α-(p-Chlorophenyl)-p-nitroacetophenone (1.18 g),[24] pale yellow crystals (EtOH); mp 115–116 °C; IR (KBr) 1687 cm^{-1}; NMR ($CDCl_3$) δ 8.18 (m, 4 H), 7.17 (m, 4 H), 4.26 (s, 2 H); MS, *m/e* 275 (3, M^+), 150 (100), 75 (48), 104 (46), 50 (45), 125 (41). Anal. Calcd for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.63; Cl, 12.86; N, 5.08. Found: C, 61.42; H, 3.60; Cl, 12.65; N, 5.37.

α-(p-Chlorophenyl)-p-methoxyacetophenone (3.01 g, 52%), white crystals (EtOH); mp 130–131 °C; IR (KBr) 1667 cm^{-1}; NMR ($CDCl_3$) δ 7.40 (m, 8 H), 4.14 (s, 2 H), 3.80 (s, 3 H). MS, *m/e* 260 (1, M^+), 135 (100), 77 (39), 92 (31). Anal. Calcd for $C_{15}H_{13}ClO_2$: C, 69.09; H, 5.01. Found: C, 68.81; H, 4.86.

α-(p-Chlorophenyl)-p-chloroacetophenone (3.58 g, 84%), pale yellow crystals (EtOH); mp 110.5–113 °C (lit.[25] mp 113–114 °C); IR (KBr) 1687 cm^{-1}; NMR ($CDCl_3$) δ 7.45 (m, 8 H), 4.17 (s, 5 H).

α-(p-Tolyl)acetophenone (3.2 g, 99%), pale yellow crystals (EtOH); mp 91–94 °C (lit.[24] mp 95.5 °C); IR (KBr) 1680 cm^{-1}; NMR ($CDCl_3$) δ 7.81 (m, 2 H), 7.32 (m, 3 H), 7.02 (s, 4 H), 4.10 (s, 2 H), 2.19 (s, 3 H).

α-(p-Tolyl)-p-nitroacetophenone (2.73 g, 92%), white crystals (EtOH); mp 130–132 °C; NMR ($CDCl_3$) δ 8.12 (d, 4 H), 7.08 (s, 4 H), 4.22 (s, 2 H), 2.28 (s, 3 H); MS, *m/e* 255 (2.5, M^+), 105 (100), 77 (19). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.68; H, 5.09; N, 5.47.

1-(2-Furyl)-2-phenylethanone (2.1 g, 100%), red-brown, viscous liquid (unpurified liquid); semicarbazone mp 165–167 °C (lit.[26] mp 166–168 °C); IR (neat) 1667 cm^{-1}; NMR ($CDCl_3$) δ 7.13 (m, 6 H), 6.26 (q, 2 H), 3.97 (s, 2 H).

1-(2-Thienyl)-2-phenylethanone (2.1 g, 87%), taupe crystals (column chromatography); mp 47–48 °C (lit.[27] mp 48–49 °C); IR (KBr) 1654 cm^{-1}; NMR ($CDCl_3$) δ 7.20 (m, 8 H), 4.00 (s, 2 H).

1-(4-Pyridyl)-2-phenylethanone, lit.[28] mp 96 °C, was isolated in 72%; recrystallization of a sample from petroleum ether–carbon tetrachloride gave an analytical sample as a colorless solid: mp 95–96 °C; NMR ($CDCl_3$) δ 8.8 (m, 2 H), 7.7 (m, 2 H), 7.3 (s, 5 H), 4.25 (s, 2 H). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.96; H, 5.49; N, 7.06.

1-(2-Pyrryl)-2-phenylethanone, lit.[29] mp 95 °C, could not be induced to crystallize from the dark purple reaction mixture. Its NMR spectrum displayed a CH_2 at δ 3.97, consistent with that expected for the homologated product; the NMR spectrum also indicated the presence of *cis*- and *trans*-stilbene in addition to benzaldehyde and benzyl bromide.

1-Phenyl-2-butanone (5.2 g, 81%), clear liquid (distillation); IR (neat) 1701 cm^{-1}; the structure was confirmed by the addition of an authentic sample[30] to the NMR sample; NMR ($CDCl_3$) δ 7.19 (s, 5 H), 3.60 (s, 2 H), 2.40 (q, 2 H), 1.00 (t, 3 H).

4-Methyl-1-phenyl-2-pentanone (1.0 g, 91%), yellow liquid (unpurified); IR (neat) 1717 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (s, 5 H), 4.1 (s, 2 H), 2.26 (d, 2 H), 1.55 (m, 1 H), 0.88 (d, 6 H).

1,1,1-Trichloro-3-phenyl-2-propanone could not be isolated from the yellow solution whose NMR spectrum displayed a sharp singlet at δ 4.18 and doublets at δ 3.80 and 4.30 (epoxide). The yields of the ketone and the epoxide were estimated from integration of the peaks; traces of benzaldehyde were detected.

Registry No. C_6H_5CHO, 100-52-7; *p*-ClC_6H_4CHO, 104-88-1; *o*-$NO_2C_6H_4CHO$, 552-89-6; *m*-$NO_2C_6H_4CHO$, 99-61-6; *p*-$NO_2C_6H_4CHO$, 555-16-8; *o*-$CH_3C_6H_4CHO$, 529-20-4; *p*-$CH_3C_6H_4CHO$, 104-87-0; *p*-$CH_3OC_6H_4CHO$, 123-11-5; 3,4-$OCH_2OC_6H_3CHO$, 120-57-0; 3,4,5-$(MeO)_3C_6H_2CHO$, 86-81-7; 2-C_4H_3SCHO, 98-03-3; 2-C_4H_3OCHO, 98-01-1; 4-C_5H_4NCHO, 872-85-5; CH_3CH_2CHO, 123-38-6; $(CH_3)_2CHCH_2CHO$, 590-86-3; $C_6H_5CHN_2$, 766-91-6; *p*-$CH_3C_6H_4CHN_2$, 23304-24-7; *p*-$ClC_6H_4CHN_2$, 19277-54-4; deoxybenzoin, 451-40-1; α-phenyl-*p*-chloroacetophenone, 1889-71-0; α-phenyl-*o*-nitroacetophenone, 29236-59-7; α-phenyl-*m*-nitroacetophenone, 55251-37-1; α-phenyl-*p*-nitroacetophenone, 3769-84-4; α-phenyl-*o*-methylacetophenone, 16216-13-0; α-phenyl-*p*-methylacetophenone, 2001-28-7; α-phenyl-*p*-methoxyacetophenone, 1023-17-2; α-phenyl-3,4,5-trimethoxyacetophenone, 87282-25-5; benzyl piperonyl ketone, 87282-26-6; α-(*p*-chlorophenyl)acetophenone, 6332-83-8; α-(*p*-chlorophenyl)-*p*-nitroacetophenone, 87282-27-7; α-(*p*-chlorophenyl)-*p*-methoxyacetophenone, 52578-11-7; α-(*p*-chlorophenyl)-*p*-chloroacetophenone, 51490-05-2; α-(*p*-tolyl)acetophenone, 2430-99-1; α-(*p*-tolyl)-*p*-nitroacetophenone, 87282-28-8; 1-(2-furyl)-2-phenylethanone, 86607-65-0; 1-(2-thienyl)-2-phenylethanone, 13196-28-6; 1-(4-pyridyl)-2-phenylethanone, 1017-24-9; 1-(2-pyrryl)-2-phenylethanone, 13169-74-9; 1-phenyl-2-butanone, 1007-32-5; 4-methyl-1-phenyl-2-pentanone, 5349-62-2; 1,1,1-trichloro-3-phenyl-2-propanone, 709-78-4.

(24) In this reaction, the concentration of (*p*-chlorophenyl)diazomethane was overestimated; thus, there was a large excess of aldehyde that prevented the calculation of the yield.
(25) S. S. Jenkins and E. M. Richardson, *J. Am. Chem. Soc.*, **55**, 3784 (1933).
(26) S. Tagaki, H. Yasuda, and M. Kono, *Yakugaku Zasshi*, **81**, 1559 (1961); *Chem. Abstr.*, **57**, 16582b (1962).
(27) A. G. Giomanini and C. Trombini, *J. Prakt. Chem.*, **317**, 897 (1975).
(28) L. Kuczynski, Z. Machou, and L. Wykret, *Diss. Pharm.*, **16**, 485–493 (1964); *Chem. Abstr.*, **63**, 11537 (1963).
(29) B. Oddo, *Ber. Dtsch. Chem. Ges.*, **43**, 1019 (1910).
(30) Commercial sample from Aldrich.
(31) V. F. Raanen and J. F. Eastman, *J. Am. Chem. Soc.*, **82**, 1349 (1960).

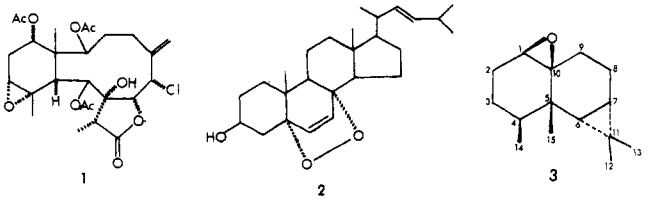
An Aristolane Sesquiterpenoid from the Sea Pen *Scytalium splendens*

Muu N. Do and Karen L. Erickson*

Jeppson Laboratory, Clark University, Worcester, Massachusetts 01610

Received April 25, 1983

The coelenterates have been extensively investigated for terpenoids, especially the orders Alcyonacea (soft corals) and Gorgonacea (sea fans and sea whips).[1] The order Pennatulacea (sea pens), on the other hand, has received relatively little attention.[1,2] Chlorinated diterpenoids of the briarein type, such as stylatulide (**1**), have been reported from two different genera of sea pens, *Ptilosarcus gurneyi* and *Stylatula* sp.,[1,2] while dechlorinated analogues were recently found in *Scytalium tentaculatum*.[3] A fourth genus, *Virgularia*, elaborates rare C_{26} steroid peroxides exemplified by **2**.[4] We now report the isolation of a rearranged sesquiterpenoid (**3**) from *Scytalium splendens* collected off Penhu Island southwest of Taiwan.



Methanol extracts of the organisms were partitioned between ethyl acetate and water, and the ethyl acetate fractions were chromatographed on silica gel to give the sesquiterpenoid in 0.06% yield (dry weight). High-resolution mass spectroscopy established its formula as $C_{15}H_{24}O$. The absence of vinyl hydrogens in the ^1H NMR spectrum and vinyl, carbonyl, or acetylenic carbons in the ^{13}C NMR spectrum requires a tetracyclic skeletal system for the molecule. IR spectroscopy confirmed the absence

(1) Tursch, B.; Braekman, J. C.; Daloze, D.; Kaisin, M. In "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2, p 247.
(2) Fenical, W. In "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2, pp 208–211.
(3) Ravi, B. N.; Marwood, J. F.; Wells, R. J. *Aust. J. Chem.* **1980**, *33*, 2307.
(4) Stonard, R. J.; Petrovich, J. C.; Andersen, R. J. *Steroids* **1980**, *36*, 81.

0022-3263/83/1948-4410$01.50/0

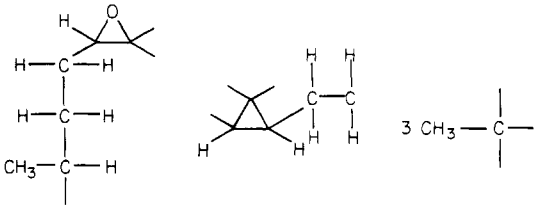
Table I. 500-MHz ^{1}H NMR Data for 3

H no.	chemical shift, ppm	multiplicity;[a] J, Hz
1	2.99	m; $J_{1,2ax} = 1.3$, $J_{1,2eq} = J_{1,3eq} = 1$
2_{ax}	1.66	od; $J_{2ax,1} = 1.3$, $J_{2ax,3eq} = 4.6$, $J_{2ax,3ax} = 12.7$, $J_{2ax,2eq} = 14.3$
2_{eq}	1.90	m; $J_{2eq,1} = 1$, $J_{2eq,3eq} = 2.3$, $J_{2eq,3ax} = 4.0$, $J_{2eq,2ax} = 14.3$
3_{ax}	1.35	dq; $J_{3ax,2eq} = 4.0$, $J_{3ax,2ax} = J_{3ax,3eq} = J_{3ax,4} = 12.7$
3_{eq}	1.03	m; $J_{3eq,1} = 1$, $J_{3eq,2eq} = 2.3$, $J_{3eq,2ax} = 4.6$, $J_{3eq,3ax} = 12.7$, $J_{3eq,4} = 2.6$
4	1.51	od; $J_{4,3eq} = 2.6$, $J_{4,3ax} = 12.7$, $J_{4,14} = 6.8$
6	0.77	d; $J_{6,7} = 9.0$
7	0.82	td; $J_{7,6} = 9.0$, $J_{7,8ax} = 3.6$, $J_{7,8eq} = 9.4$
8_{ax}	1.47	pd; $J_{8ax,7} = 3.6$, $J_{8ax,8eq} = J_{8ax,9ax} = 14.4$, $J_{8ax,9eq} = 5.2$
8_{eq}	2.0	m; $J_{8eq,7} = 9.4$, $J_{8eq,8ax} = 14.4$, $J_{8eq,9eq} = 1.3$, $J_{8eq,9ax} = 6.7$
9_{ax}	2.05	td; $J_{9ax,8ax} = 14.4$, $J_{9ax,8eq} = 6.7$, $J_{9ax,9eq} = 13$
9_{eq}	0.70	qd; $J_{9eq,8ax} = 5.2$, $J_{9eq,8eq} = 1.3$, $J_{9eq,9ax} = 13$
12[b]	1.06	s
13[b]	1.06	s
14	0.87	d; $J_{14,4} = 6.8$
15[b]	1.01	s

[a] m = multiplet, od = octet of doublets, dq = doublet of quartets, d = doublet, td = triplet of doublets, pd = pentet of doublets, s = singlet. [b] Assignments may be reversed.

of carbonyl functionality as well as hydroxyl. That the oxygen atom is epoxy in nature was indicated by the fact that the most deshielded absorption in the ^{1}H NMR spectrum is a one proton multiplet at δ 2.99. Absorptions at 63.0 (d) and 64.0 (s) in the ^{13}C NMR spectrum supported the presence of a trisubstituted epoxy moiety.

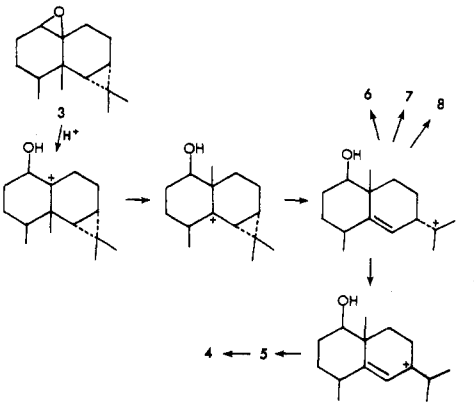
A one proton doublet at δ 0.77 and a triplet of doublets at δ 0.82 (one proton) in the ^{1}H NMR spectrum, coupled with a markedly shielded quaternary carbon at 17.8 (s) in the ^{13}C NMR spectrum, suggested a tetrasubstituted cyclopropyl ring system, which, together with the epoxide, accounts for two of the molecule's four rings. In addition, proton and carbon spectra indicated the presence of a secondary methyl group (0.87 (d), 29.3 (q)) and three quaternary methyls (1.01, 1.06, and 1.06 (s), 19.2, 18.4, and 16.0 (q)). Extensive decoupling experiments at 500 MHz in the ^{1}H NMR together with 2-D ^{1}H NMR correlated spin–echo spectroscopy (COSY) experiments at 250 MHz established the following proton sequences:



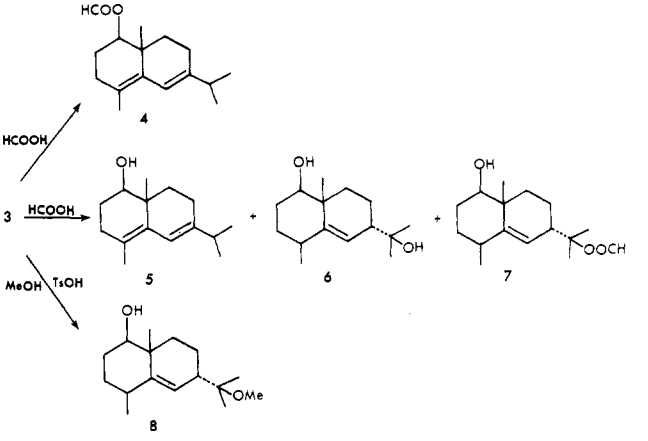
SFORD and INEPT experiments in the ^{13}C NMR confirmed the presence of four methyl, four methylene, four methine, and three quaternary carbon groups. Interestingly, one hydrogen of the methylene group β to the cyclopropyl ring is strongly shielded, absorbing in the same region as the cyclopropyl protons (Table I). This shielding effect disappeared when the epoxide, but not the cyclopropyl ring, was opened, indicating that the former is responsible for the shielding of this proton.

Attempts to open the epoxide ring without disturbing the cyclopropyl system were generally unsuccessful (zinc–copper couple, diphenyl diselenide, diphosphorus tetraiodide, methylmagnesium chloride, lithium/amine). Lithium aluminum hydride did effect epoxide opening but only in one instance. Subsequent runs resulted in quantitative recovery of starting material. Acid-catalyzed processes effected an immediate cleavage of both the epoxide and cyclopropyl ring, leading to rearranged products with selinane skeletons. Thus, treatment of **3** with formic acid for 30 min gave essentially one product identified as selinene **4**. Shorter periods of treatment gave compounds

Scheme I

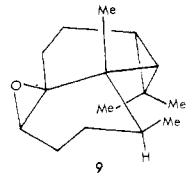


5–7. Similarly, treatment of **3** with *p*-toluenesulfonic acid in methanol gave selinene **8**. These products allow the



formulation of structure **3** as 1,10-epoxyaristolane. The isopropyl group defined the positioning of the original cyclopropyl moiety. To retain four methyl groups, adhere to the proton sequence established earlier, and explain the acid-catalyzed rearrangement products, only structure **3** will fit. Scheme I outlines a mechanistic sequence for the formation of selinenes from **3**.

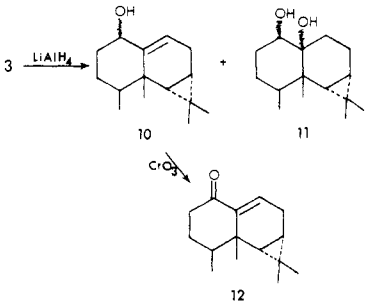
The stereochemistry of **3** can be deduced as follows. The β-placement of the C-1 OH in compounds **4–7** defines the stereochemistry of the epoxide oxygen of **3** at this position and necessitates its β-placement at C-10 as well. Assuming the less cluttered half-chair conformation for the A ring shown in **9**, and knowing that H-4 is axial ($J_{3,4}$ = 2.6, 12.7



9

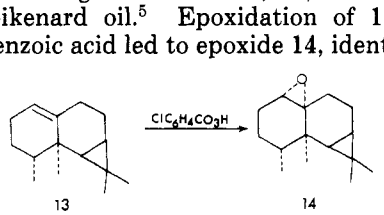
Hz), the cis relationship of the C-4 and C-5 methyls is established. The trans relationship of the cyclopropyl ring to these two methyls avoids the severe interaction that would result between the bridgehead methyl and one of the cyclopropyl methyls should these groups by cis. Aristolane skeletons of this type always display a trans-cyclopropyl-bridgehead methyl stereochemistry.[5-9] Moreover, this trans relationship explains the facile (probably concerted) migration of bridgehead methyl and cyclopropyl cleavage that occurs when **3** is exposed to acid. Evidently a conformational change occurs once the epoxide ring is opened as the C-1 OH (or OOCH) group occupies the equatorial position in compounds **4–7**.

The lithium aluminum hydride reaction products of **3** were tentatively identified as **10** and **11** from their IR and ^{1}H NMR spectra. The cyclopropyl hydrogens were clearly visible (for **10**, 0.60 (m) and 0.15 (d, J = 8 Hz); for **11**, 0.72 (m) and 0.11 (d, J = 8 Hz)), and the upfield signal for the 9_{eq} proton had shifted under the methylene groups. The formation of the hydrolysis product, diol **11**, and its dehydration product **10** was unexpected but not unprecedented. We have previously observed the incorporation of oxygen in attempting to dehalogenate cyclohexyl halides with lithium aluminum hydride.[10] Alcohol **10** afforded a conjugated ketone on oxidation, tentatively identified as **12**.



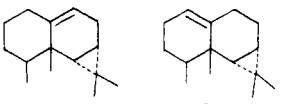
10 11 12

Final confirmation of structure **3** was made possible by chemically relating it to calarene, **13**,[11] obtained from Chinese spikenard oil.[5] Epoxidation of **13** with *m*-chloroperbenzoic acid led to epoxide **14**, identical with **3**



13 14

in all respects except optical rotation. Ourisson and coworkers have previously reported the synthesis of **14** from natural **13**. To our knowledge the occurrence of its enantiomer in *S. splendens* is the first report of it as a natural product. 9-Aristolene (**15**) and 1(10)-aristolene (**16**) have



15 16

been found previously in an Atlantic gorgonian,[8] and the aristolane system is well-known from terrestrial sources. With one exception,[9] the terrestrial-derived aristolenes are enantiomeric to the marine-derived, a phenomena no longer considered unusual.

Experimental Section

UV spectra were recorded on a Cary 210 spectrophotometer. IR spectra were taken on Perkin-Elmer 700, 337, and 1330 spectrophotometers in CCl_4. The ^{1}H NMR spectra were recorded on Bruker WP-250 and 500-MHz spectrophotometers, and the ^{13}C NMR spectra were recorded on Bruker SXP 20-100 and Bruker WP-250 spectrometers with $CDCl_3$ as solvent unless stated otherwise. Chemical shift values are reported as ppm downfield from Me_4Si. Low-resolution mass spectra were recorded on a Finigan MAT 212 or Finigan MAT 312 instrument. High-resolution mass spectra were measured on a CEC-110B spectrometer. Optical rotations were obtained in $CHCl_3$ on a Zeiss polarimeter. Analytical TLC was done on commercial Bakerflex (silica gel IB_2-F) and preparative TLC on Brinkmann HF 254 + 366, type 60 silica gel. Short-column chromatography was performed on Brinkmann TLC grade silica gel, 60H. All solvents and chemicals were reagent grade.

Isolation and Purification of β-(−)-1,10-Epoxyaristolane (3). *S. splendens* was collected, transported in ethanol, and stored at −5 °C until processing. The animals were thawed, ground in a Waring blender, and extracted with methanol for 4 days. The methanol was decanted, and the extraction was repeated with fresh methanol for another 4 days. The combined methanol extracts were concentrated and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with 5% NaCl solution and then water, and dried over $MgSO_4$. The solvent was removed to give 5 g of brown oil (2.5% based on dried animal weight after extraction).

The organic extract was subjected to short-column chromatography. A sintered glass funnel was packed with TLC grade silica gel and subjected to aspirator vacuum. Fifty-milliliter fractions were eluted with hexane, hexane/CH_2Cl_2 (1:1), CH_2Cl_2/EtOAc (1:1), and EtOAc. Repetitive preparative TLC of the CH_2Cl_2 and CH_2Cl_2/EtOAc fractions with CH_2Cl_2 or 85:15 petroleum ether/benzene yielded **3** as a colorless oil (0.06% based on dried animals).

β-(−)-1,10-Epoxyaristolane (3): R_f 0.4 (CH_2Cl_2); $[\alpha]^{25}_D$ −24.1° (c 0.332, $CHCl_3$); mass spectrum, m/z 220.1811 for $C_{15}H_{24}O$ (calcd 220.1823), 205, 202, 187, 177, 163, 161, 159, 157, 138, 135, 133, 121, 107, 93, 79; IR ν 2980, 2960, 2940, 2870, 2860, 1450, 1440, 1375, 1369, 1250, 1130, 1030, 950, 890 cm^{-1}; ^{1}H NMR, Table I; ^{13}C NMR δ 64.0 (s), 63.1 (d), 37.0 (d), 35.1 (d), 34.7 (s), 30.3 (t), 29.3 (q), 26.2 (t), 24.7 (t), 19.7 (d), 19.2 (q), 18.4 (t), 18.4 (q), 17.8 (s), 16.0 (q).

Reaction of 3 with Excess Formic Acid: 4. To a flask containing 10 mg (0.045 mmol) of **3** was added 250 μL of 98% formic acid. The mixture was stirred at 25 °C for 30 min, and then the reaction was quenched by adding water. The organic layer was extracted with ether, and the ether layer was washed with 1 N NaOH, water, and brine and dried over $MgSO_4$. The ether was removed to yield 5.0 mg of crude product. Purification by TLC with CH_2Cl_2 (3×) gave 3.2 mg of **4**:[6] UV (C_6H_{14}) λ_{max} 240, 246, 254 (sh) nm (ϵ 20 000, 21 260, 14 740); IR ν 2980, 2970, 2960, 1740, 1370, 1360, 1180, 1170, 1120, 930 cm^{-1}; ^{1}H NMR (250 MHz) δ 8.13 (1 H, s), 6.06 (1 H, br s), 4.80 (1 H, dd, J = 5, 12 Hz), 2.05–1.20 (8 H, m), 1.68 (3 H, s), 1.04 (6 H, dd, J = 1.5, 7.5 Hz), 0.99 (3 H, s); ^{13}C NMR δ 161.6, 143.5, 131.5, 125.1, 116.5, 78.8, 36.1, 35.4, 33.1, 31.4, 23.5, 22.6, 21.7, 21.2, 18.1, 17.6.

Reaction of 3 with Formic Acid: 5–7. To a flask containing 10 mg of **3** was added 50 μL of 98% formic acid. The reaction

(5) Buchi, G.; Greuter, F.; Tokoroyama, T. *Tetrahedron Lett.* **1962**, 827.
(6) Streith, J.; Pesnelle, P.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1963**, 518.
(7) Vrkoc, J.; Krepinsky, J.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1964**, *29*, 795.
(8) Weinheimer, A. J.; Washecheck, P. H.; van der Helm, D.; Hossain, M. B. *J. Chem. Soc., Chem. Commun.* **1968**, 1070.
(9) Carboni, S.; Da Settino, A.; Malaguzzi, V.; Marsili, A.; Pacini, P. L. *Tetrahedron Lett.* **1965**, 3017.
(10) Waraszkiewicz, S. M.; Erickson, K. L.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1977**, 2311.
(11) This structure appears in the literature under several names. It is identical with β-gurjunene[6,7] and enantiomeric with 1(10)-aristolene.[8] The latter name has been suggested as the preferred one for both enantiomers.[8]

mixture was stirred at 25 °C for 15 s. It was then quenched with water and extracted with ether. The ether solution was washed with 1 N NaOH, water, and brine and dried over $MgSO_4$. The solvent was removed to give 14 mg of crude material. TLC with CH_2Cl_2 (3×) afforded **5** (5 mg), **7** (3 mg), and **6**; the latter was recycled with hexane/ether (4:1, 2×), giving 3 mg of pure material.

5:[6] UV (C_6H_{14}) λ_{max} 240, 246, 253 (sh) nm (ϵ 20 000, 21 000, 14 000); IR ν 3610, 2960, 2930, 2860, 1440, 1380, 1370, 1345, 1150, 1120, 1072 cm^{-1}; ^1H NMR (250 MHz) δ 6.07 (1 H, br s), 3.45 (1 H, dd, J = 5, 12 Hz), 2.30–1.12 (9 H, m), 1.66 (3 H, s), 1.04 (3 H, dd, J = 1.5, 7.5 Hz), 1.02 (3 H, dd, J = 1.5, 7.5 Hz), 0.90 (3 H, s).

6: mass spectrum, m/z 220.181 for $C_{15}H_{24}O$ ($M^+ - H_2O$, calcd 220.182), 205, 180, 162, 147, 133, 123, 120, 107, 105, 95, 93, 91, 79, 59; IR ν 3610, 2970, 2930, 2860, 1450, 1380, 1370, 1345, 1120 cm^{-1}; ^1H NMR (250 MHz) δ 5.55 (1 H, d, J = 3 Hz), 3.30 (1 H, dd, J = 5, 11 Hz), 2.50–1.20 (10 H, m), 1.18 (6 H, s), 1.13 (3 H, d, J = 8 Hz), 1.07 (3 H, s); ^{13}C NMR δ 148.9, 123.4, 78.4, 73.4, 45.5, 40.0, 38.6, 34.8, 30.8, 27.9, 27.1, 26.5, 22.3, 20.6, 20.0.

7: mass spectrum, m/z 220.184 for $C_{15}H_{24}O$ (M^+ – HCOOH, calcd 220.182), 205, 202, 179, 176, 163, 161, 159, 147, 145, 133, 131, 119, 117, 107, 105, 95, 93, 91, 79, 71; IR ν 3610, 2980, 2930, 2860, 1740, 1380, 1370, 1345, 1195, 1120, 1015 cm^{-1}; ^1H NMR (250 MHz) δ 8.03 (1 H, s), 5.40 (1 H, d, J = 4 Hz), 3.34 (1 H, dd, J = 4, 12 Hz), 2.50–1.12 (10 H, m), 1.47 (3 H, s), 1.45 (3 H, s), 1.12 (3 H, d, J = 8 Hz), 1.06 (3 H, s).

Reaction of 3 with *p*-Toluenesulfonic Acid: 8. To a reaction flask containing 9.0 mg of **3** in 2 mL of freshly distilled methanol was added 20 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was stirred at 25 °C for 5 min. The mixture was then extracted with ether, and the ether layer washed with 5% $NaHCO_3$, water, and brine and dried over $MgSO_4$. The solvent was removed, and the crude product was purified by TLC (CH_2Cl_2/Et_2O, 95:5, 2×) to yield 3 mg of **8**: mass spectrum, m/z 237.184 for $C_{15}H_{25}O_2$ ($M^+ - CH_3$, calcd 237.185), 220, 202, 187, 145, 131, 121, 119, 115, 107, 105, 93, 91, 79, 73; IR ν 3400, 2970, 2860, 1445, 1380, 1120, 1070, 1050, 905 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 5.58 (1 H, d, J = 2.5 Hz), 3.12 (1 H, dd, J = 3, 12 Hz), 3.03 (3 H, s), 2.33–1.20 (10 H, m), 1.12 (3 H, s), 1.11 (3 H, s), 1.09 (3 H, s), 1.04 (3 H, s); ^{13}C NMR δ 147.6, 124.3, 77.3, 76.7, 48.3, 42.2, 40.2 (s), 38.8, 35.0, 30.9, 26.7, 22.6 (2C), 22.1, 20.8, 19.9.

Epoxidation of Calarene (13): 14. In a three-neck flask equipped with a dropping funnel, condenser, and thermometer was added 62.4 mg of calarene (0.26 mmol) in 1 mL of anhydrous CH_2Cl_2. *m*-Chloroperbenzoic acid (105 mg, 0.36 mmol) in 5 mL of anhydrous CH_2Cl_2 was added dropwise while maintaining the reaction temperature below 25 °C. After all the acid was added, the mixture was stirred at 25 °C overnight. The excess perbenzoic acid was destroyed by addition of 3 mL of 10% Na_2SO_3, and the benzoic acid was neutralized with 5% $NaHCO_3$. The organic layer was dried over $CaCl_2$, and the solvent was removed to give 60 mg of crude product. TLC purification with CH_2Cl_2 gave **14** as the major product (48 mg, 84%): $[\alpha]_D$ +27.5° (*c* 0.182, $CHCl_3$) (lit.[6] $(\alpha)_D$ +21.2° ($CHCl_3$)).

Acknowledgment. We thank Dr. H. H. Sun for the initial supply of organisms and Dr. Kun-Hsiung Chang of the Academia Sinica, Taipei, for subsequent collections. Special thanks to Dr. P. T. Inglefield for the 2-D ^1H NMR spectrum, Peter Demou for the 500-MHz ^1H NMR spectrum, Dr. C. E. Costello for the mass spectra, and Dr. M. R. Brennan for valuable discussions concerning these spectra. We are especially grateful to Dr. G. H. Büchi for a generous sample of calarene. We acknowledge support of the NSF Northeast Regional NMR Facility at Yale University (Grant Number CHE-7916210), the NMR Facility for Biomolecular Research at MIT (NIH Grant No. RR00995 and NSF Contract No. C-670), the Worcester Consortium NMR Facility at Clark University (NSF Grant No. DMR-8108697), and the NIH Mass Spectrometry Facility at MIT (Grant No. RR00317).

Registry No. **3**, 87332-34-1; **4**, 87261-75-4; **5**, 87261-76-5; **6**, 87261-77-6; **7**, 87261-78-7; **8**, 87279-31-0; **13**, 17334-55-3; **14**, 68926-75-0.

Synthesis of (8*E*,10*E*,12*Z*,15*Z*)-6-Oxaheneicosa-8,10,12,15-tetraenoic Acid, Secoleukotriene A_4[1]

John W. Patterson, Jr.,* and D. V. Krishna Murthy

Institutes of Organic Chemistry and Biological Sciences, Syntex Research, Palo Alto, California 94304

Received April 12, 1983

The discovery of the leukotrienes and the elucidation of the biosynthesis of these mediators of inflammatory and allergic disorders has presented synthetic chemists the opportunity of preparing analogues of the biochemical intermediates that may antagonize the biological effects of these intermediates or act as inhibitors of the enzymes that transform them into products further down the arachidonic acid cascade. Examples of this strategy include acetylenic[2] and allenic[3] analogues of arachidonic acid, a carbon analogue of (6*E*,8*Z*,11*Z*,14*Z*)-15(*S*)-hydroperoxyeicosa-6,8,11,14-tetraenoic acid (5-HPETE),[4] carbon,[4,5] nitrogen,[6] and sulfur[7] analogues of leukotriene A_4 (LTA_4), and the dimethylamide of leukotriene B_4 (LTB_4).[8]

The subject of this paper, secoleukotriene A_4, lacks the reactive oxirane moiety of LTA_4 and consequently cannot undergo enzymatic hydration giving LTB_4 or conjugation with glutathione giving LTC_4. However, seco-LTA_4 should have enough structural similarity to LTA_4 to bind with the enzyme and function as an inhibitor. For these reasons, the following synthesis of seco-LTA_4 (**7**, n = 4) outlined in Scheme I was undertaken.

Allyl alcohol was alkylated with trimethyl 5-bromoorthovalerate (**1**, n = 4) in the presence of aqueous KOH,[9] producing the ether **2**, n = 4, which upon mild acid treatment produced ester **3**, n = 4. Reaction of olefin **3**, n = 4, with a catalytic amount of ruthenium trichloride in the presence of excess sodium periodate[10] gave the aldehyde **4**, n = 4. Homologation of this aldehyde with (triphenylphosphoranylidene)crotonaldehyde[11] gave the dienal **5**, n = 4. Wittig olefination of **5**, n = 4 with the ylide derived from the reaction of [(*Z*)-non-3-en-1-yl]triphenylphosphonium bromide with *n*-butyllithium[12] gave (8*E*,10*E*,12*Z*,15*Z*)-methyl 6-oxaheneicosa-8,10,12,15-tetraenoate (**6**, n = 4). Decoupling of ^1H NMR spectrum of

(1) Contribution No. 650 from the Institute of Organic Chemistry, Syntex Research.

(2) For a survey, see Bailey, D. M.; Chakrin, L. W. *Annu. Rep. Med. Chem.* **1981**, *16*, 219.

(3) (a) Corey, E. J.; Kantner, S. S.; Lansbury, P. T., Jr. *Tetrahedron Lett.* **1983**, *24*, 265. (b) Patterson, J. W., Jr.; Pfister, J. R.; Wagner, P. J.; Murthy, D. V. K. *J. Org. Chem.* **1983**, *48*, 2572.

(4) Arai, Y.; Konno, M.; Shimoji, K.; Konishi, Y.; Niwa, H.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, *30*, 379.

(5) Nicolaou, K. C.; Petasis, N. A.; Seitz, S. P. *J. Chem. Soc., Chem. Commun.* **1981**, 1195.

(6) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 331.

(7) Corey, E. J.; Park, H.; Barton, A.; Nii, Y. *Tetrahedron Lett.* **1980**, *21*, 4243.

(8) Showell, H. J.; Otteness, I. G.; Marfat, A.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1982**, *106*, 741.

(9) The reaction conditions used here are similar to those of Freedman and Bubois [Freedman, H. H.; Bubois, R. A. *Tetrahedron Lett.* **1975**, 3251] for the preparation of ethers from alkyl chlorides and alcohols. However, in the case of ortho esters **1**, the reaction was conveniently rapid in the absence of phase-transfer agents.

(10) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. The conditions used here are essentially those reported for the cleavage of olefins to carboxylic acids except only 2.5 equiv of $NaIO_4$ is used. Little effort was made to improve the modest yield of **4**, but this procedure avoids the use of osmium tetraoxide, which is difficult to handle and store.

(11) (a) Ernest, I.; Main, A. J.; Menasse, R. *Tetrahedron Lett.* **1982**, *23*, 167. (b) Berenguer, M. J.; Castells, J.; Galard, R. M.; Moreno-Manas, M. *Ibid.* **1971**, 495.

(12) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioshowski, C.; Samuelson, B.; Hammerstrom, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436.

0022-3263/83/1948-4413$01.50/0