Synthesis and Absolute Configuration of (-)-Rothrockene, a Non-Head-to-Tail Monoterpene

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The total synthesis of (-)-rothrockene, *trans*-1-(1-methylethenyl)-2-(2-methyl-1-propenyl)cyclopropane, and its enantiomer is described. Utilization of (-)-(*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine in the synthesis allowed for resolution of a precursor, regio- and diastereoface selectivity in a Simmons–Smith cyclopropanation, determination of absolute configurations based on X-ray crystallography, and introduction of a side-chain double bond. The absolute configuration of the natural substance is shown to be 1*R*,2*S*.

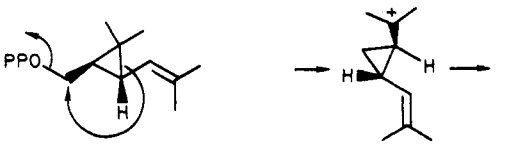
The structure and relative stereochemistry of (-)-rothrockene (**2**) [*trans*-1-(1-methylethenyl)-2-(2-methyl-1-propenyl)cyclopropane] a novel non-head-to-tail monoterpene from *Artemesia tridentate rothrockii*, whose primary skeletal structure had been predicted,[1] was recently established.[2] The suggestion has been made that non-head-to-tail monoterpene biosynthesis in plants based upon chrysanthemyl pyrophosphate (CPP) (**1**) as a key intermediate might serve as a model for the study of the CPP analogous compound, presqualene pyrophosphate, and its biosynthetic conversion to squalene in mammals.[1] In this connection Epstein and Gaudioso have speculated on the biosynthetic origin of (-)-rothrockene (**2**) and have predicted the absolute configuration on this basis[2] (Scheme I).

We have completed the synthesis of the natural (-)-rothrockene and its enantiomer and have determined by X-ray crystallography of a precursor that the absolute configuration is in accord with the above speculation. This conclusion has also been reached independently by Epstein and Brewster based on the synthesis of (+)-rothrockene (**9**) from a precursor of known absolute stereochemistry.[3]

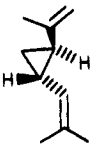
It has recently been shown[4] that cyclic prochiral enones can be converted to optically pure cyclopropyl ketones by using a process involving (1) addition of optically active sulfoximine **3** to the carbonyl of the enone, (2) separation of the resulting optically active diastereomeric allylic alcohols, (3) hydroxyl-directed Simmons–Smith cyclopropanation, and (4) thermal reversal of the sulfoximine addition to release optically pure ketone (Scheme II).

The successful application of this methodology to the appropriate acyclic dienone precursor **4** of rothrockene would require that the hydroxyl group of the adduct **5** control both regio- and diastereoface selectivity. Literature precedence indicates that the double bond nearer the hydroxyl should be preferentially attacked.[5] In the case of acyclic trans allylic alcohols the "erythro"/"threo" ratio in cyclopropanation has been found to be only slightly in favor of "erythro". "Erythro" cyclopropanation is much more favored in the case of cis allylic alcohols.[5]

Scheme I

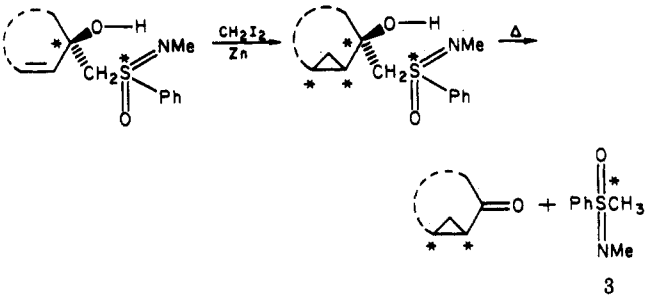


1, chrysanthemyl pyrophosphate (1**R**,3**R**)



2, rothrockene (1**R**,2**S**)

Scheme II



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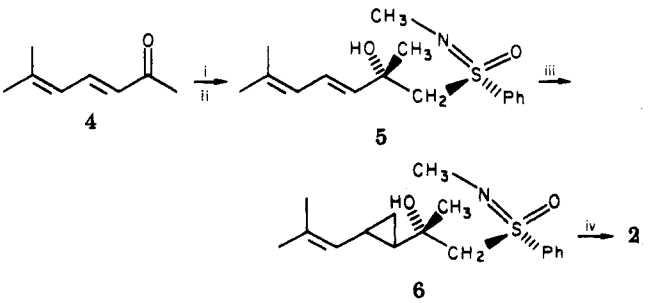
Scheme III[a]



4 **5** **6**

[a] (i) **3**, *n*-BuLi, THF, −78 °C, then aqueous NH_4Cl (96%) (7/1 major/minor diastereomer); (ii) silica gel chromatography (hexane/ethyl acetate); (iii) Zn(Ag), CH_2I_2, Et_2O, reflux, 10 min (15/1 major product/three minor products); (iv) Al(Hg), HOAc, H_2O, HOAc, THF (60%).

Addition of (-)-(*R*)-**3** to ketone **4** gave major diastereomer **5**, a gum, $[\alpha]^{25}_D$ −160.5° (*c* 1.27, $CHCl_3$), which was cyclopropanated to give **6** as the major product (76% isolated yield), $[\alpha]^{25}_D$ −67.7° (*c* 1.27, $CHCl_3$), in addition to three minor products which were incompletely characterized (Scheme III). X-ray crystallography revealed the

(1) Epstein, W. L.; Pouler, C. D. *Phytochemistry* **1972**, *12*, 737.
(2) Epstein, W. W.; Gaudioso, L. A. *J. Org. Chem.* **1982**, *47*, 175. In this paper the absolute stereochemistry illustrated by the structural formula for rothrockene was correct but an error was made in the designation. The name and descriptors for the structure should be (1*R*,2*S*)-1-(1-methylethenyl)-2-(2-methyl-1-propenyl)cyclopropane.
(3) Epstein, W. W.; Brewster, G. B., personal communication.
(4) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 4290.
(5) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A. *Org. React.* (*N.Y*) **1972**, *20*, 1. Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereye, M. *J. Chem. Res. Synop.* **1978**, 179. Corey, E. J.; Yamamoto, H.; Herron, D. K.; Achiwa, K. *J. Am. Chem. Soc.* **1970**, *92*, 6635.

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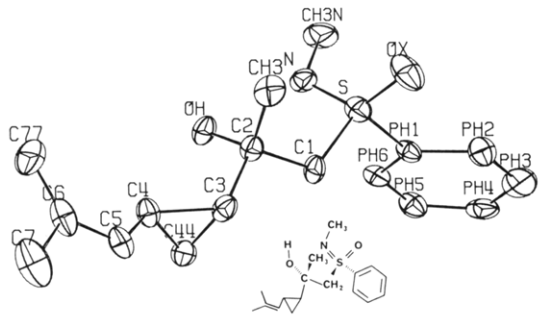

Figure 1. X-ray structure of adduct (−)-**6** prepared from (−)-(*R*)-**3**.

detailed structure of **6** as shown in Figure 1. The absolute configurations at the chiral carbons were related to the known absolute stereochemistry at sulfur.[6] Treatment of **6** with aluminum amalgam[7] gave rothrockene, $[\alpha]^{25}_D$ −65.5° (*c* 1.32, $CHCl_3$). Repetition of the sequence using (+)-(*S*)-**3** produced the enantiomer of natural rothrockene with $[\alpha]^{25}_D$ +62.5° (*c* 1.33, $CHCl_3$). The natural substance is reported to have $[\alpha]^{25}_D$ −64.8° (*c* 1.33, $CHCl_3$).

It is interesting to note the multifaceted role of sulfoximine chemistry in the above sequence. Incorporation of the β-hydroxy sulfoximine moiety allowed for resolution of a precursor, regio- and diastereoface selectivity in cyclopropanation, determination of absolute configurations based on the sulfur stereochemistry, and introduction of the final carbon–carbon double bond.

Experimental Section

***trans*-2,6-Dimethyl-1-(*N*-methylphenylsulfonimidoyl)-3,5-heptadien-2-ol (5).** A flame-dried (under argon) 100-mL flask, equipped with a magnetic stirring bar and charged with (−)-(*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (1.692 g, 10 mmol), triphenylmethane (15 mg), and dry THF (50 mL) was cooled to 0 °C with stirring. A solution of butyllithium (1.5 M in hexane) was added until an orange color persisted. After stirring at room temperature for 15 min the solution was cooled to −78 °C and *trans*-6-methyl-3,5-heptadien-2-one (1.242 g, 10 mmol) in dry THF (10 mL) was added over 5 min. After stirring for 45 min the cold reaction mixture was poured into a mixture of diethyl ether (50 mL) and saturated ammonium chloride (50 mL). The mixture was transferred to a separatory funnel and vigorously shaken; the layers were separated and the aqueous layer was extracted twice with 50-mL portions of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to provide crude **5** as a pale yellow gum (ratio of diastereomers 7.4:1). The diastereomers were separated by flash chromatography over silica gel with 3:1 hexanes/ether as eluent (96%). The faster eluting major diastereomer was obtained as a colorless gum with the following characteristics: $[\alpha]^{25}_D$ −160.5° (*c* 1.27 $CHCl_3$); IR ($CHCl_3$) 3220 (br), 3070 (w), 3035 (w), 3000 (s), 2920 (s), 1660 (m), 1588 (w), 1450 (s), 1379 (m), 1245 (s), 1147 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0–7.7 (m, 2 H), 7.7–7.4 (m, 3 H), 6.95 (br s, 1 H), 6.6 (dd, J_1 = 15 Hz, J_2 = 11 Hz, 1 H), 5.7 (d, *J* = 11 Hz, 1 H), 5.35 (d, *J* = 15 Hz, 1 H), 3.25 (ABq, J_{AB} = 14 Hz, 2 H), 2.7 (s, 3 H), 1.8 (s, 6 H), 1.63 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.78, 135.73, 135.47, 132.99, 129.36 (partially resolved, 2 C), 125.20, 124.36, 71.67, 64.84, 28.78, 28.39, 25.92, 18.32; high-resolution mass spectrum, *m*/*e* 293.1459, calcd for $C_{16}H_{23}NO_2S$, *m*/*e* 293.1449. The minor diastereomer was a colorless gum with $[\alpha]^{25}_D$ +26.5° (C 0.51, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 3220 (br), 3065 (w), 3040 (w), 2980 (s), 2930 (s), 1660 (m), 1588 (w), 1450 (s), 1379 (m), 1245 (s), 1160 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1–7.75 (m, 2 H), 7.75–7.46 (m, 3 H), 6.7 (dd, J_1 = 15 Hz, J_2 = 10 Hz, 1 H), 6.37 (br s, 1 H), 5.83 (d, *J* = 10 Hz, 1 H), 5.75 (d, *J* = 15 Hz, 1 H), 3.35 (ABq, J_{AB} = 14 Hz, 2 H), 2.64 (s, 3 H), 1.82 (s, 6 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.17, 135.34, 134.50, 132.99, 129.49, 129.17, 125.27, 124.62, 71.99, 65.23, 29.95, 28.91, 25.99, 18.32; high-resolution mass spectrum, *m*/*e* 293.1443, calcd for $C_{16}H_{23}NO_2S$, *m*/*e* 293.1449.

Utilization of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine in the above protocol provided a major diastereomer with $[\alpha]^{25}_D$ +162.1° (*c* 1.30, $CHCl_3$) and a minor diastereomer with $[\alpha]^{25}_D$ −27.3° (*c* 1.25, $CHCl_3$).

1-(*N*-Methylphenylsulfonimidoyl)-2-[*trans*-2-(2-methyl-1-propenyl)cyclopropyl]-2-propanol (6). A 100-mL three-necked flask equipped with a heating mantle and magnetic stirring bar was charged with glacial acetic acid (50 mL) and silver acetate (50 mg); the suspension was brought to boiling. The heating mantle was turned off and then 10 mesh granular zinc (5.583 g, 85.4 mol) was added all at once to the stirring hot solution. After 30 s the liquid was carefully decanted and the zinc–silver couple was washed with five 50-mL portions of anhydrous diethyl ether. Diethyl ether (40 mL) was then poured onto the coupled, a condenser and addition funnel were fitted to the flask, and the atmosphere was replaced with argon. A small crystal of iodine was added to the stirred ethereal suspension and the mixture was brought to reflux. Diiodomethane (3.4 mL, 42.7 mmol) was then added dropwise via the addition funnel. After the addition was complete the suspension was refluxed a further 15 min and then stirred at room temperature for 1 h. The major diastereomer (−)-**5** (1.253 g, 4.3 mmol) in diethyl ether (10 mL) was then added and the mixture gently refluxed. The reaction progress was carefully monitored by TLC (2:1 hexane/ethyl acetate). After 5 min the starting material was consumed and the reaction mixture was filtered through glass wool into ice-cold saturated ammonium chloride (100 mL). After vigorous shaking the layers were separated and the aqueous layers was extracted twice with 50-mL portions of diethyl ether. The combined organic extracts were washed successively with saturated aqueous ammonium chloride and saturated sodium hydrogen carbonate, then dried over $MgSO_4$, filtered, and concentrated. The crude yellow gum (15:1 ratio of desired product to three minor products) was purified by medium-pressure liquid chromatography over silica gel (15:1 hexane/ethyl acetate as eluent) to provide (−)-**6** as a white, crystalline solid (76%): mp 62–63 °C; $[\alpha]^{25}_D$ −67.7° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 3240 (br), 3080 (w), 3040 (w), 3010 (s), 2935 (s), 1607 (w), 1590 (w), 1452 (s), 1380 (m), 1250 (s), 1156 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1–7.8 (m, 2 H), 7.8–7.5 (m, 3 H), 6.63 (br s, 1 H), 4.58 (d, *J* = 8.5 Hz, 1 H), 3.25 (ABq, J_{AB} = 14 Hz, 2 H), 2.65 (s, 3 H), 1.75 (s, 3 H), 1.70 (s, 6 H), 1.17–0.10 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 138.92, 133.14, 130.60, 129.63, 128.91, 127.35, 70.04, 64.78, 31.84, 28.72, 27.03, 25.47, 18.13, 13.06, 9.82. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20. Found: C, 66.26; H, 7.99.

Use of the major diastereomer (+)-**5** derived from (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine yielded (+)-**6** with $[\alpha]^{25}_D$ +65.5° (*c* 1.13, $CHCl_3$).

(−)-(1*R*,2*S*)-*trans*-1-(1-Methylethenyl)-2-(2-methyl-1-propenyl)cyclopropane (Rothrockene) (2). The β-hydroxy sulfoximine (−)-**6** (0.872 g, 2.8 mmol) was dissolved in tetrahydrofuran (20 mL), and acetic acid (10 mL) and water (10 mL) were then added. Granular aluminum (60 mesh, 1.225 g, 45.4 mol), which had been stirred for 2 min with 2% aqueous mercuric chloride (30 mL), filtered, and washed successively with water and ethanol, was added to the reaction mixture. Stirring was continued until TLC (6:1 hexane/ethyl acetate) showed no starting material (30 min). The mixture was filtered through Celite and washed with tetrahydrofuran. The filtrate was diluted with water (100 mL) and extracted three times with 100-mL portions of pentane. The pentane extracts were washed twice with 25-mL portions of 20% aqueous sodium hydroxide and once with water (25 mL) and dried ($MgSO_4$). The pentane was removed in vacuo without heating and the crude rothrockene was flash chromatographed over silica gel with pentane as the eluent to provide (−)-**2** as a colorless oil (60%): $[\alpha]^{25}_D$ −65.5° (*c* 1.32, $CHCl_3$; IR ($CHCl_3$) 3080 (m), 3030 (w), 2970 (s), 2920 (s), 1645 (m), 1635 (m), 1450 (s), 1375 (s), 880 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 4.65 (m, 3 H), 1.74 (s, 3 H), 1.70 (s, 6 H), 1.6–0.43 (m, 4 H); ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (m, 3 H), 1.72 (s, 3 H), 1.67 (s, 6 H), 1.52 (m, 1 H), 1.28 (m, 1 H), 0.88 (m, 1 H), 0.59 (m, 1 H). The spectral data obtained for synthetic (−)-**2** are in accord with the data published for the naturally occuring substance.

(6) Johnson, C. R.; Jonsson, E. U.; Wambsgans, A. *J. Org. Chem.* **1979**, *44*, 2061.
(7) Johnson, C. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 3602.

Reductive elimination of (+)-6 using the same protocol provided unnatural (+)-2 with $[\alpha]^{25}_D$ +62.5° (c 1.33, $CHCl_3$).

X-ray Structural Determination of (-)-6. The compound crystallizes in the monoclinic space group C2 with a = 22.648 (6) Å, b = 6.619 (2) Å, c = 12.638 (5) Å, β = 104.92 (3), V = 1816 (1), Z = 4, density = 1.12 (1) (obs), 1.124 (calcd). Data were collected with Mo K radiation, scan rate = 2.0°/min, scan width = 2.0° plus dispersion, background counts = 30 s, θ-2θ technique. Of the 1358 data examined from 0°-45°, 918 were considered observed. The structure was solved by a combination of MULTAN 78 and Fourier analyses. Full-matrix anisotropic refinement (without hydrogen atoms) led to discrepancy factors of R = 0.079 and w_R = 0.095. Analysis of thermal parameters, bond distances, hydrogen bonding, and alternate refinements led to unambiguous assignment of the methyl and hydroxide groups. Details on the programs and techniques used are available.[8]

Acknowledgment. This work was supported by a grant from the National Science Foundation.

Registry No. (-)-2, 80082-35-5; (+)-2, 90580-44-2; (-)-3, 80482-67-3; (+)-3, 33993-53-2; 4, 16647-04-4; (-)-5, 90433-70-8; (+)-5, 90433-71-9; (-)-6, 90433-72-0; (+)-6, 90528-05-5.

Supplementary Material Available: Bond angles, bond distances, and final atomic parameters (3 pages). Ordering information is given on any current masthead page.

(8) Corey, E. R.; Corey, J. Y.; Glick, M. D. *J. Organomet. Chem.* **1977**, *129*, 17.

Essential Oil Constituents of *Artemisia tridentata rothrockii*. The Isolation and Characterization of Two New Irregular Monoterpenes[1]

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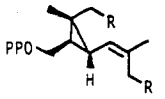
The neutral pentane extract of the leaves and flower heads of *Artemisia tridentata rothrockii* was found to contain two new non-head-to-tail monoterpenes, rothrockene (8) and neolyratol (19), in addition to several previously characterized monoterpenes. The absolute stereochemical structures of these compounds have been established by chemical and spectral means.

We have been interested in the biosynthesis of non-head-to-tail monoterpenes primarily as a model for the study of the formation of the biologically important steroid precursor squalene in mammals.[2] The biogenesis of these irregular terpenes presumably involves ionization and subsequent rearrangement of the structurally analogous cyclopropyl intermediates, chrysanthemyl pyrophosphate (**1a**) and presqualene pyrophosphate (**1b**).[2,3] As a result



1a: R=H
2b: R=geranyl

of this analogy, three additional irregular C_{10} skeketal systems **2**, **3**, and **4**, might occur in addition to the known artemisyl **5**, chrysanthemyl **6**, and santolinyl **7** systems (Scheme I). The isolation of monoterpenes possessing these carbons skeletons would provide support for the proposed biosynthetic sequence and for the idea that plant enzyme systems might act as simple models of mammalian squalene synthetase. Furthermore, since irregular monoterpenes with artemisyl, chrysanthemyl, and santolinyl skeletons have thus far been identified only in plants of the Anthemideae tribe of the Asteraceae family, this class of compounds may function as a useful taxonomic tool as well.

To these ends, we have been screening plants of the Asteraceae for non-head-to-tail monoterpenes. In a recent communication we described the isolation and structure elucidation of a novel irregular monoterpene hydrocarbon possessing a heretofore unknown skeletal system from the sagebrush, *Artemisia tridentata rothrockii*.[4,5] We now

Scheme I

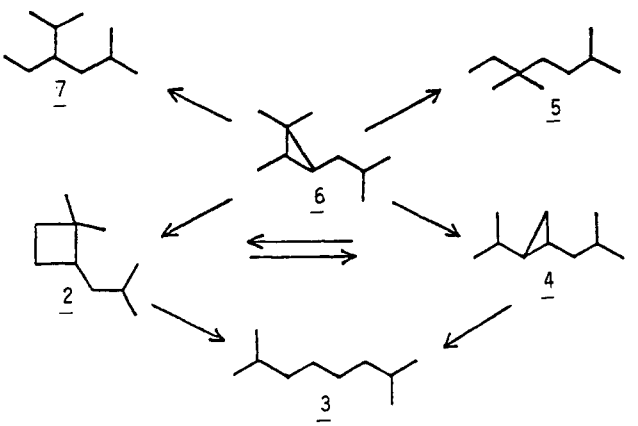


Table I. GC/MS Survey—Monoterpenes Found in *Artemisia tridentata rothrockii*[6]

compd	composition, %	compd	composition, %
artemiseole	25.2	1,8-cineole	5.3
unknown	13.8	p-cymene	5.0
santolina triene	12.8	camphor	2.9
camphene	12.1	β-pinene	1.8
α-pinene	11.2	limonene	1.5
oxidosantolina triene	7.9	artemisia alcohol	0.4

(1) Research supported by NIH Grants GM 20196 and GM 26245.
(2) Epstein, W. W.; Poulter, C. D. *Phytochemistry* **1973**, *12*, 737.
(3) Poulter, C. D.; Muscio, O. J.; Goodfellow, R. J. *Biochemistry* **1974**, *13*, 1530.
(4) Epstein, W. W.; Gaudioso, L. A. *J. Org. Chem.* **1982**, *47*, 175.

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