure at the C(3)-C(4) double bond (*Z* configuration) but a mixture of *E* and *Z* configurations at the C(5)-C(6) double bond.[3] Only the 6-acetoxy-2,4-cyclohexadien-1-ones[4a-d] and two 6-(benzoyloxy)-2,4-cyclohexadien-1-ones[4d] had been reported to undergo highly stereoselective photoisomerization to diene ketenes. For example, photolysis of 6-acetoxy-2,4,6-trimethyl-2,4-cyclohexadien-1-one (**3a**) in methanol gives **4a** in 93% yield and the corresponding C(5)-C(6) isomer (2%).[4b] In marked contrast, the unsaturated hydrocarbon analogue **3b** gives **4b** (~70%) along with the C(5)-C(6) isomer (~30%).



3a, X = O
b, X = CH_2

4

During the conversion **1** → **2**, there also is the potential for enantioselection in the protonation of the diene ketene

(1) Schultz, A. G.; Ranganathan, R.; Kulkarni, Y. S. *Tetrahedron Lett.* **1982**, *23*, 4527.

(2) Nitta, M.; Omata, A.; Sugiyama, H. *Chem. Lett.* **1980**, 1615.

(3) For reviews of 2,4-cyclohexadienone photochemistry, see: (a) Quinkert, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 211. (b) Quinkert, G. *Agnew. Chem., Int. Ed. Engl.* **1972**, *11*, 1072. (c) Quinkert, G. *Pure Appl. Chem.* **1973**, *33*, 285.

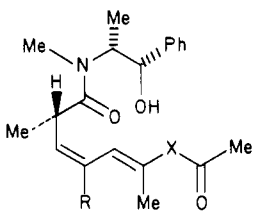
(4) (a) Baldwin, J. E.; McDaniel, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6118. (b) Quinkert, G.; Bronstert, B.; Schmieder, K. R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 637. The isomeric, fully conjugated diene carboxylic ester also is obtained (5%) from irradiation of **3a** in methanol. (c) Morris, M. R.; Waring, A. J. *J. Chem. Soc., Chem. Commun.* **1969**, 526. (d) Waring, A. J.; Morris, M. R.; Islam, M. M. *J. Chem. Soc. C* **1971**, 3274. The highly stereoselective photoisomerization of ten 6-acetoxy-2,4-cyclohexadien-1-ones are reported. (e) For discussions of factors which may control diene stereoselectivity, see ref 4a and 4d.

0022-3263/84/1949-5202$01.50/0

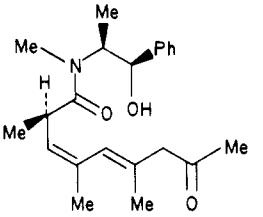
intermediate at C(2). Asymmetric induction has been reported for the reaction of ketenes with optically active amines and alcohols.[5] Several mechanisms for the reaction of amines with ketenes have been proposed, but experimental results which would provide a clear mechanistic understanding are not available. Furthermore, we are not aware of any effort devoted to development of synthetic aspects of this reaction. In this paper, we present the first study of the reaction of optically active amines with ketenes generated by photorearrangement of 2,4-cyclohexadien-1-ones.

Results and Discussion

High asymmetric induction in base-catalyzed reactions of ethylphenylketene with optically active 1-phenylethanol has been reported by Salz and Rüchardt.[6,7] Optically pure (−)-(*S*)-1-phenylethanol, the reagent used in the Salz and Rüchardt study, fails to produce a significant diastereoselection in photoreactions with **1a**. (*S*)-(−)-α-Methylbenzylamine gives little diastereoselectivity (~6% de) over the temperature range 25 °C to −70 °C in benzene (25 °C), toluene (−25 °C), or THF (−70 °C) solution; however, a 70:30 mixture of amide diastereoisomers is obtained when irradiation of **1a** is performed in THF in the presence of 1 equiv of *d*-ephedrine. The two diastereoisomers are easily separated by flash chromatography on silica gel and pure **5a** is obtained in ~50% isolated yield from **1a**. ^{1}H



5a, R = Me, X = CH_2
b, R = H, X = CH_2
c, R = Me, X = O

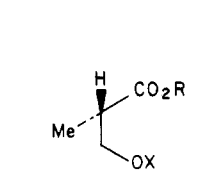


6

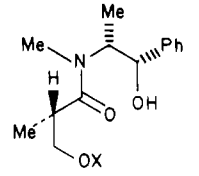
NMR analysis (200 MHz) of the photoreaction mixture is used to determine diastereoisomer ratios. While there are several qualitative differences between **5a** and its C(2) epimer (not shown), sharp singlets for the *N*-methyl absorption at δ 2.69 (major isomer) and 2.65 (minor isomer) provide the means for rapid quantitative analysis of diastereoisomer ratios.

Significantly, photoreaction of **1a** with *l*-ephedrine produces the same diastereoisomeric mixture as revealed by ^{1}H NMR analysis. The major isomer is isolated by chromatography and is assigned structure **6**, the enantiomer of **5a**. A CD spectrum of **5a** (~10^{-4} M in 95% ethanol at 25 °C) shows a positive, single Cotton effect curve with a peak at 232 nm and that of **6** shows an identical but negative curve. Photorearrangement of **1b** in the presence of *d*-ephedrine gives a 72:28 mixture of amide diastereoisomers; with the 6-acetoxy derivative **3a**, selectivity is reduced to a 60:40 diastereoisomer ratio. The major isomers **5b** and **5c**, respectively, are isolated by flash chromatography.

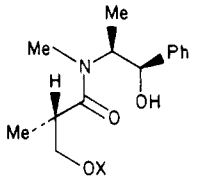
Configurational assignments at C(2) in **5a** and **6** were made by chemical degradation and correlation studies with (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**7a**).[8] Esterification of **7a** with diazomethane gives methyl ester **7b**,



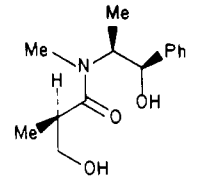
7a, R = X = H
b, R = Me; X = H
c, R = Me; X = *t*-BuMe$_2$Si



8a, X = *t*-BuMe$_2$Si
b, X = H



9a, X = *t*-BuMe$_2$Si
b, X = H



10

and this is converted to silyl ether **7c** by reaction with *tert*-butyldimethylchlorosilane. Conversion of **7c** to the *d*-ephedrine derived amide **8a** is accomplished by the trimethylaluminum procedure of Weinreb and co-workers;[9] silyl ether cleavage gives diol **8b**, isolated as a diastereoisomerically pure crystalline substance (mp 123–124 °C). In an analogous manner, **7c** is converted to **9b** (oil) by reaction with *l*-ephedrine/trimethylaluminum to give **9a**, followed by silyl ether cleavage.

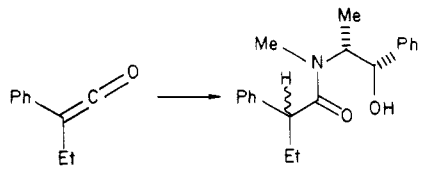
Photoproduct **5a** is degraded to **8b** (mp 123–124 °C) by ozonolysis in methanol, followed by sodium borohydride reduction. Similarly, **6** is converted to **10** (mp 123–124 °C), the enantiomer of **8a**. Whereas **5a** and **6** display resonances compatible with rapidly interconverting amide rotational isomers (on the NMR time scale), spectra of **8b**, **9b**, and **10** clearly demand the presence of two isomers in a ratio of ~80:20. That these mixtures are composed of amide rotational isomers is demonstrated by the reversible simplification of ^{1}H NMR spectra of **8b**, **9b**, and **10** in the temperature range 25–140 °C (Me_2SO-d_6 solution). ^{1}H NMR spectra of **8b** and **10** are identical and clearly different from spectra obtained with **9b**. Thus, configurational integrity at C(2) is maintained during the chemical interconversions relating **7a** with **5a** and **6**.

These chemical and NMR studies provide rigorous assignments of configuration at C(2) for **5a** and **6**. Configurational assignments at C(2) for **5b** and **5c** are based upon a consideration of ^{1}H NMR and CD spectra of **5b** and **5c** in relation to those of **5a** (Experimental Section).

The temperature-independent distribution of diastereoisomers produced by reaction of the ketene derived from **1a** with optically active (*S*)-(−)-α-methylbenzylamine (vide supra) stands in marked contrast to the reported behavior of methylphenylketene with (*S*)-(−)-α-methylbenzylamine.[5] We have examined the effect of temperature on the photoreaction of **1a** with *d*-ephedrine in THF solution and find that the distribution of amide diastereoisomers also is invarient between 25 °C and −70 °C. However, reaction of ethylphenylketene (**11**) with *d*-ephedrine in toluene gives **12** with 10% de at 25 °C, 20% de at 0 °C, and 50% de at −78 °C.

The efficiency of diastereoselectivity of photoreactions of **1a** in the presence of *d*-ephedrine is somewhat de-

(5) Morrison, J. D.; Mosher, H. S. In "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1976; pp 276–282. Several important references for the addition of optically active amines and alcohols to ketenes are available in this reference work.
(6) Salz, U.; Rüchardt, C. *Tetrahedron Lett.* **1982**, *23*, 4017.
(7) (a) Jähme, J.; Rüchardt, C. *Tetrahedron Lett.* **1982**, *23*, 4011. (b) Jähme, J.; Rüchardt, C. *Angew, Chem., Int. Ed. Engl.* **1981**, *20*, 885.
(8) (a) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505, 3512. (b) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158.
(9) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.



11 12

pendent on solvent composition, with ~20% de in hydrocarbon solvents such as hexane or benzene, ~30% de in *tert*-butyl alcohol, and 40% de in THF, THF–pyridine or up to 20% H_2O in THF. Finally, we have examined the suitability of other readily available optically active amines and find that L-prolinol, (+)-norephedrine, and *l*-epinephrine provide little diastereoselection.

Conclusion

The induction of optical activity in reactions *d* and *l*-ephedrine with photochemically generated ketenes provides a setting for further exploration of the mechanism and synthetic utility of the process. While enantioselection is not particularly dramatic at this stage of development, the process is already of some synthetic utility. Both *d*- and *l*-ephedrine are inexpensive commercially available reagents and only 1 molar equiv of ephedrine is required for complete conversion of 2,4-cyclohexadienone to photoproduct. The photolysis requirements are minimal (standard mercury-arc light source, Pyrex glassware, an ~366 nm glass filter, ~0.2 M reactant concentrations, and ~2-h photolysis time) and purification of diastereoisomeric photoproducts by silica gel flash chromatography is rapid and complete.

Experimental Section

^{1}H NMR spectra were recorded on Varian T-60 (60 MHz), Varian XL-200 (200 MHz), and Hitachi-Perkin-Elmer R-600 (60 MHz) NMR spectrometers (tetramethylsilane internal standard). ^{13}C NMR spectra were obtained on the Varian XL-200 spectrometer. Infrared spectra were recorded on either a Perkin-Elmer 137b or 298 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer 552 spectrometer and circular dichroism spectra were recorded on a Perkin-Elmer ORD/UV-5 spectrometer. Mass spectra were obtained on Finnigan OWA-1020 and Hewlett-Packard 5987A GC–MS systems. Preparative HPLC was performed on a Waters Associates preparative LC 500 with Prep Pak 500 silica gel cartridges. Elemental analyses were determined by Spang Microanalytical Laboratories, Eagle Harbor, MI. The 366-nm light source consisted of a water-cooled Hanovia 679A36 450-W mercury arc lamp fitted with Corning color filters 0-52 and 7-54. *d*- and *l*-ephedrine were purchased from Aldrich Chemical Co. Solvents for photochemical studies were used as received without further purification.

General Procedure for the Photoreaction of Cyclohexadienones in the Presence of Amines. A solution containing the 2,4-cyclohexadien-1-one (0.1 mmol) and the amine (0.1 mmol) in THF (1 mL) was degassed for 15 min by using argon and irradiated for 2 h with a 366-nm light source. The solvent was removed under reduced pressure and the crude mixture of the two diastereoisomers was separated by flash chromatography (silica gel) using an appropriate solvent system. For larger scale reactions, a 0.05–0.1 M solution of the 2,4-cyclohexadienone and the amine in THF was degassed as above and irradiated by using the 450-W mercury arc lamp and an uranium filter sleeve. The reaction was usually complete after 1 h. The separation of components was accomplished by HPLC.

Preparation of (1′*R*,2′*S*,2*S*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-8-oxo-*N*,2,4,6-tetramethylnona-3,5-dienamide (5a). A solution containing **1a** (19.2 mg, 0.1 mmol) and *d*-ephedrine (16.5 mg, 0.1 mmol) in THF (1 mL) was irradiated by using the above general procedure to give 33 mg (94%) of a pale yellow oil which consisted of a 70:30 mixture of the two diastereoisomers. The major isomer **5a** was isolated by flash chromatography (silica gel, 70% ethyl acetate in hexane): 17 mg (48%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (d, 3 H, J = 7.0 Hz), 1.21 (d, 3 H, J = 7.0 Hz), 1.58 (d, 3 H, J = 1.2 Hz), 1.75 (br s, 3 H), 2.15 (s, 3 H), 2.69 (s, 3 H), 3.14 (s, 2 H), 3.42 (dq, 1 H, J = 9.6 Hz, 7.0 Hz), 4.19 (d, 1 H, J = 3.2 Hz), 4.49 (dq, 1 H, J = 7.0 Hz, 4.2 Hz), 4.81 (dd, 1 H, J = 4.2 Hz, 3.2 Hz), 5.42 (br d, 1 H, J = 9.6 Hz), 5.63 (br s, 1 H), 7.25–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.42, 17.59, 17.87, 23.53, 29.42, 32.38, 37.02, 53.78, 57.38, 77.09, 126.31, 127.32, 127.93, 128.07, 128.49, 131.45, 132.90, 141.77, 176.59, 206.61; IR (film) 2.75, 2.8–3.25, 5.85, 6.17, 8.25, 9.6, 14.3 μm; UV (95% ethanol) λ_{max} 225 nm (ϵ 7500); **5a** exhibited a positive CD curve; λ_{max} 232 nm (c 5.6 × 10^{-5} M, 95% ethanol).

Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74. Found: C, 73.75, H, 8.71.

Preparation of (1′*S*,2′*R*,2*R*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-8-oxo-*N*,2,4,6-tetramethylnona-3,5-dienamide (6). A solution containing **1a** (19.2 mg, 0.1 mmol) and *l*-ephedrine (16.5 mg, 0.1 mmol) in THF (1 mL) was irradiated by using the above general procedure to give 32 mg (92%) of a 70:30 mixture of the two diastereoisomers. The major isomer **6** was isolated by flash chromatography (silica gel, 70% ethyl acetate in hexane); 16 mg (46%); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.03 (d, 3 H, J = 7.0 Hz), 1.21 (d, 3 H, J = 7.0 Hz), 1.58 (d, 3 H, J = 1.2 Hz), 1.75 (br s, 3 H), 2.15 (s, 3 H), 2.70 (s, 3 H), 3.14 (s, 2 H), 3.42 (dq, 1 H, J = 9.6 Hz, 7.0 Hz), 4.12 (d, 1 H, J = 3.2 Hz), 4.49 (dq, 1 H, J = 7.0 Hz, 4.2 Hz), 4.81 (dd, 1 H, J = 4.2 Hz, 3.2 Hz), 5.42 (br d, 1 H, J = 9.6 Hz), 5.63 (br s, 1 H), 7.25–7.4 (m, 5 H); IR (film) 2.75, 2.8–3.25, 5.85, 6.17, 8.25, 9.6, 14.3 μM; UV (95% ethanol) λ_{max} 228.5 (ϵ 7400); **6** exhibited a negative CD curve, λ_{max} 232 nm (c 1.09 × 10^{-4} M, 95% ethanol).

Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74. Found: C, 74.06; H, 8.79.

Preparation of (1′*R*,2′*S*,2*S*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-8-oxo-*N*,2,6-trimethylnona-3,5-dienamide (5b). A solution of **1b** (17.8 mg, 0.1 mmol) and *d*-ephedrine (16.5 mg, 0.1 mmol) in THF (1 mL) was irradiated by using the above procedure. A 72:28 mixture of the two diastereoisomers was obtained (32 mg, 96%). The major isomer **5b** was isolated by flash chromatography (silica gel, 70% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.13 (d, 3 H, J = 6.8 Hz), 1.21 (d, 3 H, J = 7.0 Hz), 1.78 (br s, 3 H), 2.14 (s, 3 H), 2.71 (s, 3 H), 3.16 (s, 2 H), 3.63 (dq, 1 H, J = 9.8 Hz, 7.0 Hz), 3.97 (d, 1 H, J = 2.4 Hz), 4.52 (dq, 1 H, J = 6.8 Hz, 4.2 Hz), 4.81 (dd, 1 H, J = 4.2 Hz, 2.4 Hz), 5.47 (t, 1 H, J = 9.8 Hz), 6.07 (d, 1 H, J = 10.8 Hz), 6.21 (dd, 1 H, J = 10.8 Hz, 9.8 Hz), 7.22–7.46 (m, 5 H); IR (film) 2.75, 2.8–3.25, 5.87, 6.2, 7.14, 8.25, 14.3 μM; UV (95% ethanol) λ_{max} 244 nm (ϵ 21 300); **5b** exhibited a positive CD curve; λ_{max} 245 nm (c 6.62 × 10^{-5} M, 95% ethanol).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51. Found: C, 73.39; H, 8.46.

Preparation of (1′*R*,2′*S*,2*S*)-6-Acetoxy-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-*N*,2,4,6-tetramethylhexa-3,5-dienamide (5c). A solution containing 6-acetoxy-2,4,6-trimethyl-2,4-cyclohexadien-1-one (**3a**) (19.4 mg, 0.1 mmol) and *d*-ephedrine (16.5 mg, 0.1 mmol) in THF (1 mL) was irradiated by using the above general procedure to give 34 mg (97%) of a 60:40 mixture of the two diastereoisomers. The major isomer was isolated by flash chromatography (silica gel, 65% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.03 (d, 3 H, J = 7.0 Hz), 1.20 (d, 3 H, J = 7.2 Hz), 1.79 (br s, 6 H), 2.10 (s, 3 H), 2.73 (s, 3 H), 3.51 (dq, 1 H, J = 10.2 Hz, 7.0 Hz), 4.03 (d, 1 H, J = 3.0 Hz), 4.5 (m, 1 H), 4.75 (m, 1 H), 5.46 (br d, 1 H, J = 10.2 Hz), 5.54 (br s, 1 H), 7.2–7.5 (m, 5 H); IR (film) 2.8, 2.85–3.3, 5.75, 6.17, 7.13, 8.25, 11.1, 14.3 μM; UV (95% ethanol) λ_{max} 229.5 nm (ϵ 5300); the major isomer exhibited a positive CD curve, λ_{max} 232 nm (c 9.19 × 10^{-5} M, 95% ethanol).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.16; H, 8.13. Found: C, 70.10; H, 7.94.

Preparation of (1′*R*,2′*S*,2*S*)-*N*,2-Dimethyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-hydroxypropionamide (8b) (from 5a). A solution containing **5a** (100 mg, 0.28 mmol) in absolute methanol (10 mL) was reacted with ozone at −78 °C. The resulting dark blue solution was purged with dry nitrogen for 10 min and sodium borohydride (107 mg, 2.8 mmol) was added in small portions. The solution was allowed to warm to 0 °C and stirred at 0 °C for 1 h. After warming to room temperature, water (2 mL) was added. The solvents were removed under reduced

pressure and the residue was extracted several times with diethyl ether. The combined ether layers were dried and evaporated under reduced pressure to give **8b** as a pale yellow oil. This was further purified by flash chromatography (silica gel, 5% methanol in ethyl acetate) followed by recrystallization from benzene to afford 63 mg (90%) of **8b** (mp 123–124 °C) as a mixture (80:20) of two conformational isomers: ^{1}H NMR ($CDCl_3$, 200 MHz) (major isomer) δ 0.91 (d, 3 H, J = 7.2 Hz), 1.26 (d, 3 H, J = 7.0 Hz), 2.72 (tq, 1 H, J = 7.2 Hz, 4.8 Hz), 2.74 (s, 3 H), 3.2 (br s, 1 H), 3.65 (d, 2 H, J = 4.8 Hz), 3.7 (br s, 1 H), 4.62 (dq, 1 H, J = 7.0 Hz, 4.8 Hz), 4.78 (d, 1 H, J = 4.8 Hz), 7.24–7.46 (m, 5 H); ^{1}H NMR ($CDCl_3$, 200 MHz) (minor isomer) δ 1.05 (d, 3 H, J = 7.2 Hz), 1.42 (d, 3 H, J = 6.8 Hz), 2.72 (tq, 1 H, J = 7.2 Hz, 4.2 Hz), 2.80 (s, 3 H), 2.91 (d, 2 H, J = 4.2 Hz), 3.2 (br s, 1 H), 3.7 (br s, 1 H), 4.62 (dq, 1 H, J = 6.8 Hz, 4.8 Hz), 4.78 (d, 1 H, J = 4.8 Hz), 7.24–7.46 (m, 5 H); IR ($CHCl_3$) 2.7–3.25, 6.19, 7.1, 9.7, 13.3, 14.2 μM; UV (95% ethanol) λ_{max} 259 nm (ϵ 100), 264 nm (ϵ 86); chemical ionization mass spectrum, m/e 251 (M^+), 234, 148; **8b** exhibited a negative CD curve, λ_{max} 222 nm (c 1.51 × 10^{-4} M, 95% ethanol).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.77; H, 8.29; N, 5.43.

Preparation of (1′*S*,2′*R*,2*R*)-*N*,2-Dimethyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-hydroxypropionamide (10). Ozonolysis and reduction of **6** (50 mg, 0.14 mmol) in absolute methanol (5 mL), followed by purification by flash chromatography (silica gel, 5% methanol in ethyl acetate) and recrystallization from benzene, gave 32 mg (92%) of **10** (mp 123–124 °C) as an 80:20 mixture of two conformational isomers: ^{1}H NMR ($CDCl_3$, 200 MHz) (major isomer) δ 0.91 (d, 3 H, J = 7.2 Hz), 1.26 (d, 3 H, J = 7.0 Hz), 2.72 (tq, 1 H, J = 7.2 Hz, 4.8 Hz), 2.74 (s, 3 H), 3.2 (br s, 1 H), 3.65 (d, 2 H, J = 4.8 Hz), 3.7 (br s, 1 H), 4.62 (dq, 1 H, J = 7.0 Hz, 4.8 Hz), 4.78 (d, 1 H, J = 4.8 Hz), 7.24–7.46 (m, 5 H); ^{1}H NMR ($CDCl_3$, 200 MHz) (minor isomer) δ 1.05 (d, 3 H, J = 7.2 Hz), 1.42 (d, 3 H, J = 6.8 Hz), 2.72 (tq, 1 H, J = 7.2 Hz, 4.2 Hz), 2.80 (s, 3 H), 2.91 (d, 2 H, J = 4.2 Hz), 3.2 (br s, 1 H), 3.7 (br s, 1 H), 4.62 (dq, 1 H, J = 6.8 Hz, 4.8 Hz), 4.78 (d, 1 H, J = 4.8 Hz), 7.24–7.46 (m, 5 H); IR ($CHCl_3$) 2.7–3.25, 6.19, 7.1, 9.7, 13.3, 14.2 μM; UV (95% ethanol) λ_{max} 259 nm (ϵ 113), 264 nm (ϵ 93); chemical ionization mass spectrum, m/e 251 (M^+), 234, 148; **10** exhibited a positive CD curve: λ_{max} 222 nm (c 3.34 × 10^{-4} M, 95% ethanol).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.98; H, 8.42; N, 5.48.

Isolation of (*S*)-(+)-3-Hydroxy-2-methylpropanoic Acid (7a). A 25.6-g sample of a fermentation broth[8] was carefully neutralized at 0 °C by using 50% H_2SO_4 solution (approximately 4.1 mL) until the pH was 1.2 (pH meter). The resulting solution was saturated by the addition of potassium bisulfate (20 g) and extracted several times with diethyl ether. The combined ether layers were dried and evaporated to give ~4 g of a mixture of isobutyric acid and **7a**. This crude mixture was dissolved in methylene chloride (25 mL), dried, and evaporated. The residue was heated to 40 °C at 0.1 mm for several hours to remove the isobutyric acid. The residue, after drying (1.16 g), contained the unstable **7a** and was used directly in the subsequent step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.16 (d, 3 H, J = 7.0 Hz), 2.69 (dq, 1 H, J = 7.0 Hz, 6.0 Hz), 3.74 (d, 2 H, J = 6.0 Hz), 7.7 (br s, 2 H); IR (film) 2.7–3.7, 5.87, 6.83, 9.72 μm.

Preparation of (*S*)-(+)-Methyl 3-Hydroxy-2-methylpropionate (7b). To a solution of the crude acid **7a** (208 mg, 2 mmol) in diethyl ether (10 mL) was added a solution of diazomethane in ether at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and at room temperature overnight. The reaction mixture was dried and evaporated to afford the crude hydroxy ester **7b**. Purification by flash chromatography (silica gel, 55% ethyl acetate in hexane) followed by distillation (bp 45–50 °C at 7.0 mm) gave 108 mg (55%, based on 85% purity of the acid **7a**) of **7b**; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (d, 3 H, J = 7.2 Hz), 2.56–2.76 (m, 2 H), 3.73 (s, 3 H), 3.72 (d, 2 H, J = 6.0 Hz); IR (film) 2.73–3.25, 5.8, 8.32, 9.65 μM; mass spectrum, m/e 118 (M^+), 101, 85, 73, 45, 28.

Preparation of (*S*)-(+)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropionate (7c). A mixture containing **7b** (59 mg, 0.5 mmol), *tert*-butyldimethylchlorosilane (150 mg, 1 mmol), imidazole (170 mg, 2.5 mmol), and dimethylformamide (1 mL) was heated at 35 °C overnight. Solvent was removed under reduced pressure (25–30 °C (0.6 mm)). The residue was dissolved in diethyl ether (25 mL) and was washed with water (3 × 10 mL). After drying and evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, 5% ethyl acetate in hexane) followed by distillation (bp 35–40 °C (0.2 mm)) to give **7c** in 50–70% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 6 H), 0.84 (s, 9 H), 1.10 (d, 3 H, J = 7.2 Hz), 2.78–2.92 (m, 1 H), 3.85 (dd, 1 H, J = 9.5 Hz, 6.0 Hz), 3.89 (s, 3 H), 3.98 (dd, 1 H, J = 9.5 Hz, 6.0 Hz); IR (film) 3.3–3.6, 5.75, 6.8, 8.0, 11.9, 13.0 μM.

Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.83; H, 10.52.

Preparation of (1′*R*,2′*S*,2*S*)-*N*,2-Dimethyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-[(*tert*-butyldimethylsilyl)oxy]propionamide (8a). To a solution containing trimethylaluminum (2.1 mL of a 25% solution in hexane, 7.0 mmol) in dry benzene (15 mL) was added a solution containing *d*-ephedrine (0.54 g, 3.25 mmol) in dry benzene (10 mL) at −20 °C. The resulting mixture was allowed to warm to room temperature and stirred for 45 min.[9] A solution containing **7c** (0.3 g, 1.3 mmol) in dry benzene (10 mL) was added and the mixture was refluxed for 4 days. The mixture was cooled to room temperature and HCl (10.5 mL, 0.67 M, 7.0 mmol) was added. The mixture was stirred for 30 min, after which the two phases were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL) and the organic layers were combined and washed with saturated sodium bicarbonate solution (1 × 25 mL) and water (1 × 25 mL), dried, and evaporated under reduced pressure. Purification by flash chromatography (silica gel, 40% ethyl acetate in hexane), followed by distillation (bp 90–95 °C (0.2 mm)) gave 0.13 g (27%; 90% based on recovered **7c**) of **8a** as a low melting solid (mp 69–70 °C). The chromatography also provided 0.21 g (70%) of recovered ester **7c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.84 (s, 9 H), 0.9 (d, 3 H, J = 7.0 Hz), 1.2 (d, 3 H, J = 7.2 Hz), 2.72 (s, 3 H), 2.96–3.18 (m, 2 H), 3.49 (dd, 1 H, J = 9.5 Hz, 6.0 Hz), 3.76 (dd, 1 H, J = 9.5 Hz, 8.0 Hz), 4.56 (dq, 1 H, J = 7.2 Hz, 4.0 Hz), 4.76 (d, 1 H, J = 4.0 Hz), 7.46–7.7 (m, 5 H); IR (film) 2.78–3.22, 6.2, 6.85, 8.0 μm; UV (95% ethanol) λ_{max} 256 nm (ϵ 228), 262 nm (ϵ 190); chemical ionization mass spectrum, m/e 365 (M^+), 350, 308, 258, 232; **8a** exhibited a negative CD curve, λ_{max} 222 (c 2.41 × 10^{-4} M, 95% ethanol).

Anal. Calcd for $C_{20}H_{35}NO_3Si$: C, 65.71; H, 9.65; N, 3.83. Found: C, 65.23; H, 9.31; N, 3.41.

Preparation of (1′*R*,2′*S*,2*S*)-*N*,2-Dimethyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-hydroxypropionamide (8b) (from 8a). Method A. A mixture containing **8a** (36.5 mg, 0.1 mmol) and tetrabutylammonium fluoride (79 mg, 0.3 mmol) in dry THF (2 mL) was stirred at room temperature overnight. The solvent was evaporated and the residue was extracted with an ether–water mixture. The ether layer was separated and washed with water, dried, and evaporated to give **8b**; purification by flash chromatography (silica gel, 5% methanol in ethyl acetate) followed by recrystallization from benzene gave 15 mg (60%) of **8b** (mp 123–124 °C). **Method B.** A mixture containing **8a** (36.5 mg, 0.1 mmol) in THF (1 mL) and a 3:1 mixture of acetic acid–water (1 mL) was stirred at room temperature overnight. The solvents were removed under reduced pressure and the residue was treated with diethyl ether (10 mL) and saturated sodium bicarbonate solution (2 mL). The ether layer was separated, evaporated, and purified as in method A to give 20 mg (80%) of **8b** (mp 123–124 °C). **8b** prepared by methods A and B gave a correct elemental analysis as well as ^{1}H NMR, IR, UV, CD, mass spectra identical with those of **8b** prepared from **5a**.

Preparation of (1′*S*,2′*R*,2*S*)-*N*,2-Dimethyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-[(*tert*-butyldimethylsilyl)oxy]propionamide (9a). Prepared from **7c** (348 mg, 1.5 mmol) and *l*-ephedrine (660 mg, 4.0 mmol) by using the procedure for the preparation of **8a**. **9a** was obtained as an 85:15 mixture of two conformational isomers (100 mg, 18%, 60% based on recovered **7c**): ^{1}H NMR ($CDCl_3$, 200 MHz) (major isomer) δ 0.00 (s, 3 H), 0.04 (s, 3 H), 0.84 (s, 9 H), 1.00 (d, 3 H, J = 6.8 Hz), 1.15 (d, 3 H, J = 7.2 Hz), 2.77 (s, 3 H), 2.74–2.92 (m, 1 H), 3.44 (dd, 1 H, J = 10.0 Hz, 6.0 Hz), 3.65 (dd, 1 H, J = 16.0 Hz, 10.0 Hz), 4.27 (dq, 1 H, J = 7.2 Hz, 4.8 Hz), 4.84 (d, 1 H, J = 4.8 Hz), 7.2–7.4 (m, 5 H); ^{1}H NMR ($CDCl_3$, 200 MHz) (minor isomer) δ 0.00 (s,

3 H), 0.04 (s, 3 H), 0.41 (d, 3 H, J = 7.0 Hz), 0.81 (s, 9 H), 1.33 (d, 3 H, J = 7.2 Hz), 2.77 (s, 3 H), 2.74-2.94 (m, 1H), 3.44 (dd, 1 H, J = 10.0 Hz, 6.0 Hz), 3.65 (dd, 1 H, J = 16.0 Hz, 10.0 Hz), 4.1-4.44 (dq, 1 H, J = 7.2 Hz, 4.8 Hz), 4.84 (d, 1 H, J = 4.8 Hz), 7.2-7.4 (m, 5 H); IR ($CHCl_3$) 2.68, 2.75-3.2, 3.33-3.6, 6.2, 6.85, 8.0, 9.2, 12.0, 14.3 μm; UV 95% ethanol) λ_{max} 259 nm (ε 85), 264 nm (ε 85); chemical ionization mass spectrum, m/e 365 (M^+), 350, 308, 258, 216, 148; **9a** exhibited a positive CD curve, λ_{max} 222 nm (c 1.53 × 10^{-4} M, 95% ethanol).

Anal. Calcd for $C_{20}H_{35}NO_3Si$: C, 65.71; H, 9.65; N, 3.83. Found: C, 65.85; H, 9.62; N, 3.81.

Preparation of (1′*S*,2′*R*,2*S*)-*N*,2-Dimethyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-hydroxypropionamide (9b) (from 9a). Prepared from **9a** (36.5 mg, 0.1 mmol) by using method B described for the preparation of **8b**. **9b** (colorless oil) was obtained as a 90:10 mixture of two conformational isomers after flash chromatography (silica gel, 5% methanol in ethyl acetate) and distillation (bp 90-95 °C (0.2 mm)); ^1H NMR ($CDCl_3$, 200 MHz) (major isomer) δ 1.06 (d, 3 H, J = 7.0 Hz), 1.25 (d, 3 H, J = 7.2 Hz), 1.72 (br s, 1 H), 2.72 (tq, 1 H, J = 7.0, 4.8 Hz), 2.8 (s, 3 H), 3.43-3.74 (m, 3 H), 4.6 (dq, 1 H, J = 7.2 Hz, 4.2 Hz), 4.84 (d, 1 H, J = 4.2 Hz), 7.24-7.5 (m, 5 H); (minor isomer) δ 0.67 (d, 3 H, J = 7.0 Hz), 1.39 (d, 3 H, J = 7.2 Hz), 1.72 (br s, 1 H), 2.72 (tq, 1 H, J = 7.0 Hz, 4.8 Hz), 2.88 (s, 3 H), 3.43-3.74 (m, 3 H), 4.6 (dq, 1 H, J = 7.2 Hz, 4.2 Hz), 4.84 (d, 1 H, J = 4.2 Hz), 7.24-7.5 (m, 5 H); IR ($CHCl_3$) 2.78 , 2.85-3.2, 3.3-3.55, 6.2, 7.0, 9.6, 14.3 μm; UV (95% ethanol) λ_{max} 258 nm (ε 209), 264 nm (ε 180); chemical ionization mass spectrum, m/e 251 (M^+), 234, 148; **9b** exhibited a positive CD curve, λ_{max} 222 nm (2.39 × 10^{-4} M, ethanol).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.22; H, 8.59; N, 5.43.

Preparation of (1′*R*,2′*S*,2*S*)-*N*-Methyl-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-2-phenylbutyramide (12). A stirred solution containing 2-phenylbutyroyl chloride (0.365 g, 2 mmol) in dry toluene (5 mL) was cooled to 0 °C and a solution containing triethylamine (0.202 g, 2 mmol) in dry toluene (5 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. The solvents were then removed and the ethylphenylketene (**11**) was distilled and stored at -78 °C (bp 75-77 °C at 2 mm). To **11** in dry toluene (10 mL) at -78 °C was added a solution of *d*-ephedrine (0.413 g, 2.5 mmol) in dry toluene (5 mL). The resulting mixture was stirred at -78 °C for 15 min and allowed to warm to room temperature. The solution was washed with 2 N HCl (1 × 25 mL), saturated sodium bicarbonate (1 × 25 mL), and water (1 × 25 mL). It was then dried and evaporated under reduced pressure to give a 75:25 mixture of two diastereoisomers. The major isomer was obtained by fractional crystallization from 30% ethyl acetate in hexane (mp 118-119 °C, 375 mg, 60%): ^1H NMR ($CDCl_3$, 200 MHz) δ 0.81 (t, 3 H, J = 7.2 Hz), 1.16 (d, 3 H, J = 7.2 Hz), 1.56-1.8 (m, 1 H), 1.94-2.18 (m, 1 H), 2.66 (s, 3 H), 3.51 (dd, 1 H, J = 8.0 Hz, 6.0 Hz), 3.99 (d, 1 H, J = 2.8 Hz), 4.48 (dq, 1 H, J = 7.2 Hz, 3.2 Hz), 4.82 (dd, 1 H, J = 3.2 Hz, 2.8 Hz), 7.33-7.4 (m, 10 H); IR ($CHCl_3$) 2.78, 2.82-3.2, 3.25-3.55, 6.2, 6.9, 7.15, 8.3, 14.4 μm; UV (95% ethanol) λ_{max} 252 nm (ε 510), 259 nm (ε 570), 264 nm (ε 405); chemical ionization mass spectrum, m/e 311 (M^+), 294, 204, 177, 148.

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.19; H, 8.10; N, 4.53.

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Organotin-Mediated Selective Desulfurization: Tri-*n*-butyltin Hydride Reduction of Unsymmetric Sulfides

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Tri-*n*-butyltin hydride (TBTH) has been evaluated as a selective agent for the reductive cleavage of one C-S bond in unsymmetric sulfides **1** ($R \neq R^1$). Sulfides **1** [where combinations of R and R^1 included primary, secondary, tertiary, benzylic, phenyl, allylic, and α-(to carbonyl) carbon bound to sulfur] were each reacted with 1 equiv of TBTH in the presence of AIBN initiator. Reduction by TBTH occurs initially at the R^1-S bond (where R^1 can form the more stable carbon radical intermediate) in sulfide **1** selectively, if not specifically, to yield hydrocarbon **4** and tributylstannyl alkyl sulfide **3**. However, this specificity can be negated by an enhanced reactivity toward reduction by TBTH which the C-S bond in **3** exhibits, producing hydrocarbon **6** and bis(tributyltin) sulfide. The degree of selectivity in desulfurization is determined by the competition between unsymmetric sulfide **1** and alkyl organotin sulfide **3** for TBTH. The reduction of secondary and primary alkyl C-S bonds in **1** is so slow as to discount the synthetic utility of trialkyltin hydride reduction for such sulfides.

The broad distribution of sulfur in natural products and medicinal compounds has prompted considerable effort in the synthetic aspects of organosulfur chemistry. Work in this laboratory has been directed toward the development of methodology for the manipulation of specific C-S bonds in molecules wherein several are present. One area of special interest to us has been the reduction of unsymmetric sulfides **1**.[1]

We have reported the use of tri-*n*-butyltin hydride (hereafter abbreviated TBTH) as an effective and selective reducing agent for 1,3-dithiolanes.[2] The observation that 1 equiv of this organotin reagent could cleave as well as discriminate between primary, secondary, and benzylic C-S bonds implied it could be a general, yet selective, desulfurization agent. We now report the scope and limitations of the use of TBTH for selective reduction of unsymmetric sulfides **1**.[3]

As in many reactions of TBTH, the reductions we now describe appear to be free radical processes, initiated by

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