Anti Selective Spirocarbomercuration: Synthesis and Stereochemistry of the Spirobicyclic Sesquiterpenes Spirojatamol and Erythrodiene

He Huang and Craig J. Forsyth*

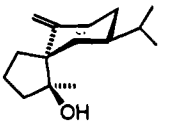
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455-0431

Received December 22, 1994[⊗]

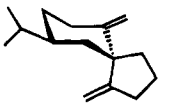
The stereoselectivity of mercuric salt-induced spirocarbannulation reactions of substituted and unsubstituted 2-(4-pentynyl)-1-[(trimethylsilyl)oxy]cyclohexenes has been examined. This intramolecular alkyne carbomercuration reaction has been applied to the first enantioselective syntheses of the natural products erythrodiene and spirojatamol. Treatment of 2-(4-pentynyl)-1-[(trimethylsilyl)oxy]cyclohexene with $HgCl_2$ gave 7(*E*)-mercuriomethylenespiro[4.5]decan-6-one, the product of anti selective carbomercuration. Similar intramolecular carbomercuration of (*S*)-4-isopropyl-2-(4-pentynyl)-1-[(trimethylsilyl)oxy]cyclohexene, derived from (*S*)-(−)-perillyl alcohol, gave diastereomeric axial and equatorial spirocarbannulation products in a 7:3 ratio and high yield. Both *C*-vinylation products, (1*S* and 1*R*, 5*S*,7*E*)-5-isopropyl-7-mercuriomethylenespiro[5.4]decan-2-one), bear (*E*)-exocyclic vinyl mercurials. The major (1*S*,5*S*)-*C*-vinylation product was converted into both (−)-erythrodiene and (−)-spirojatamol in one and three steps, respectively. Thus, (−)-erythrodiene, a spirobicyclic sesquiterpene hydrocarbon from the Caribbean gorgonian coral *Erythropodium caribaeorum*, was synthesized from (*S*)-(−)-perillyl alcohol in 10 steps and approximately 35% overall yield using the mercuric salt-induced spirocarbannulation reaction as the key step. (−)-Spirojatamol, the enantiomer of the natural product isolated from the Indian plant *Nardostachys jatamansi*, was similarly prepared from (*S*)-(−)-perillyl alcohol in 12 steps and ca. 20% overall yield. This work indicates that the absolute configuration of (−)-erythrodiene ((1*S*,5*S*)-(−)-5-isopropyl-2,7-dimethylenespiro[5.4]decane) is enantiomeric to the carbon skeleton of (1*S*,5*R*,8*S*)-(+)-spirojatamol, the only other naturally occurring sesquiterpene known to posses the 5-isopropyl-2-methylenespiro[5.4]decane skeleton.

Introduction

The Indian plant *Nardostachys jatamansi* has been used extensively in traditional medicine for the treatment of numerous disorders including epilepsy, hysteria, and convulsions.[1] Phytochemical investigations of this plant led to the isolation of spirojatamol (**1**), a novel sesquiterpene bearing an unprecedented spirobicyclic skeleton.[2] A second natural product sharing the spirojatamane ring system, (−)-erythrodiene (**2**), was isolated recently from the Caribbean gorgonian *Erythropodium caribaeorum*.[3] The carbon skeletons of these natural products share the same relative stereochemistry, but **1** differs from **2** by hydration of the exocyclic alkene on the five-membered ring. The absolute configuration of naturally occurring **1** was assigned previously on the basis of circular dichroism analysis of a derivative,[2] but the absolute configuration of **2** had not been determined. We reported recently a synthesis of (±)-**2** based upon an intramolecular carbomercuration reaction for the formation of the unique spirobicyclic spirojatamane system.[4] Here, we describe the enantioselective syntheses of (−)-**1** and (−)-**2** and experiments that define the stereoselectivity of the central spirocarbannulation process. Interestingly, this work indicates that the similar carbon skeletons of the terrestrial and marine natural products are enantiomeric to one another, with the absolute configurations shown.



1
(+)-Spirojatamol



2
(-)-Erythrodiene

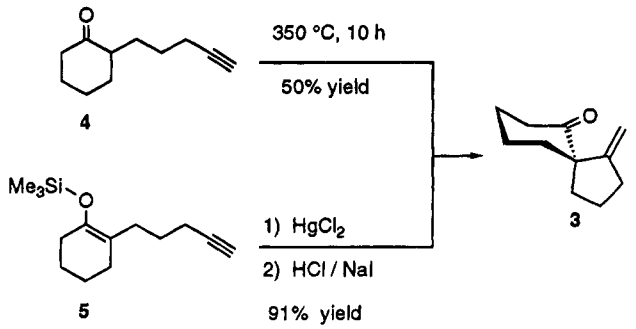
The synthesis of the spirojatamane skeleton relies upon an efficient mercuric salt-induced spirocarbannulation process.[4] In 1973, Conia and co-workers reported that the 7-methylenespiro[4.5]decan-2-one system (**3**) could be obtained in 50% yield by thermal cyclization (350 °C, 10 h) of 2-(4-pentynyl)-cyclohexanone (**4**).[5] It was subsequently determined that similar ene-type reaction products could be obtained more efficiently by treating alkynyl tethered silyl enol ethers with mercuric salts.[6–8] In particular, **3** was obtained in 91% yield by treating the trimethylsilyl enol ether **5** with mercuric chloride, followed by protio-demercuration.[6] This simple modification of the thermal Conia ene reaction conveniently avoids the necessity of inducing the rate-limiting enolization thermally and the problems associated with such conditions, including endocyclic migration of the alkene.

We recognized that spirocarbannulation using a 4-isopropyl-2-(4-pentynyl)-cyclohexanone derivative under similar conditions could provide access to the isopropyl

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1995.

(1) Nadkarni, A. K. In *The Indian Materia Medica*; 3rd ed.; New Delhi, 1954; Vol. 1, p 840.
(2) Bagchi, A.; Oshima, Y.; Hikino, H. *Tetrahedron* **1990**, *46*, 1523–1530.
(3) Pathirana, C.; Fenical, W.; Corcoran, E.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 3371–3372.
(4) Huang, H.; Forsyth, C. J. *Tetrahedron Lett.* **1993**, *34*, 7889–7890.
(5) Mandville, G.; Leyendecker, F.; Conia, J.-M. *Bull. Soc. Chim. Fr.* **1973**, 963–971.
(6) Boaventura, M. A.; Drouin, J. *Bull. Soc. Chim. Fr.* **1987**, 1015–1026.
(7) Drouin, J.; Boaventura, M. A.; Conia, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1726–1729.
(8) Boaventura, M. A.; Drouin, J.; Theobald, F.; Rodier, N. *Bull. Soc. Chim. Fr.* **1987**, 1006–1014.

0022-3263/95/1960-2773$09.00/0



substituted spirojatamane system if sufficient stereocontrol could be achieved. The sterically demanding isopropyl substituent would likely impose conformational constraints upon an alkynyl tethered cyclohexanone derivative in the spirocarbomercuration process. The extent to which such a conformational bias would effect the configuration of the newly formed quaternary center would reflect the mechanism of the intramolecular carbomercuration process. Several alternative mechanistic hypotheses had been offered for this type of *C*-vinylation reaction. Drouin and co-workers reported that intramolecular carbomercuration reactions leading to simple monocyclic products resulted exclusively in (*Z*)-exocyclic vinyl mercurials, with the mercuric salt residing syn to the carbonyl group.[7,8] These results were postulated to result from either a four-centered addition of a transient α-keto mercurial to the tethered alkyne, or an unstable *O*-mercury enolate undergoing an ene-type reaction analogous to the thermal Conia reaction. In contrast, intramolecular carbomercuration leading to the *cis*-6-oxobicyclo[3.3.0]oct-3-en-2-one ring system was found to occur with exclusive anti selectivity, consistent with anti addition of the enolate α-carbon to the mercuric activated, tethered alkyne.[9] Given literature precedents for both syn and anti selective intramolecular carbomercuration reactions, and at least three separate mechanistic hypotheses for this process, the mechanism and stereoselectivity of spirocarbomercuration were uncertain at the outset of this investigation. Thus, in addition to describing the enantioselective syntheses and stereochemical relationship between **1** and **2**, this work also illuminates the mechanism of the central spirocarbomercuration process.

Results and Discussion

Stereoselectivity of Spirocarbomercuration. The proposal that intramolecular carbomercuration occurs via syn addition of a transient α-keto mercurial to the tethered alkyne[7,8] leads to a predictable stereochemical result in the cyclization of 2-(4-pentynyl)cyclohexanone derivatives. If a chairlike cyclohexanone bearing an α-keto mercurial were involved, then axial *C*-vinylation would lead to a sterically encumbered vinyl mercurial (Scheme 1). Thus, equatorial *C*-vinylation would be favored. In the parent cyclohexanone system **4**, equatorial vs axial syn *C*-vinylation products would be indistinguishable due to a simple chair–chair ring flip. However, with an equatoriallike isopropyl substituent anchoring the conformation of the cyclohexanone ring, equatorial *C*-vinylation products expected to predominate via an α-keto mercurial would be observable.

Assembly of the spirojatamane ring system by annulation of the five-membered ring upon a chair-like cyclohexanone bearing an equatorial isopropyl substituent would require axial selective *C*-vinylation. Whereas spirocarbomercuration occurring through an α-keto mercurial might favor equatorial *C*-vinylation, we postulated that axial selectivity would be associated with a pathway involving the anti addition of a chairlike cyclohexanone enolate and a mercuric salt to the tethered alkyne (Scheme 2). Anti selective axial *C*-vinylation of a chairlike cyclohexanone enolate would be favored over equatorial vinylation due to enhanced enolate bond overlap,[10] and avoidance of a 1,3-syn-axial interaction between the *i*-Pr substituent and a cyclohexyl ring proton. The axial vs equatorial *C*-vinylation selectivity of intramolecular carbomercuration occurring through boat-like transition states, or a six-membered transition state involving an *O*-mercury enolate would be more difficult to predict.

When **5**[6] was treated with $HgCl_2$,[9] an unstable vinyl mercurial product (**6**) was obtained as an oil (Scheme 3). Attempts to chromatographically purify **6** led to degradation, therefore it was subjected to either protio-, or deuteriodemercuration without isolation. Demercuration conditions that do not cause alkene migration[7] and which retain configuration[11] (HCl/H_2O or DCl/D_2O, NaI) were used. The corresponding alkene products **3** and **7** were thus obtained in good yields after workup and chromatography. The chemical shifts of the syn and anti alkene protons were assigned on the basis of NOE experiments. The syn vinyl proton of **3** (δ 4.83, $CDCl_3$) is shielded relative to the anti proton (δ 5.09, $CDCl_3$) due to its proximity to the shielding region of the carbonyl group. Comparison of the ^1H NMR spectra of **3** and **7** clearly indicated that the deuterium resides in the (*E*)-alkene position in **7**.[11] Hence, the spirocarbomercuration product **6** is an anti vinyl mercurial.

That the parent α-substituted cyclohexanone enol ether gave only the anti vinyl mercurial spirocarbomercuration product supported the likelihood that this process might also favor axial *C*-vinylation of an isopropyl substituted cyclohexanone derivative. The extent to which the stereogenicity of an isopropyl substituent on the cyclohexyl ring could be used to establish the relative configuration of the newly formed quaternary center was determined in the syntheses of **1** and **2**.

Synthesis and Stereochemistry of Spirojatamol and Erythrodiene. The syntheses of (−)-**1** and (−)-**2** began with the partial hydrogenation of the monoterpene (*S*)-perillyl alcohol to give the known cyclohexene **8**[12] (Scheme 4). The remaining alkene allowed regioselective installation of an alkynyl side chain on the cyclohexyl ring. Alcohol **8** was converted into the *p*-methoxybenzyl (PMB) ether **9**, and the alkene was epoxidized with MCPBA to give a 1:1 ratio of diastereomeric epoxides

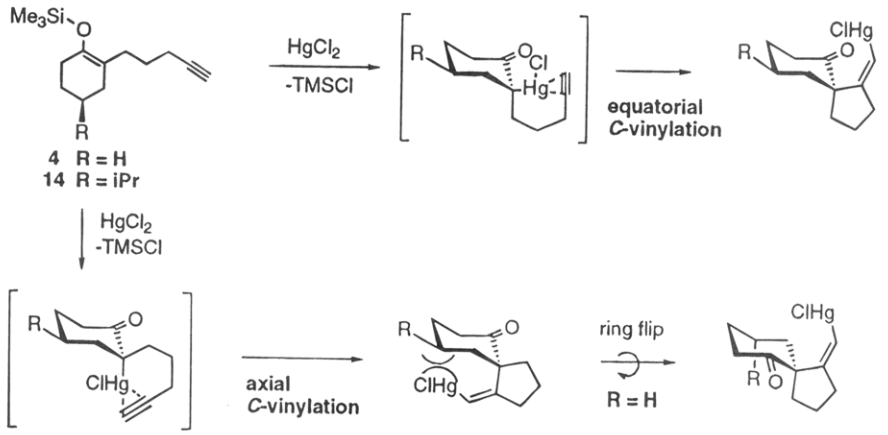
(9) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3497–3505.

(10) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.

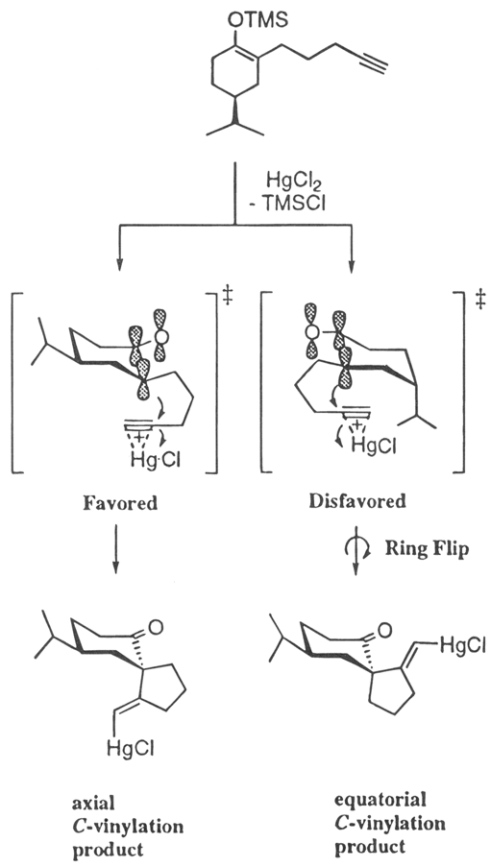
(11) Because the extent and regiochemistry of deuterium incorporation was assayed by comparision and integration of the ^1H NMR spectra of **3**, **7**, **19**, and **20**, and adventitous protonation may compete to some extent with deuteration, the practical limit of detection is ca. 10%. Therefore, upwards of ca. 10% of the deuterated product could contain the (*Z*)-isomer, although we found no evidence for such a regioisomer.

(12) Human, J. P. E.; Macbeth, A. K.; Rodda, H. J. *J. Chem. Soc.* **1949**, 350–352.

Scheme 1

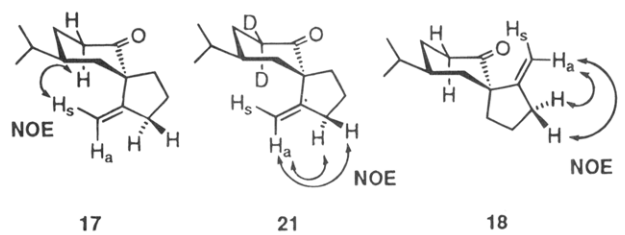


Scheme 2



10.[13] Copper-assisted opening[14] of the epoxides was effected by treatment with CuCN (1.0 equiv) and the Grignard reagent prepared from 1-(trimethylsilyl)-5-bromo-1-pentyne (2.5 equiv) and activated[15] Mg. Diastereomeric alkylated products **11** were obtained in 92% combined yield from **10**. The PMB and trimethylsilyl groups were removed by sequential DDQ treatment[16] and methanolysis to give diols **12** in 83% yield from **11**. Oxidative cleavage with $NaIO_4$ then gave the desired (4*S*)-2,4-disubstituted cyclohexanone **13** as an approximate 1:1 mixture of α-keto epimers and in ca. 70% overall yield from (*S*)-perillyl alcohol.

Ketone **13** was converted efficiently into the thermodynamic trimethylsilyl enol ether **14**.[17] Addition of **14** to a stirred suspension of $HgCl_2$ (1.1 equiv) and HMDS (0.2 equiv) in dry CH_2Cl_2 at room temperature[7] gave spirocarbannulation products **15** and **16** in a 7:3 ratio and high yield (Scheme 5). As with the parent cyclohexanone derivative **5**, the unstable vinylmercurials could be isolated, but it was more convenient to convert them in situ into the corresponding protio-demercuration products **17** and **18**. After workup and chromatography, the one-pot carbomercuration−demercuration sequence gave the axial *C*-vinylation product **17** in 65% isolated yield and the equatorial diastereomer **18** in 29% yield. Stereospecific replacement of the mercury with deuterium[7,11] similarly gave deuterated alkenes **19** and **20**.[18] The α-keto protons of **17** were exchanged with deuterium (CH_3OD/K_2CO_3) to give the dideuterio derivative **21**, thereby eliminating the ^1H NMR spectral overlap with the allylic protons. NMR analyses of **17**−**21** confirmed the relative configurations at the spiro junctions and indicated that the alkene configurations of both axial and equatorial spirocarbannulation products **15**, **16**, **19**, and **20** are (*E*).[19] The indicated NOEs observed for **17**, **18**, and **21** were used to unambiguously assign the syn and anti alkene proton resonances.



Attempts to enhance the ratio of axial to equatorial *C*-vinylation products, including variations in reaction

(13) Compounds **10**−**13** were used in the synthetic sequence as ca. 1:1 mixtures of diastereomers arising from the epoxidation of **9**. That these intermediates are diastereomeric mixtures is inconsequential because they converge to a single homochiral diastereomer at the stage of intermediate **9**.

(14) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305−2307.

(15) Baker, K. V.; Brown, J. M.; Hughe, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698−703.

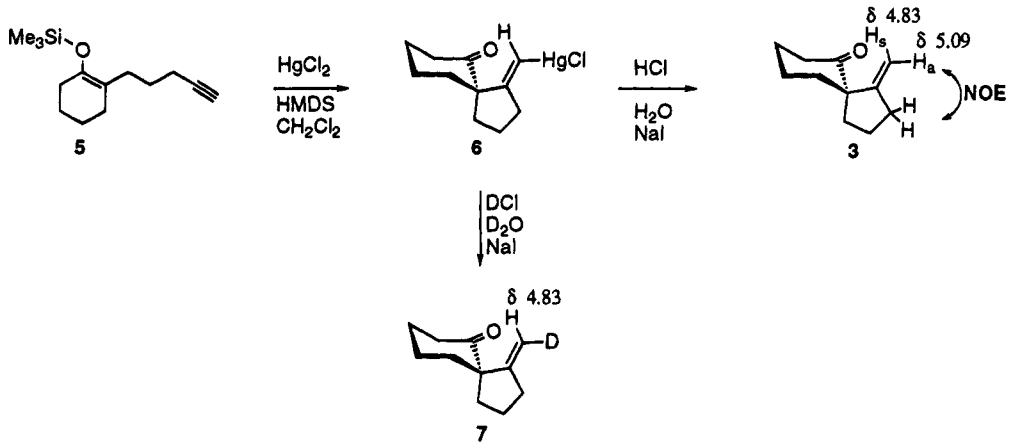
(16) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O.; Fukyama, T. *Tetrahedron* **1986**, *42*, 3021−3028.

(17) Cazeau, P.; Moulines, F.; Laprote, D.; Duboudin, F. *J. Organomet. Chem.* **1980**, *201*, C9-C13.

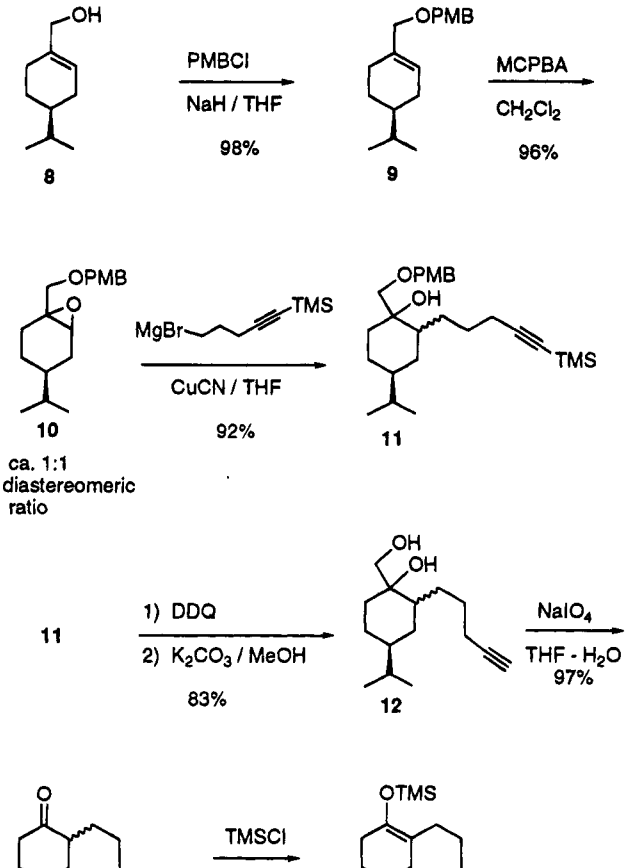
(18) Compounds **19** and **20** were prepared from (±)-**14** (compound **6** in ref 4) and thus are not optically active.

(19) The (*E*)- and (*Z*)-vinyl proton resonances of **17** [δ 5.02 (H_E) and δ 5.11 (H_Z), $CDCl_3$] and **18** [δ 5.13 (H_E) and δ 4.79 (H_Z)] were assigned on the basis of observed unique NOEs. The resonance at δ 5.02 in **19** was reduced to <5% of the intensity of the δ 5.11 resonance due to stereospecific deuteriodemercuration of the (*E*)-vinyl mercurial **15**. Similarly, the resonance at δ 5.13 in **20** was reduced <5% of the intensity of the δ 4.79 peak.

Scheme 3



Scheme 4



temperature, mercuric salt counterion, silyl enol ether silicon substitution, and solvent were not fruitful. Combined, these results are consistent with spirocarbannulation occurring preferentially through a relatively late transition state and involving a chairlike cyclohexanone enolate adding in a trans fashion to the tethered, metal-activated alkyne, as illustrated in Scheme 2.

Wittig olefination of the major spirocarbannulation-demercuration product **17** gave (−)-**2** as a colorless oil in 74% yield after purification by preparative TLC. Characterization data obtained for synthetic (*S*,*S*)-(−)-**2** matched those of the natural product (LREIMS, HREIMS, ^{1}H NMR, ^{13}C NMR, and specific rotation),[20] thereby establishing the absolute configuration of (−)-**2**. Hence, (−)-erythrodiene was synthesized from (*S*)-(−)-perillyl alcohol in 10 steps and approximately 35% overall yield.

In addition to methylenation of the carbonyl, conversion of spirocarbannulation product **17** into spirojatamol required hydration of the alkene. Oxymercuration−demercuration was initially attempted. Treatment with $Hg(OAc)_2$ in H_2O−THF completely consumed **17** (TLC); however, all attempts at reductive demercuration (e.g. $NaBH_4$/NaOH) resulted in recovery of only an alkene. The rapidly formed oxymercuration product apparently underwent complete elimination in situ.[21] Alternatively, we found that enone **17** could be converted into (−)-**1** in 42% overall yield by a simple three-step sequence initiated by alkene epoxidation. After a brief survey of metal-based epoxidation systems,[22] we found that simple MCPBA treatment of **17** gave the best results in providing a 1:1 ratio of chromatographically separable diastereomeric epoxides in 90% combined yield. When subjected to Wittig methylenation, the desired epoxide diastereomer **22** gave alkene **23** in 93% yield. Regioselective lithium aluminum hydride opening of the epoxide provided (−)-**1** in essentially quantitative yield. Characterization data obtained for (−)-**1** matched those reported for the natural product,[2] except that the sign of the specific rotation was opposite.[23] Thus, (−)-**1** was prepared in 12 steps and ca. 20% overall yield from (*S*)-perillyl alcohol. This synthesis confirms the assignment of absolute configuration made previously for naturally occurring (+)-**1**.[2] It is interesting to note that (+)-**1** and (−)-**2**, isolated from widely diverse organisms, have enantiomeric carbon skeletons.

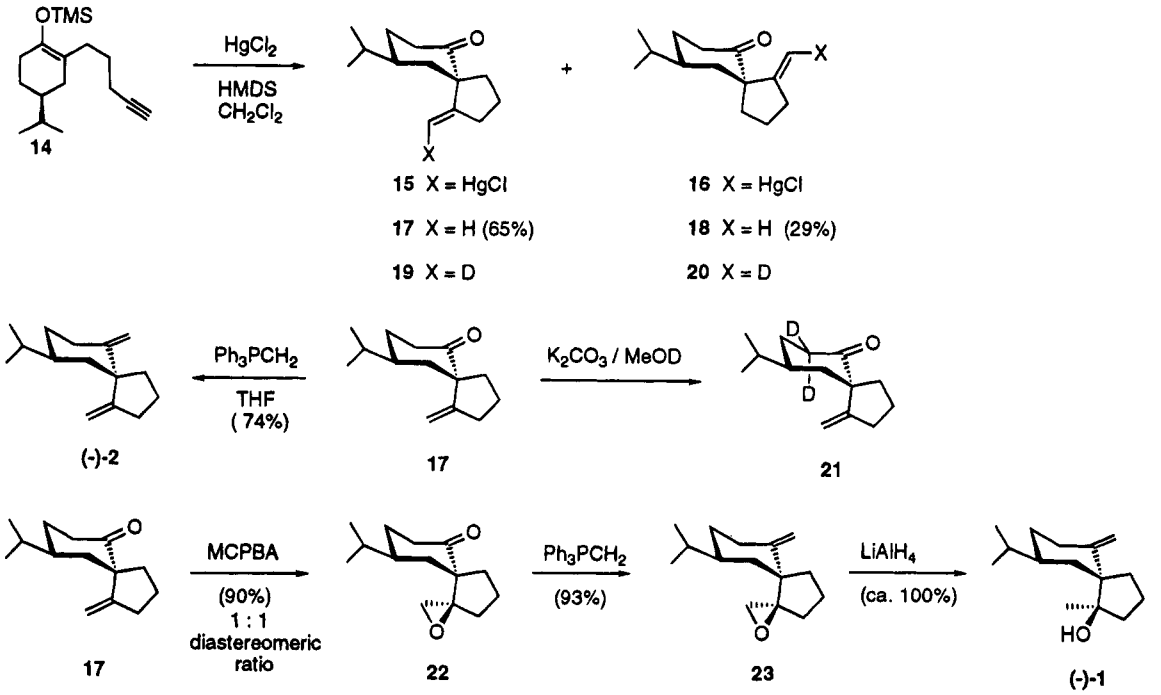
(20) The specific rotation of synthetic **2** is $[\alpha]^{23}_D$ −118° (*c* 0.60, $CHCl_3$). We have reexamined the specific rotation of naturally occurring **2** and have found it to be $[\alpha]^{23}_D$ −121° (±11°) (*c* 0.30, $CHCl_3$), rather than the originally reported (ref 3) value of $[\alpha]^{23}_D$ −30.8° (*c* 0.24, $CHCl_3$). The ^{13}C NMR resonance reported at δ 109.9 in ref 3 is a typographical error and actually occurs at δ 105.9. We thank Prof. Fenical for providing these data and a sample of naturally occurring **2** for chiroptical and spectral comparison.

(21) The propensity for oxymercuration products to eliminate to the starting olefins is a common problem. For a brief discussion of several alternative demercuration conditions designed to alleviate this problem see: Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863−870.

(22) We attempted epoxidation of **12** using *t*-BuOOH and $Mo(CO)_6$ or $W(CO)_6$ [Sheldon, R. A.; Van Doorn, J. A. *J. Catalysis* **1973**, *31*, 427−437], and (*R*,*R*)- and (*S*,*S*)-Jacobsen catalyst systems [Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801−2803], but obtained unsatisfactory results.

(23) The specific rotation of synthetic **1** is: $[\alpha]_D^{26}$ −18° (*c* 0.38, $CHCl_3$). That of the isolated natural product **1** is reported (ref 2) to be: $[\alpha]_D$ +18.0° (*c* 4.20, $CHCl_3$).

Scheme 5



Conclusion

This work features a stereoselective spirocarbannulation reaction of an alkynyl-tethered cyclohexanone enol ether for the enantioselective construction of the unique spirobicyclic spirojatamane carbon skeleton of erythrodiene and spirojatamol. We have determined that the key spirocarbannulation reaction occurs through an anti selective intramolecular carbomercuration process that is distinct from the syn selective pathways proposed previously[6,7] for similar *C*-vinylation reactions. Simple elaboration of the spirocarbannulation product **17** gave both (−)-erythrodiene and (−)-spirojatamol. This synthesis allows the assignment of absolute configuration to (−)-erythrodiene and indicates that the similar isopropyl-substituted spirobicyclic skeletons of the terrestrial and marine natural products are enantiomeric to one another. Further, the central spirocarbomercuration reaction may offer a general method for the stereoselective formation of quaternary centers using conformationally or sterically biased cycloalkanone derivatives. We are continuing to explore the synthetic utility of these remarkably mild and efficient intramolecular carbomercuration reactions.

Experimental Section

General Procedures. Unless otherwise noted, all reactions were carried out under an argon or nitrogen atmosphere in oven dried glassware using standard syringe, cannula, and septa techniques.

Diethyl ether, tetrahydrofuran, and toluene were distilled under nitrogen from Na/benzophenone ketyl. Acetonitrile, diethylisopropylamine, hexamethyldisilazane, methylene chloride, 2-propanol, pyridine, triethylamine, and trimethylsilyl chloride were distilled under nitrogen from CaH_2. Other solvents were used as received. CuCN, $HgCl_2$, K_2CO_3, LiBr, NaI, tetrabutylammonium iodide, and triphenylmethylphosphonium bromide were dried under vacuum (0.3 Torr, ca. 6−12 h) immediately prior to use. DCl (20 wt % soln in D_2O, 99.5 atom % D) was purchased from Aldrich Chemical Co., Milwaukee, WI. Flash chromatography was performed using Baker Flash silica gel 60 (40 μm) or ICN Silitech 60 (63−200 μm) and the solvent systems indicated. Analytical and preparative TLC was performed with 0.25 mm or 0.50 mm EM silica gel 60 F_{254} plates, respectively. NMR spectra were obtained in $CDCl_3$ and are referenced to residual $CHCl_3$ at 7.25 ppm (^1H) and 77.0 ppm (^{13}C). Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

7-Methylenespiro[5.4]decan-2-one (3). This compound was prepared as previously described.[6] ^1H NMR (300 MHz): δ 5.09 (s, 1H), 4.83 (s, 1H), 2.44 (m, 4H, allylic and α-keto protons), 2.10 (m, 1H), 1.93−1.56 (m, 9H). NOE (500 MHz): irradiation of the broad envelope centered at δ 2.44 (allylic and α-keto protons) enhanced the (*anti* vinyl proton) resonance at δ 5.09, but not the (*syn* vinyl proton) resonance at δ 4.83.

7-(*E*-Deuteriomethylene)spiro[5.4]decan-2-one (7). To a solution of 1-[(trimethylsilyl)oxy]-2-(4-pentynyl)-1-cyclohexene[6] (**5**, 118 mg, 500 μmol) and HMDS (21 μL, 100 μmol) in CH_2Cl_2 (5 mL) was added $HgCl_2$ (150 mg, 0.66 mmol) at rt. The resulting mixture was stirred for 30 min, and then cooled to 0 °C before a 20% solution of DCl in D_2O (190 μL, 1.00 mmol), NaI (225 mg, 1.50 mmol), and THF (1 mL) were added. The resulting mixture was stirred for 1 h, solid $NaHCO_3$ (250 mg) was added, and the mixture stirred for an additional 10 min. The mixture was filtered and the filtrate concentrated and purified by column chromatography (25 g SiO_2, hexanes−ethyl acetate, 20:1) to give **7** as an oil (70 mg, 0.42 mmol, 85%). IR (neat): 1710, 1450 cm^{-1}. ^1H NMR (300 MHz): δ 5.09 (s, < 0.10H), 4.83 (s, 1H), 2.44 (m, 4H, allylic and α-keto protons), 2.10 (m, 1H), 1.93−1.56 (m, 9H). ^{13}C NMR (50 MHz): δ 212.9, 154.9, 107.3, 60.5 (C), 39.2, 38.5, 38.1, 33.9, 26.7, 22.8, 22.3. HRMS calcd for $C_{11}H_{15}DO$: 165.1264, found: (M + H^+) at 166.1352.

(4*S*)-(−)-4-Isopropyl-1-[[(4-methoxyphenyl)methoxy]methyl]-1-cyclohexene (9). To a solution of (*S*)-4-isopropyl-1-cyclohexen-1-methanol (7.71 g, 50.0 mmol) in THF (100 mL) at 0 °C under argon was added NaH (60% dispersion in mineral oil, 2.40 g, 60 mmol), and the resulting mixture was stirred for 1 h. Tetrabutylammonium iodide (1.85 g, 5 mmol) and (4-methoxyphenyl)methyl chloride (11.2 g, 70 mmol) were added, and the mixture was stirred for 14 h. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with ethyl acetate (5 × 30 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation, and the residue was purified by column chromatography (150 g SiO_2, hexanes−ethyl acetate, 5:1) to give **9** (13.44 g, 49.0

mmol, 98%) as a colorless oil: $[\alpha]^{23}_D$ −47.7° (*c* 0.94, $CHCl_3$). IR (neat): 1700, 1600, 1510, 1460 cm^{-1}. ^1H NMR (300 MHz): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.68 (s, 1H), 4.38 (s, 2H), 3.85 (s, 2H), 3.81 (s, 3H), 2.08 (m, 3H), 1.78 (m, 2H), 1.78 (m, 1H), 1.22 (m, 2H), 0.89 (d, *J* = 3.6 Hz, 3H), 0.87 (d, *J* = 3.6 Hz, 3H). ^{13}C NMR (50 MHz): δ 159.3, 135.0, 130.9, 129.4(2C), 125.1, 113.9(2C), 74.6, 71.4, 55.4, 40.3, 32.4, 28.9, 26.9, 26.3, 20.1, 19.8. HRMS calcd for $C_{18}H_{26}O_2$: 274.1933, found: 274.1935. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.85; H, 9.56. Found: C, 78.61; H, 9.43.

(4*S*)-(−)-4-Isopropyl-1-[[(4-methoxyphenyl)methoxy]-methyl]-l-cyclohexene oxides (10). To a solution of **9** (500 mg, 1.82 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added portionwise *m*-chloroperbenzoic acid (50−60%, 552 mg). The reaction was monitored carefully by TLC; upon complete disappearance of starting material the reaction mixture was directly filtered though a column of silica gel (20 g) with CH_2Cl_2. Evaporation of the filtrate gave **10** as a mixture of epoxide diastereomers (508 mg, 1.75 mmol, 96%): $[\alpha]^{28}_D$ −26.0° (*c* 1.04, $CHCl_3$). IR (neat): 1610, 1580, 1510, 1460 cm^{-1}. ^1H NMR (300 MHz): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87(d, *J* = 8.4 Hz, 2H), 4.47 (m, 2H), 3.78 (s, 3H), 3.46 (m, 2H), 3.08 (m, 1H), 2.12 (m, 2H), 1.72 (m, 1H), 1.40 (m, 4H), 1.10 (m, 1H), 0.83 (m, 6H). HRMS calcd for $C_{18}H_{26}O_3$: 290.1882, found: 290.1881.

(4S)-(−)-4-Isopropyl-2-[5-(trimethylsilyl)-4-pentynyl]-1-[[(4-methoxyphenyl)methoxy]methyl]-1-cyclohexanol (11). Mg turnings (4.86 g, 200 mmol) were dry-stirred in a 50 mL round bottom flask under argon for 24 h with a Teflon-coated magnetic stir bar. A solution of 1-(trimethylsilyl)-5-bromo-1-pentyne (4.38 g, 20.0 mmol) in THF (30 mL) was added to the powdered magnesium at room temperature under argon. After 10 min, TLC showed no remaining bromide, and the Grignard reagent mixture was added via cannula to a 0 °C suspension of **10** (2.32 g, 8.00 mmol) and CuCN (720 mg, 8.00 mmol) in THF (10 mL). The resulting mixture was stirred for 12 h before a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with ethyl acetate (5 × 20 mL), and the separated organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation, and the residue was purified by column chromatography (50 g SiO_2, hexanes−ethyl acetate 20:1) to give **11** as a pale yellow, viscous oil (3.17 g, 7.36 mmol, 92%): $[\alpha]^{23}_D$ −3.6° (*c* 1.06, $CHCl_3$). IR (neat): 3550, 2170, 1610, 1510, 1450 cm^{-1}. ^1H NMR (300 MHz): δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.36 (d, *J* = 8.8 Hz, 1H), 3.22 (d, *J* = 8.8 Hz, 1H), 2.19 (m, 3H), 1.70−1.20 (m, 12H), 0.85 (m, 6H), 0.13 (s, 9H, TMS). ^{13}C NMR (partial, 75 MHz): δ 159.0, 130.0, 128.9 (2C), 113.5 (2C), 55.0, 0.00. HRMS calcd for $C_{26}H_{42}O_3Si$: 430.2903, found: 430.2894. Anal. Calcd for $C_{26}H_{42}O_3Si$: C, 72.60; H, 9.84. Found: C, 72.80; H, 10.00.

(4S)-(+)-4-Isopropyl-2-(4-pentynyl)-1-(hydroxymethyl)-1-cyclohexanol (12). To a mixture of **11** (1.55 g, 3.59 mmol) in CH_2Cl_2 (30 mL), *tert*-butyl alcohol (3 mL), and H_2O (3 mL) at room temperature was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.45 g, 10.8 mmol). The biphasic mixture was stirred rapidly for 15 min before aqueous NaOH (1 M, 10 mL) was added, and the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were concentrated, and the residue was dissolved in methanol (30 mL). Solid K_2CO_3 (ca. 100 mg) was added and the mixture stirred for 30 min. The resulting solution was concentrated and the residue purified by column chromatography (50 g SiO_2, hexanes−ethyl acetate, 5:1) to give **12** as a pale yellow solid (709 mg, 2.99 mmol, 83%): mp 55−56 °C; $[\alpha]^{23}_D$ +7.7° (*c* 0.26, $CHCl_3$). IR ($CHCl_3$): 3400, 3100, 2150 cm^{-1}. ^1H NMR (300 MHz): δ 3.58−3.41 (m, 2H), 2.17 (m, 3H), 1.94 (m, 3H), 1.66 (m, 3H), 1.45 (m, 6H), 1.14 (m, 3H), 0.87 (m, 6H). HRMS calcd for $C_{15}H_{26}O_2$: 238.1933, found: 238.1940.

(4S)-(−)-4-Isopropyl-2-(4-pentynyl)-1-cyclohexanone (13). To a solution of **12** (173 mg, 725 μmol) in THF (3 mL) and H_2O (3 mL) was added $NaIO_4$ (171 mg, 798 μmol), and the resulting mixture was stirred for 2 h. The mixture was filtered though Celite and concentrated. The residue was chromatographed (50 g SiO_2, hexanes−ethyl acetate, 5:1) to give **13** as a clear oil (145 mg, 703 μmol, 97%): $[\alpha]^{23}_D$ −62.2° (*c* 0.20, $CHCl_3$). IR (neat): 3290, 2120, 1710 cm^{-1}. ^1H NMR (200 MHz): δ 2.32 (m, 3H), 2.16 (m, 2H), 1.95 (m, 2H), 1.73 (m, 2H), 1.53 (m, 7H), 0.91 (m, 6H). HRMS calcd for $C_{14}H_{22}O$: 206.1671, found: 206.1651. Anal. Calcd for $C_{14}H_{22}O$: C, 81.56; H, 10.76. Found: C, 81.47; H, 10.72.

(4S)-(−)-4-Isopropyl-2-(4-pentynyl)-1-[(trimethylsilyl)-oxy]-1-cyclohexene (14). To a room temperature solution of **13** (562 mg, 2.72 mmol) in acetonitrile (10 mL) were sequentially added NaI (420 mg, 2.80 mmol), triethylamine (1.95 mL, 14.0 mmol), and trimethylsilyl chloride (1.07 mL, 8.40 mmol). The resulting mixture was stirred at room temperature for 20 min before being extracted with hexanes (5 × 10 mL). The combined hexanes extract was concentrated, and the residue was applied directly to a silica gel column (50 g) and eluted with hexanes−ethyl acetate−pyridine (20:1:0.1) to give **14** as a pale yellow oil (689 mg, 2.64 mmol, 97%): $[\alpha]^{23}_D$ −40.0° (*c* 0.34, $CHCl_3$). IR (neat): 3300, 2120, 1720 cm^{-1}. ^1H NMR (300 MHz): δ 2.14 (m, 3H), 2.11 (m, 3H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.87 (m, 1H), 1.74 (m, 2H), 1.58 (m, 2H), 1.46 (m, 1H), 1.24 (m, 2H), 0.89 (s, 3H), 0.86 (s, 3H), 0.15 (s, 9H). ^{13}C NMR (75 MHz): δ 143.6, 114.1, 85.0, 68.0, 40.5, 31.9, 31.3, 30.6, 29.6, 26.8, 26.7, 20.0, 19.9, 18.4, 0.79 (3C). HRMS calcd for $C_{17}H_{30}OSi$: 278.2066, found: 278.2084.

(1*S*,5*S*)-(−)-5-Isopropyl-7-methylenespiro[5.4]decan-2-one (17) and (1*R*,5*S*)-(−)-5-isopropyl-7-methylenespiro-[5.4]decan-2-one (18). To a room temperature solution of **14** (279 mg, 1.00 mmol) and HMDS (42 μL, 0.20 mmol) in CH_2Cl_2 (10 mL) was added $HgCl_2$ (299 mg, 1.10 mmol). The resulting mixture was stirred for 30 min and cooled to 0 °C, and aqueous HCl (5 M, 400 μL, 2.00 mmol), NaI (450 mg, 3.00 mmol) and THF (2 mL) were added. After stirring for 1 h, solid powdered $NaHCO_3$ was added, and the resulting mixture was stirred for an additional 10 min before being filtered and concentrated. The residue was purified by column chromatography (50 g SiO_2, hexanes−ethyl acetate, 20:1) to give **17** (135 mg, 654 μmol, 65%) and **18** (60 mg, 0.29 mmol, 29%) as colorless oils. **17**: $[\alpha]^{23}_D$ −227° (*c* 1.00, $CHCl_3$). IR (neat): 1700, 1640 cm^{-1}. ^1H NMR (500 MHz): δ 5.11 (t, *J* = 2.5 Hz, 1H), 5.02 (t, *J* = 2.5 Hz, 1H), 2.66 (ddd, *J* = 6, 13, 13 Hz, 1H), 2.46 (m, 1H), 2.38 (m, 2H), 2.00 (m, 2H), 1.87 (m, 1H), 1.75 (m, 1H), 1.61 (m, 1H), 1.47 (m, 1H), 1.38 (m, 2H), 1.30 (m, 2H), 0.90 (d, *J* = 5.5 Hz, 3H), 0.89 (d, *J* = 5.5 Hz, 3H). ^{13}C NMR (75 MHz): δ 212.3, 156.0, 107.7, 58.9, 41.7, 39.1, 38.6, 38.2, 34.5, 32.3, 29.0, 22.5, 19.9, 19.6. HRMS calcd for $C_{14}H_{22}O$: 206.1671, found: 206.1666. Anal. Calcd for $C_{14}H_{22}O$: C, 81.56; H, 10.76. Found: C, 81.49; H, 10.68. NOE (500 MHz): irradiation of the δ 2.66 (axial α-keto) proton resonance enhanced the (*syn* vinyl) proton resonance at δ 5.11; irradiation of the δ 5.11 (*syn* vinyl) proton resonance enhanced the (axial) proton resonances at δ 2.66 and δ 1.87; irradiation of the δ 2.46 or δ 2.38 (allylic proton) resonances enhanced the (*anti* vinyl) proton resonance at δ 5.02.

18: $[\alpha]^{23}_D$ −20.0° (*c* 0.52, $CHCl_3$). IR (neat): 1700, 1650 cm^{-1}. ^1H NMR (500 MHz): δ 5.13 (s, 1H), 4.79 (s, 1H), 2.56 (ddd, *J* = 6, 13, 13 Hz, 1H), 2.47 (m, 1H), 2.38 (m, 2H), 2.01 (m, 2H), 1.77 (m, 2H.47 (m, 1H), 0.92 (s, 3H), 0.91(s, 3H). ^{13}C NMR (50 MHz): δ 213.0, 154.9, 107.2, 60.1, 41.9, 39.8, 39.0, 38.5, 33.7, 32.1, 29.6, 22.9, 19.9, 19.7. HRMS calcd for $C_{14}H_{22}O$: 206.1671, found: (M + NH_4^+) at 206.1665. Anal. Calcd for $C_{14}H_{22}O$: C, 81.56; H, 10.76. Found: C, 81.39; H, 10.67. NOE (500 MHz): irradiation at δ 2.56 (axial α-keto proton) led to no NOE enhancement of either vinyl proton peak; irradiation at δ 2.46 or δ 2.38 (allylic protons) enhanced the (*anti* vinyl) proton resonance at δ 5.02.

(1*S,5*S**)-5-Isopropyl-7-(*E*-deuteriomethylene)spiro-[5.4]decan-2-one (19) and (1*R**,5*S**)-5-Isopropyl-7-(*E*-deuteriomethylene)spiro[5.4]decan-2-one (20).** To a solution of (±)-**14**[18] (67 mg, 0.24 mmol) and HMDS (11 μL, 50 μmol) in CH_2Cl_2 (4 mL) was added $HgCl_2$ (75 mg, 0.28 mmol) at room temperature. The resulting mixture was stirred for 30 min and then cooled to 0 °C before a 20% solution of DCl in D_2O (94 μL, 0.50 mmol DCl), NaI (113 mg, 0.75 mmol), and THF (1 mL) were added. After stirring for 1 h at 0 °C, solid $NaHCO_3$ (100 mg) was added and the mixture was stirred for an additional 10 min. Filtration and concentration gave a residue that was purified by TLC (SiO_2, hexanes−ethyl

acetate, 5:1) to give **19** (33 mg, 0.16 mmol, 66%) and **20** (14 mg, 68 μmol, 28%). **19**: IR (neat): 1700, 1638 cm^{-1}. ^1H NMR (200 MHz): δ 5.10 (t, J = 2.1 Hz, 1H), 5.02 (t, <0.05 H), 2.65 (m, 1H), 2.40 (m, 3H), 2.00 (m, 2H), 1.78–1.23 (m, 8H), 0.91 (d, J = 6 Hz, 3H), 0.88 (d, J = 6 Hz, 3H). HRMS calcd for $C_{14}H_{21}DO$: 207.1733, found: 207.1721.

20: IR (neat): 1700, 1647 cm^{-1}. ^1H NMR (200 MHz): δ 5.12 (t, <0.05 H), 4.77 (t, J = 2.5 Hz, 1H), 2.50–2.30 (m, 4H), 2.00 (m, 2H), 1.60 (m, 1H), 1.64–1.49 (m, 7H), 0.92 (s, 3H), 0.90 (s, 3H). HRMS calcd for $C_{14}H_{21}DO$: 207.1733, found: 207.1718.

(1*S*,5*S*)-(−)-5-Isopropyl-2,7-dimethylenespiro[5.4]-decane [(−)-2, (−)-erythrodiene]. To a stirred suspension of triphenylmethylphosphonium bromide (911 mg, 2.5 mmol) in THF (2 mL) under argon at room temperature was added *n*-butyllithium (2.5 M in hexanes, 1.00 mL, 2.5 mmol). The resulting solution was stirred at room temperature for 1 h before a solution of 17 (101 mg, 490 μmol) in THF (2 mL) was added. The resulting mixture was heated at reflux for 12 h. After cooling to room temperature, the mixture was concentrated and the residue was purified by preparative TLC (hexanes) to give 2 as a colorless oil (74 mg, 0.36 mmol, 74%): $[\alpha]^{23}_D$ −118° (*c* 0.60, $CHCl_3$). IR (neat): 3080, 1630 cm^{-1}. ^1H NMR (300 MHz): δ 4.96 (s, 1H), 4.85 (s, 1H), 4.75 (s, 1H), 4.72 (s, 1H), 2.41 (m, 3H), 2.28 (m, 1H), 2.09 (m, 1H), 1.75 (m, 2H), 1.68 (m, 2H), 1.48 (m, 3H), 1.08 (m, 2H), 0.86 (d, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H). ^{13}C NMR (75 MHz): δ 157.9, 152.7, 106.5, 105.8, 51.1, 40.9, 39.5, 39.4, 33.6, 32.9, 32.3, 30.8, 20.6, 19.9, 19.5. HRMS calcd for $C_{15}H_{24}$: 204.1878, found: 204.1877.

(3*R*,4*S*,6*R*)-(−)-6-Isopropyl-1-oxadispiro[2.0.5.3]dodecan-9-one (22). To a stirred solution of **17** (206 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) at room temperature was added *m*-chloroperbenzoic acid (Aldrich, 80–85% purity, 303 mg, ca. 1.40 mmol). After 2 h, **17** was completely consumed (TLC). Saturated $NaHCO_3$ (10 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 10 mL). The combined extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC (hexanes–ethyl acetate, 5:1) to give **22** as a clear, colorless oil (99 mg, 0.45 mmol, 45%): $[\alpha]^{26}_D$ −67° (*c* 0.30, $CHCl_3$). IR (neat): 1700 cm^{-1}. ^1H NMR (300 MHz): δ 2.65 (m, 2H), 2.41 (m, 2H), 2.22 (m, 1H), 2.17 (m, 1H), 1.87 (m, 3H), 1.73 (m, 2H), 1.60 (m, 1H), 1.46–1.30 (m, 3H), 1.24 (m, 1H), 0.89 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H). ^{13}C NMR (75 MHz): δ 213.8, 68.0, 54.8, 51.2, 40.5, 38.7, 38.1, 36.3, 32.3, 32.2, 28.4, 20.0, 19.9, 19.5. HRMS calcd for $C_{14}H_{22}O_2$: 222.1620, found: 222.1604.

(3*R*,4*R*,6*S*)-(−)-6-Isopropyl-9-methylene-1-oxadispiro-[2.0.5.3]decane (23). To a stirred suspension of **22** (14 mg, 63 μmol) and triphenylmethylphosphonium bromide (104 mg, 293 μmol) in dry toluene (0.5 mL) at room temperature was added KHMDS (0.91 M in toluene, 260 μL, 0.24 mmol) under argon. The mixture was heated to 80 °C for 20 min and then cooled to room temperature. Preparative TLC (hexanes–ethyl acetate, 5:1) of the crude product mixture gave **23** as a clear, colorless oil (13 mg, 59 μmol, 93%): $[\alpha]^{26}_D$ −41° (*c* 0.65, $CHCl_3$). IR (neat): 1640 cm^{-1}. ^1H NMR (300 MHz): δ 4.73 (s, 1H), 4.67 (s, 1H), 2.71 (d, J = 5 Hz, 1H), 2.50 (d, J = 5 Hz, 1H), 2.16–2.05 (m, 4H), 1.88–1.60 (m, 7H), 1.40 (m, 1H), 1.38–1.23 (m, 2H), 0.86 (d, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H). ^{13}C NMR (75 MHz): δ 152.1, 106.8, 68.7, 51.0, 46.7, 38.9, 38.3, 36.4, 33.4, 32.4, 30.6, 30.4, 19.8, 19.2, 18.0. HRMS calcd for $C_{15}H_{24}O$: 220.1827, found 220.1829.

(1*R*,5*S*,7*R*)-(−)-5-Isopropyl-7-methyl-2-methylenespiro-[5.4]decan-7-ol [(−)-1, (−)-spirojatamol]: To a stirred solution of **23** (7.0 mg, 32 μmol) in dry ether (0.5 mL) at 0 °C was added $LiAlH_4$ (1.0 mg, 26 μmol). The resulting mixture was allowed to warm to rt and stir over 1 h before 2-propanol (100 μL) was added. The resulting mixture was filtered through a pad of silica gel and evaporated to give **1** as a clear, colorless oil (7.0 mg, 32 μmol, ca. 100%): $[\alpha]^{26}_D$ -18° (*c* 0.38, $CHCl_3$). IR (neat): 3480, 1650 cm^{-1}. ^1H NMR (300 MHz): δ 4.80 (s, 1H), 4.65 (s, 1H), 2.28–2.25 (m, 2H), 2.14 (m, 1H), 2.01 (m, 1H), 1.89-1.70 (m, 5H), 1.57 (s, OH), 1.55–1.22 (m, 3H), 1.18 (s, 3H), 0.99–0.92 (m, 2H), 0.86 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H). ^{13}C NMR (75 MHz): δ 153.3, 108.4, 82.4, 52.7, 40.6, 40.4, 39.2, 38.2, 35.4, 33.2, 31.2, 27.6, 20.2, 19.3, 18.5. HRMS calcd for $C_{15}H_{26}O$: 222.1984, found: 222.1981.

Acknowledgment. We thank Prof. W. Fenical for providing an authentic sample of natural product **2** and for helpful discussions. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also thank the 3M company for a 3M/Alumni endowment and the donation of laboratory equipment.

Supplementary Material Available: Copies of the ^1H NMR spectra of synthetic products (−)-**1**, (−)-**2**, **3**, **7**, **9**, **12**, **14**, and **19**–**23**; copies of the ^{13}C NMR spectra of (−)-**1**, (−)-**2**, **9**, and **21**–**23**, and a copy of the ^1H NMR NOE spectrum of **3** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO942170Y