7.19. Found: C, 64.14; H, 7.41.

(±)-(1α,2α,4bβ,10α)-Ethyl 8,8-(Ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-(4-tolylsulfonyloxy)gibb-4a(10a)-ene-10-carboxylate. This compound was prepared in 74% yield as described for the corresponding 2α-benzenesulfonate and crystallized from ether: mp 157–159 °C; ^{1}H NMR 7.70 (d, J = 8 Hz, 2 H, ArH), 7.25 (d, J = 8 Hz, 2 H, ArH), 4.70, 4.58 (ABq, J = 7 Hz, 2 H, OCH_2O), 4.40 (dd, J = 4, 12 Hz, 1 H, H-2), 4.09 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.93 (m, 4 H, OCH_2CH_2O), 3.65 (s, 3 H, CO_2CH_3), 3.24 (s, 3 H, OCH_3), 2.42 (s, 3 H, $ArCH_3$), 1.24 (t, J = 7 Hz, CH_2CH_3), 1.04 (s, 3 H, CH_3); IR 1725, 1320 cm^{-1}; m/z 634 (2%, M$^+$), 589 (25), 515 (22), 486 (10), 462 (15), 430 (14), 417 (100). Anal. Calcd for $C_{32}H_{42}O_{11}S$: C, 60.55; H, 6.67. Found: C, 60.48; H, 6.59.

Acknowledgment. We are indebted to Dr A. J. Baker and Professor H. J. E. Loewenthal for helpful correspondence and to Drs L. Lombardo and J. V. Turner for useful suggestions. We gratefully acknowledge technical assistance by the late A. L. Cossey and V. Richardson.

Registry No. 8, 73177-45-4; (±)-8a, 91127-18-3; (±)-10, 54099-85-3; (±)-11a, 75758-96-2; (±)-11b, 91156-85-3; (±)-12, 75758-88-2; 13, 15184-99-3; 15, 73177-51-2; 18, 91127-19-4; (±)-19, 91127-20-7; (±)-20, 75758-89-3; (±)-20 methyl ester, 75758-84-8; (±)-21 (R = CH_2Cl), 75758-92-8; (±)-21 (R = Cl_2CH), 91127-21-8; (±)-22 (R = Cl_2CH), 91156-86-4; (±)-22 (R = CH_2Cl), 75758-93-9; (±)-23a, 75758-95-1; (±)-23b, 91156-78-4; (±)-24a, 91127-22-9; (±)-24b, 91127-23-0; (±)-24c, 91127-24-1; (±)-25a, 91127-25-2; (±)-25b, 91127-26-3; (±)-26a, 91156-87-5; (±)-26b, 91127-27-4; (±)-32, 75758-97-3; (±)-33, 75758-99-5; (±)-34, 75759-00-1; (±)-36, 91127-28-5; methyl 6-[(*N*,*N*-dimethylamino)methyl]-2-methoxybenzoate, 91127-29-6; methyl 6-(chloromethyl)-2-methoxybenzoate, 91127-30-9; (±)-2-(dichloroacetoxy)-7-methoxy-1,2,3,4-tetrahydro-8-(methoxycarbonyl)fluorene-2-carboxylate, 91127-31-0; (±)-2-(chloroacetoxy)-7-methoxy-8-(methoxycarbonyl)-1,2,3,4-tetrahydrofluorene-2-carboxylic acid, 75758-90-6; (±)-methyl 8,8-(ethylenedioxy)-7-hydroxy-2-methoxygibba-1,3,4a(10a),4b-tetraene-1-carboxylate, 75758-94-0; (±)-methyl 8,8-(ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a),4b-tetraene-1-carboxylate, 75758-85-9; (±)-(1α,4bβ,10α)-8,8-(ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-oxogibb-4a(10a)-ene-10-carboxylic acid, 91156-88-6; (±)-(1α,2α,4bβ,10α)-8,8-(ethylenedioxy)-2-hydroxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-10-carboxylic acid, 91156-89-7; (±)-(1α,2α,4bβ,10α)-2-(benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-1-carboxylic acid, 75758-98-4; (±)-(1α,2α,4aα,4bβ,10β)-2-(benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-hydroxy-1-methylgibbane-1,4a-carbolactone, 75759-01-2; (±)-(1α,2α,4bβ,10α)-ethyl 8,8-(ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-(4-tolylsulfonyloxy)gibb-4a(10a)-ene-10-carboxylate, 91156-90-0; (±)-(1α,2α,4bβ,10α)-ethyl 8,8-(ethylenedioxy)-1-(methoxycarbonyl)-2-(phenylsulfonyl)-7-[(methoxymethyl)-oxy]-1-methylgibb-4a(10a)-ene-10-carboxylate, 91127-32-1; *m*-methoxybenzyl bromide, 874-98-6; 2,5-dimethoxybenzoic acid, 2785-98-0.

Phospholipid Studies of Marine Organisms. 7.[1] Stereospecific Synthesis of (5*Z*,9*Z*)-, (5*Z*,9*E*)-, (5*E*,9*Z*)-, and (5*E*,9*E*)-5,9-Hexacosadienoic Acid

Philippe L. Mena, Olivier Pilet,[2] and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

Received February 27, 1984

(5*Z*,9*Z*)-5,9-Hexacosadienoic acid (**5a**) and its stereoisomers **9a**, **15a**, and **21a** were synthesized stereospecifically. The difunctionalized (4*Z*)-1,1-dimethoxy-8-tosyl-4-octene (**2b**) prepared by selective ozonolysis of (1*Z*,5*Z*)-1,5-cyclooctadiene (**1**) was coupled with tridecylmagnesium bromide to afford the cis acetal **3**. The corresponding trans acetal **7** was obtained by olefin inversion in 98% stereoisomeric purity. The aldehydes **4** and **8** obtained by hydrolysis of the acetals **3** and **7** were coupled with the Wittig salt of 5-bromovaleric acid to give the 5*Z*,9*Z* (**5a**) and 5*Z*,9*E* (**9a**) acids, respectively. Reaction of **4** and **8** with vinylmagnesium bromide gave the appropriate allylic alcohols **10** and **16** which upon Claisen rearrangement led stereospecifically to (4*E*,8*Z*)- and (4*E*,8*E*)-4,8-pentacosadienoic acid methyl esters **11** and **17**. The stereoisomeric pair 5*E*,9*Z* (**15a**) and 5*E*,9*E* (**21a**) were prepared by standard one-carbon chain extension: lithium aluminum hydride reduction, mesylation, displacement by cyanide, and hydrolysis. Differentiation of these four isomers among themselves is possible by reversed-phase HPLC with silver nitrate in the mobile phase as well as on the basis of ^{13}C NMR measurements.

Recent phospholipid studies from our laboratory[3-8] have revealed the presence of high levels of unusual fatty acids in certain marine invertebrates. Litchfield et al.[9] reported the occurrence of a new class of C_{24-30} "demospongic" acids in marine sponges; in addition to unusual chain length, many of these acids possess the uncommon *cis*,*cis*-$\Delta_{5,9}$-diene systems. In order to understand the stereochemical effect of such double bonds in fatty acyl moieties of phospholipids, we have undertaken a stereospecific synthesis of the four geometrical isomers of the naturally occurring (5*Z*,9*Z*)-5,9-hexacosadienoic acid (**5a**) for eventual incorporation into phospholipids needed for model membrane studies.

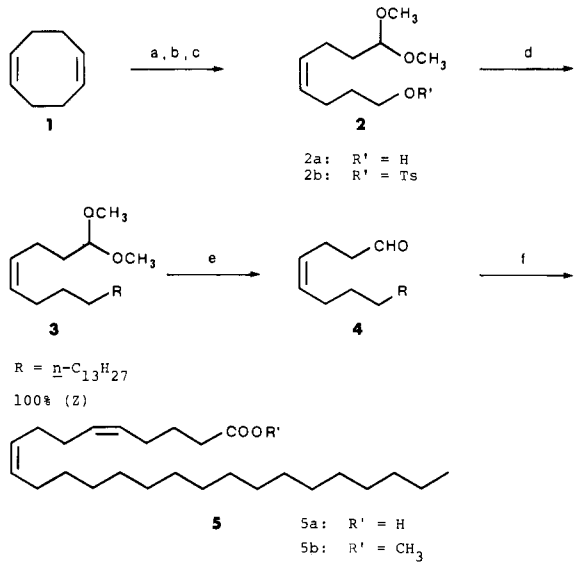
Results and Discussion

Since stereochemical purity is of great importance in nature, we selected a synthetic approach by taking advantage of the cis configuration in the readily available (1*Z*,5*Z*)-1,5-cyclooctadiene (**1**) to introduce the C-9 double bond. Selective ozonolysis of this diene has already been used in pheromone synthesis[10] although no experimental

(1) For part 6 in this series, see ref 8.
(2) Present address: Departement Analytique, CIBA-GEIGY SA, 1870 Monthey, Switzerland.
(3) Walkup, R. D.; Jamieson, G. C.; Ratcliff, M. R.; Djerassi, C. *Lipids* **1981**, *16*, 631–646.
(4) Ayanoglu, E.; Walkup, R. D.; Sica, D.; Djerassi, C. *Lipids* **1982**, *17*, 617–625.
(5) Ayanoglu, E.; Kornprobst, J. M.; Aboud-Bichara, A.; Djerassi, C. *Tetrahedron Lett.* **1983**, *24*, 1111–1114.
(6) Ayanoglu, E.; Popov, S.; Kornprobst, J. M.; Aboud-Bichara, A.; Djerassi, C. *Lipids* **1983**, *18*, 830–836.
(7) Lankelma, J.; Ayanoglu, E.; Djerassi, C. *Lipids* **1983**, *18*, 853–858.
(8) Ayanoglu, E.; Wegmann, A.; Pilet, O.; Marbury, G. D.; Hass, J. R.; Djerassi, C. *J. Am. Chem. Soc.*, in press.
(9) Jefferts, E.; Morales, R. W.; Litchfield, C. *Lipids* **1974**, *9*, 244–247.

0022-3263/84/1949-3260$01.50/0

Scheme I[a]



[a] (a) 1 equiv of O_3, MeOH, −78 °C; (b) TsOH catalyst, room temperature, 1 h; (c) 1.2 equiv of $NaBH_4$, −10 °C; (d) n-$C_{13}H_{27}MgBr$, THF, Li_2CuCl_4 catalyst, 0 °C, 2 h; (e) acetone, concentrated HCl (20:1), room temperature, 1 h; (f) $Ph_3P^+CH_2CH_2CH_2CH_2COOHBr^-$, KH, Me_2SO, room temperature, 2 h.

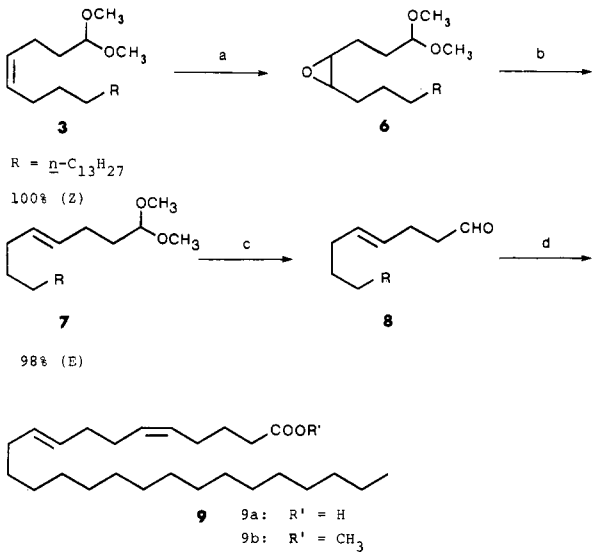
detail is described. The cleavage of one double bond of this diene provides not only the required 100% *cis*-olefin but also two functional groups needed for chain elongation (Scheme I). Thus, ozonolysis of **1** with 1 equiv of O_3 in MeOH at −78 °C followed by acetal formation via acid treatment and reduction with $NaBH_4$ afforded 35% of the alcohol–acetal **2a**. Tosylation of **2a** followed by cross-coupling with tridecylmagnesium bromide in the presence of a catalytic amount of Li_2CuCl_4[11] gave the key intermediate **3**.

Since the stereochemical control of the Wittig olefination has been extensively studied,[12] the C-5 double bond was introduced by coupling **3**, after removal of the acetal protective group, with the phosphonium salt of 5-bromovaleric acid. The naturally occurring (5*Z*,9*Z*)-5,9-hexacosadienoic acid (**5a**) was obtained in 80% yield (based on the aldehyde) in 95% stereochemical purity, characterized as its methyl ester **5b**. Coinjection on capillary GC of the synthetic product with natural material isolated from *Axinella verrucosa* gave only one peak, and their mass spectra were identical.

The 5*Z*,9*E* acid (**9a**) was synthesized from **3** by alkene inversion[13] followed by Wittig cis-olefination (Scheme II). Thus, epoxidation of the cis acetal **3** with 1.1 equiv of *m*-chloroperbenzoic acid in dichloromethane afforded the epoxide **6** in 90% yield. The required key intermediate **7** for the 5*Z*,9*E* (**9a**) and the 5*E*,9*E* (**21a**) acids could be obtained (80% yield) by treatment of **6** with 2 equiv of lithium diphenylphosphine followed by addition of excess methyl iodide.

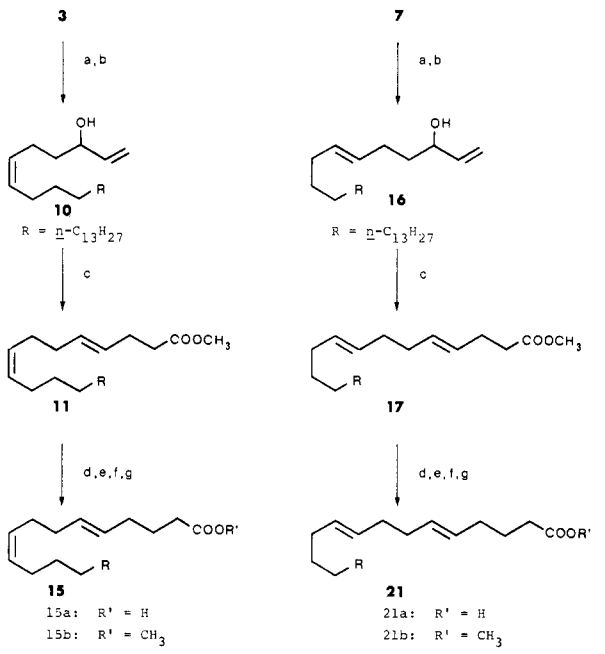
The stereospecific feature of the Claisen rearrangement[14] was used to introduce the critical C-5 double bond in the

Scheme II[a]



[a] (a) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h; (b) $LiPPh_2$, THF, room temperature, 3 h, then CH_3I; (c) acetone, concentrated HCl (20:1), 1 h, room temperature; (d) $Ph_3P^+(CH_2)_4COOHBr^-$, KH, Me_2SO, room temperature, 2 h.

Scheme III[a]



[a] (a) Acetone, concentrated HCl (20:1), room temperature, 1 h; (b) CH_2=$CHMgBr$, THF, room temperature, 2 h; (c) $CH_3C(OCH_3)_3$, $CH_3CH_2CH_2COOH$ catalytic, 140 °C, 1 h; (d) $LiAlH_4$, Et_2O, room temperature, 1 h; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (f) NaCN, Me_2SO, 65 °C, 3 h; (g) KOH, EtOH, reflux, 48 h.

5*E*,9*Z* and 5*E*,9*E* acids (Scheme III). Each pure isomer **3** and **7** was separately converted into the corresponding aldehyde and treated with vinyl magnesium bromide in THF to afford in good yield the respective allylic alcohols **10** and **16**. The resulting stereoisomers **10** and **16** were then subjected to a Claisen rearrangement with trimethyl orthoacetate to generate exclusively either the 4*E*,8*Z* (**11**) or the 4*E*,8*E* (**17**) methyl ester. Subsequent carbon-chain elongation by a standard multistep sequence (LAH–ether; MsCl, Et_3N, CH_2Cl_2; NaCN–Me_2SO; KOH–EtOH) afforded the acids **15a** and **21a**, respectively.

(10) Odinokov, V. N.; Tolstikov, G. A.; Galeyava, R. I.; Kargapoltseva, T. A. *Tetrahedron Lett.* **1982**, *23*, 1371–1372. Tolstikov, G. A.; Odinokov, V. N.; Galeyava, R. I.; Bakeeva, R. S. *Ibid.* **1978**, 1857–1858.
(11) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305.
(12) Bestmann, H. J.; Vostrowsky, O. *Chem. Phys. Lipids* **1979**, *24*, 335–389.
(13) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822–825.
(14) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

Table I. ^{13}C NMR Chemical Shifts of Stereoisomers of 5,9-Hexacosadienoic Acid, Methyl Esters[a]

atom	chemical shift, ppm			
	5b	9b	15b	21b
C-1	174.015	174.009	173.217	173.454
C-2	34.055	33.478	34.265	34.065
C-3	24.706	24.802	24.679	24.711
C-4	26.412	26.548	31.906	31.505
C-5	128.425	128.427	128.828	127.726
C-6	131.997	132.001	131.194	130.420
C-7	27.235	27.405	32.592	32.214
C-8	27.116	32.581	27.236	33.711
C-9	128.595	128.595	128.253	128.949
C-10	132.136	132.139	130.343	130.802
C-11	27.116	31.916	27.133	32.153
C-12	29.554	29.674	29.673	29.274

[a] Chemical shifts of carbon atoms 13–24 are less informative, and their assignments are subject to ambiguity.

Alternatively, the 5*E*,9*Z* (**15a**) and 5*E*,9*E* (**21a**) isomers were prepared by Wittig trans-olefination under Schlosser conditions from **4** and **8**. Although we followed closely the described procedure,[15] appreciable amounts (ca. 25%) of isomers **5a** or **9a** were generated along with the desired isomer, due to partial equilibration of the Wittig intermediates.

Brief mention should be made of our efforts to employ an acetylenic route for the synthesis of the four stereoisomers. Several trials were carried out with the cross-coupling of 1-bromo-3-eicosyne or (3*Z*)-3-eicosenyl tosylate with the dilithio derivative of 5-hexynoic acid and in no case was any or little (10%) reaction observed. The lack of reactivity is presumably due to the stereoelectronic effect of the triple or double bond in β-position to the leaving group and the chain length of the alkyl halide.

Analysis

It has been shown that differentiation of stereoisomeric mixtures of unsaturated compounds can be achieved by capillary GLC,[16] partial argentation resin chromatography,[17] HPLC,[18] and reversed-phase HPLC using $AgNO_3$ in the mobile phase.[19] Although no separation of the 5*E*,9*Z* (**15**) isomer from its 5*Z*,9*E* (**9**) counterpart was observed, the last method enabled us to determine the stereochemical purity of the presently described fatty acids. Since the isomeric purity of the C-9 double bond is >98% as determined by capillary GLC and no stereomutation is expected in Wittig or Claisen rearrangement conditions, the only possible isomeric pairs formed in these reactions are the 5*Z*,9*Z* (**5**)/5*E*,9*Z* (**15**) and 5*Z*,9*E* (**9**)/5*E*,9*E* (**21**) mixtures. They are well resolved on a RP-Altex Ultrasphere ODS 5-μm/column using silver nitrate (50 mM) in the mobile phase (5% aqueous methanol). The Wittig reaction afforded predominantly the 5*Z*,9*Z* (**5a**) and the 5*Z*,9*E* (**9a**) acid in 95% and 96% stereoisomeric purity, respectively. Except for the Claisen rearrangement products **15a** and **21a** no other isomers were detected.

In Table I, we summarize the ^{13}C NMR data of the four stereoisomers **5b**, **9b**, **15b**, and **21b**. Diagnostic differences can be noted in the chemical shift of the C-4, C-7, C-8, and C-11 signals due to the γ-shift effect induced by the geometry of the double bond at C-5,6 or C-9,10. The two methylenic carbons directly bonded to the *cis*-CH=CH moiety are shifted at higher field with respect to the trans double bond (ca. 5 ppm). Assignment of the chemical shifts of the listed carbons was made by calculations based on the parameters previously reported.[20-22] Experimental and calculated values are in good agreement (0.08 ppm).

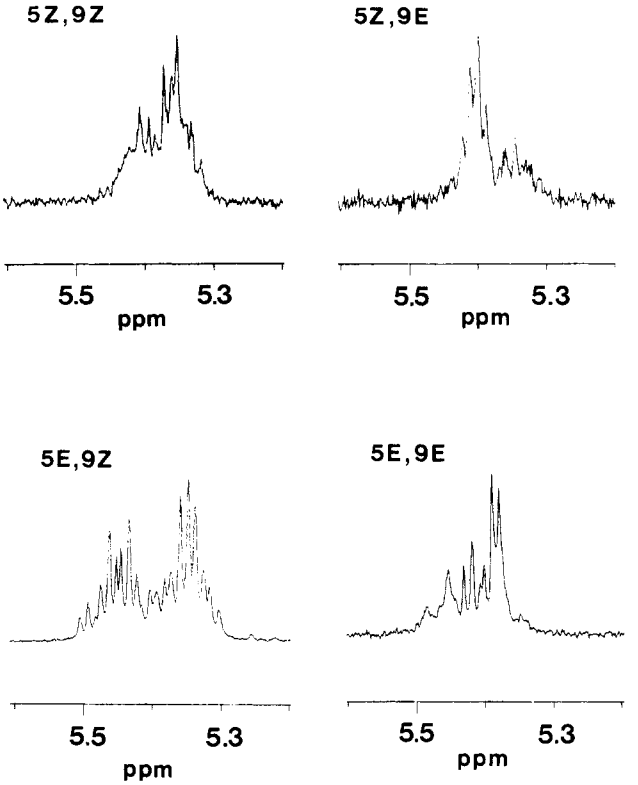


Figure 1. Olefinic region in 500-MHz ^1H NMR spectra of 5*Z*,9*Z* (**5**), 5*Z*,9*E* (**9**), 5*E*,9*Z* (**15**), and 5*E*,9*E* (**21**) hexacosadienoic acids.

The 500-MHz ^1H NMR spectra (Figure 1) show different patterns of the olefinic region in such dimethylene-interrupted diene systems, information that can now be used for structure determination.

The FT-IR spectrum of the 5*Z*,9*Z* isomer exhibits a notable absence of absorption at 966 cm^{-1}, and this can be used for partial differentiation. Mass spectrometry, however, proved useless since the mass spectra of **5b**, **9b**, **15b**, and **21b** were identical. Therefore, the best way to establish stereochemical purity for such diene systems is RP-HPLC using silver nitrate in the mobile phase.

Experimental Section

Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in chloroform solutions on a Nicolet Model 7199 Fourier-transform spectrometer. ^1H NMR spectra were obtained on a Nicolet NT 300 WB (300 MHz) spectrometer or a JEOL FX 500 spectrometer (500 MHz), using $CDCl_3$ as solvent and tetramethylsilane (Me_4Si) as internal reference. ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer. Mass spectra were obtained on a gaschromatograph/mass spectrometer Hewlett-Packard HP 5995.

High-pressure liquid chromatography (HPLC) was performed on a Waters Associates system (M 6000 pump, R 403 differential

(15) Schlosser, M.; Christmann, K. F. *Liebigs Ann. Chem.* **1967**, *708*, 1–35.
(16) Heckers, H.; Melcher, F. W.; Schloeder, U. *J. Chromatogr.* **1977**, *136*, 311–317.
(17) Adlof, R. O.; Emken, E. A. *J. Am. Oil Chem. Soc.* **1981**, 99–101. Schoffield, C. R. In "Geometrical and Positional Fatty Acid Isomers"; Emken, E. A., Button, H. S., Eds.; The American Oil Chemist Society: Champain, 1979.
(18) Wood, R.; Lee, T. *J. Chromatogr.* **1983**, *254*, 237–240.
(19) Phelan, P. L.; Miller, J. R. *J. Chromatogr. Sci.* **1981**, *19*, 13–17.
(20) Gunstone, F. D.; Pollard, M. R.; Scrimgeour, C. M.; Vedenayagam, H. S. *Chem. Phys. Lipids* **1977**, *18*, 113–129.
(21) Bus, I.; Sies, I.; Lie Ken Jie, M. S. F. *Chem. Phys. Lipids* **1977**, *18*, 130–144.
(22) Bus, I.; Sies, I.; Lie Ken Jie, M. S. F. *Chem. Phys. Lipids* **1976**, *17*, 501–518.

refractometer) and a reversed-phase Altex Ultrasphere 5-μm ODS column, 25 cm, using 5% aqueous methanol containing 50 mM silver nitrate as the mobile phase. Gas chromatography (GLC) was obtained from a Carlo Erba Fractovap chromatograph equipped with a FID detector, using a SE-54 (30 m, 0.32 mm) column.

Column chromatography was performed on Merck grade silica gel 60 or Fischer Scientific Co. neutral alumina, activity III (6% H_2O). By "usual workup", we mean dilution with water, extraction with ether, washing with water, drying over anhydrous Na_2SO_4, filtration, and evaporation under vacuo. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, qq = quintuplet, m = multiplet, br = broad.

(4*Z*)-1,1-Dimethoxy-4-octen-8-ol (2a). (1*Z*,5*Z*)-1,5-Cyclooctadiene (1) (5.0 g, 46.3 mmol) was ozonolyzed for 30 min (46 mmol of O_3) at −78 °C in methanol (40 mL). The reaction mixture was warmed to room temperature and a flow or argon was passed through. A few crystals of *p*-toluenesulfonic acid were added, and after stirring for 1 h at room temperature, the mixture was cooled to −10 °C and allowed to react with $NaBH_4$ (2.08 g, 55 mmol) for 20 min. Hydrolysis with ice–water and usual workup gave the cis alcohol **2a** in 35% yield after chromatography on neutral alumina, activity III; with hexane–ethyl acetate (1:1) as eluent R_f 0.40; IR (neat) 3609 (OH), 3010 (CH=CH), 1129 (CH[OCH_3]$_2$), 720 (CH=CH cis); ^{1}H NMR (300 MHz) δ 1.382 (1 H, br s, 8-OH), 1.684 (4 H, 7, 2-, 7-CH_2), 2.130 (4 H, m, 3-, 6-CH_2), 3.313 (6 H, s, 1-, 1-OCH_3), 3.632 (2 H, t, *J* = 7 Hz, 8-CH_2), 4.382 (1 H, t, *J* = 6.5 Hz, 1-C*H*[OCH_3]$_2$), 5.391 (2 H, br t, 4-, 5-CH=CH); mass spectrum, *m*/*z* (relative intensity) 188 (M^+, 0.1), 170 (2), 155 (10), 154 (13), 124 (21), 41 (100).

(4*Z*)-1,1-Dimethoxy-4-heneicosene (3). A solution of the cis alcohol **2a** (2.0 g, 10.6 mmol) in 30 mL of pyridine was cooled to 0 °C, and *p*-toluenesulfonyl chloride (4.0 g, 21 mmol) was added in small portions over a period of 30 min. The reaction was stirred for 2 h at this temperature, and after the usual workup, the tosylate **2b** was obtained in 91% yield (3.31 g): ^{1}H NMR (300 MHz) δ 1.676 (4 H, br m, 2-, 7-CH_2), 2.093 (4 H, m, 3-, 6-CH_2), 2.453 (3 H, s, OSOPhC*H*$_3$), 3.313 (6, s, 8-, 8-OCH_3), 4.382 (1 H, t, *J* = 6.5 Hz, 8-C*H*[OCH_3]$_2$), 4.028 (2 H, t, *J* = 6.5 Hz, CH_2OTs), 5.391 (2 H, br m, 4-, 5-CH=CH), 7.363 and 7.808 (4 H, 2 d, *J* = 8.5 Hz, OSO_2*Ph*CH_3).

The crude tosylate, dissolved in 30 mL of dry THF, was cooled to 0 °C, 1 mL of a 0.1 M solution of Li_2CuCl_4 (prepared from anhydrous 8.5 mg of LiCl and 13.4 mg of $CuCl_2$ in 1 mL of THF) was added, followed by tridecylmagnesium bromide (prepared from 1.20 g of Mg and 12.0 g of tridecyl bromide in 20 mL of THF), and the solution was stirred for 3 h at 0 °C under argon. Saturated ammonium chloride solution was added and the usual workup afforded a crude product which was purified by column chromatography on neutral alumina (6% H_2O) with hexane–ether (10:1), R_f 0.59.

The desired cis acetal **3** was obtained as colorless liquid: 2.59 g (76%); IR (neat) 1130 (CH[OCH_3]$_2$), 721 (CH=CH cis); ^{1}H NMR (300 MHz) δ 0.912 (3 H, t, *J* = 6.5 Hz, 21-CH_3), 1.410 (14 H, b s, aliphatic CH_2), 1.676 (2 H, m, 2-CH_2), 2.070 (4 H, m, 3-, 6-CH_2), 3.313 (6 H, s, 1-, 1-OCH_3), 4.382 (1 H, t, *J* = 6.5 Hz, 1-C*H*[OCH_3]$_2$), 5.386 (2 H, br m, olefinic protons); mass spectrum, *m*/*z* (relative intensity) 354 (M^+, 3), 323 (10), 322 (17), 290 (23), 267 (10), 264 (10), 201 (11), 135 (12), 84 (56), 75 (100).

(4*Z*)-4-Heneicosen-1-al (4). A solution of the cis acetal **3** (988 mg, 2.79 mmol) in 20 mL of acetone–HCl (20:1) was stirred at room temperature for 1 h. The usual workup gave 850 mg (98%) of the cis aldehyde **4** which was used without purification: IR (neat) 3010 (CH=CH), 1725 (C=O); ^{1}H NMR (300 MHz) δ 0.911 (3 H, t, *J* = 5.5 Hz, 21-CH_3), 1.410 (14 H, br s, aliphatic CH_2), 2.337 (2 H, m, 2-CH_2), 9.751 (1 H, t, *J* = 2 Hz, CHO); mass spectrum, *m*/*z* (relative intensity) 308 (M^+, 0.1), 290 (0.2), 264 (0.4), 135 (0.5), 123 (0.8), 98 (17.7), 84 (84.8), 69 (21.1), 55 (54.6), 41 (100).

(5*Z*,9*Z*)-5,9-Hexacosadienoic Acid (5a,b). To a solution of dimsylpotassium in Me_2SO (prepared from 342 mg, 8.5 mmol, of potassium hydride and 15 mL of Me_2SO at room temperature for 2 h) was added 2.215 g (5 mmol) of (4-carboxybutyl)triphenylphosphonium bromide (dried in vacuo overnight at 110 °C). To the resulting red solution, 778 mg (2.52 mmol) of the above described crude aldehyde in 10 mL of dry Me_2SO:THF (1:1) was added dropwise. After being stirred for 2 h, the reaction mixture was poured onto ice–water, acidified to pH 3 with 30% H_3PO_4, and extracted with petroleum ether. The oil obtained by removal of solvent was purified by column chromatography over silica gel with ether–hexane (2:1) to yield 875 mg (80%) of the pure acid **5a** characterized as its methyl ester **5b** by treatment with CH_2N_2: IR (film) 3005 (CH=CH), 1740 (C=O), 721 (CH=CH cis); ^{1}H NMR (300 MHz) δ 0.889 (3 H, t, *J* = 5.5 Hz, 26-CH_3), 1.262 (28 H, s, aliphatic CH_2), 1.694 (2 H, qq, *J* = 6 Hz, 3-CH_2), 1.98–2.11 (8 H, m, 4-, 7-, 8-, 11-CH_2), 2.336 (2 H, t, *J* = 6 Hz, 2-CH_2), 3.684 (3 H, s, OCH_3), 5.30–5.45 (4 H, br m, olefinic protons); mass spectrum, *m*/*z* (relative intensity) 406 (M^+, 0.3), 182 (0.6), 150 (2.7), 141 (6.9), 136 (2.7), 123 (2.0), 109 (13.3), 97 (9.4), 81 (43.2), 55 (63.5), 43 (100).

This material was identical in all respects with a sample isolated from *Axinella verrucosa*.[23]

***cis*-1,1-Dimethoxy-4-heneicosene 4,5-Epoxide (6).** A solution of 344 mg (2 mmol) of *m*-chloroperbenzoic acid dissolved in 2 mL of dry CH_2Cl_2 was slowly added to a solution of 580 mg (1.65 mmol) of **3** in 10 mL of CH_2Cl_2 at 0 °C. At the end of the addition, a white precipitate appeared and the reaction was stirred further for 2 h at this temperature. Inverted filtration and recrystallization in pentane afforded 547 mg (90%) of **6**: 89–90 °C; ^{1}H NMR (300 MHz) δ 0.902 (3 H, t, *J* = 5.5 Hz, 21-CH_3), 3.036 (2 H, br m, 4-H and 5-H), 3.305 (6 H, s, 1-, 1-OCH_3), 4.348 (1 H, t, *J* = 7 Hz, C*H*[OCH_3]$_2$).

(4*E*)-1,1-Dimethoxy-4-heneicosene (7). Finely cut lithium wire (250 mg) was washed with hexane under argon. Freshly distilled THF (20 mL) was added followed by 1.06 g (0.86 mL, 4.80 mmol) of chlorodiphenylphosphine (Aldrich, technical grade) and the mixture vigorously stirred at room temperature for 2 h. To a solution of epoxide **6** (64 mg, 0.17 mmol) in 1 mL of dry THF under argon was added dropwise 3.5 mL of freshly prepared solution of lithium diphenylphosphine described above. The resulting deep red solution was allowed to stand until the color was discharged. After 3 h at room temperature and a TLC check, 100 μL of CH_3I was added and the mixture was allowed to stand for 30 min. Pentane was then added and the precipitate filtered. A short column chromatography (Alox, activity III) afforded 43.1 mg (81%) of pure **7**. Gas chromatography on a 30-m SE-54 column with a temperature programmed from 200 °C to 250 °C (5°/min) showed the product to be 98% trans: IR (film) 1120 (CH[OCH_3]$_2$), 966 (CH=CH trans). The ^{1}H NMR and mass spectra of **7** were identical with those of **3**.

(5*Z*,9*E*)-5,9-Hexacosadienoic Acid (9a,b). A 919-mg (2.59 mmol) sample of trans acetal **7** and 2.0 g of acidic ion-exchange resin Dowex 50X4-400 in 50 mL of dry acetone were stirred overnight under nitrogen at room temperature. Filtration and evaporation of the solvent afforded 778 mg (97%) of **8**. The above crude aldehyde (629 mg, 2.04 mmol) in 10 mL of dry THF was added at room temperature to a stirred mixture of phosphonate salt in Me_2SO (prepared from the addition of 2.215 g, (5 mmol) of (4-carboxybutyl)triphenylphosphine bromide in 10 mL of Me_2SO to 342 mg (8.5 mmol) of potassium hydride in 10 mL of Me_2SO, under argon at room temperature with subsequent stirring for 1 h). After 3 h at room temperature, the mixture was hydrolyzed with ice–water, acidified with 30% H_3PO_4, and extracted with hexane. Column chromatography on silica gel with hexane–ether (2:1) afforded 607 mg (76%) of the desired acid **9a**: IR (film) 3006 (CH=CH), 1742 (C=O), 966 (CH=CH trans), 722 (CH=CH cis). The spectral data (300-MHz ^{1}H NMR, MS) of **9b** were identical with those of **5b**.

(*Z*)- and (*E*)-Tricosa-1,6-dien-3-ol (10 and 16). Vinyl bromide (107 mg, 10 mmol) was added dropwise to a suspension of magnesium (300 mg, 12 mmol) in dry THF (5 mL) at 0 °C under argon and stirred for 1 h at 0 °C. A solution of the cis aldehyde **4** (510 mg, 1.65 mmol) in dry THF (5 mL) was added to the Grignard reagent at room temperature and stirred for 3 h. The reaction was quenched by the addition of saturated ammonium chloride solution, and the usual workup afforded a crude crystalline compound **10** which was used without purification in the next step: yield 473 mg (86%); mp 38–39 °C; IR ($CHCl_3$) 3600 (OH), 3005 (CH=CH), 721 (CH=CH cis); ^{1}H NMR (300 MHz)

(23) Ayanoglu, E.; Djerassi, C., unpublished results. This acid was also isolated from *Petrosia ficiformis*, see ref 4 and 7.

δ 0.894 (3 H, t, J = 5.5 Hz), 4.105 (1 H, br m, 3-H), 4.80–6.20 (5 H, olefinic protons and ABX system); mass spectrum, m/z (relative intensity) M^+ absent, 318 (0.1), 264 (0.2), 149 (0.5), 135 (1.5), 111 (10.6), 94 (11.8), 55 (65), 43 (100).

The trans aldehyde **8** (418 mg) was converted to the allylic alcohol **16** in the same way: IR ($CHCl_3$) 3600 (OH), 3010 (C-H=CH), 967 (CH=CH trans). The ^1H NMR spectrum of **16** was similar to that of **10**.

(4*E*,8*Z*)- and (4*E*,8*E*)-4,8-Pentacosadienoic Acid, Methyl Ester (11 and 17). A solution of the cis alcohol **10** (420 mg, 1.25 mmol), trimethyl orthoacetate (5 mL), and a few drops of propionic acid was heated under argon at 140 °C for 1 h with removal of methanol. Evaporation of the excess trimethyl orthoacetate under vacuum and chromatography on 14.0 g of silica gel with hexane–ether (1:1) as eluent afforded 465 mg (95%) of **11** as a yellowish oil: R_f 0.79; IR ($CHCl_3$) 3006 (CH=CH), 1741 (C=O), 966 (CH=CH trans); ^1H NMR (300 MHz) δ 0.886 (3 H, t, J = 5.5 Hz), 1.258 (28 H, br s, aliphatic CH_2), 2.328 (2 H, t, J = 6.5 Hz, 3-CH_2), 2.338 (2 H, t, J = 6.5 Hz, 2-CH_2), 3.682 (3 H, s, OCH_3), 5.35–5.51 (4 H, br m, olefinic protons); mass spectrum, m/z (relative intensity) 392 (M^+, 0.3), 168 (0.6), 136 (2.5), 95 (14), 43 (100).

Claisen rearrangement of the trans alcohol **16** under the same conditions as for **10** gave the ester **17**: IR ($CHCl_3$) 3006 (CH=CH), 1741 (C=O), 966 (CH=CH trans). The ^1H NMR and mass spectra of **17** were similar to those of **11**.

(4*E*,8*Z*)- and (4*E*,8*E*)-4,8-Pentacosadienol (12 and 18). To a suspension of lithium aluminum hydride (229 mg, 6 mmol) in dry THF (10 mL) was added dropwise a solution of the ester **11** (465 mg) in dry ether (5 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Addition of 986 mg (9 mmol) of oxalic acid dihydrate and filtration over Celite afforded the alcohol **12**: 358 mg (90%); R_f 0.36; IR (neat) 3605 (OH), 967 (CH=CH trans); ^1H NMR (300 MHz) δ 0.901 (3 H, t, J = 5.5 Hz), 3.671 (2 H, t, J = 6.5 Hz, 1-CH_2), 5.435 (4 H, m, olefinic protons); mass spectrum, m/z (relative intensity) M^+ absent, 346 (0.1), 207 (1.4), 83 (20), 55 (65), 43 (100).

The ester **17** was reduced in the same way to give the alcohol **18**. Its spectroscopic data were identical with those of **12**.

(4*E*,8*Z*)- and (4*E*,8*E*)-4,8-Pentacosadienol Methanesulfonate (13 and 19). A solution of the alcohol **12** (358 mg, 1.18 mmol) in 5 mL of CH_2Cl_2 and 0.5 mL of Et_3N was treated dropwise with 0.2 mL of MsCl at 0 °C and stirred for 1 h. The usual workup afforded the mesylate **13**: 438 mg (93%) after purification on chromatography on silica gel using hexane–ether (1:1), R_f 0.33.

The alcohol **18** was converted to the mesylate **19** in the same way. Both isomers **13** and **19** have the same spectral properties: IR ($CHCl_3$) 1371, 1350, 1178 (OSO_2CH_3); ^1H NMR (300 MHz) δ 0.890 (3 H, t, J = 5.5 Hz), 2.978 (3 H, s, CH_3SO_3), 4.256 (2 H, t, J = 6 Hz, 1-CH_2), 5.432 (4 H, br m, olefinic protons).

(4*E*,8*Z*)- and (4*E*,8*E*)-1-Cyano-4,8-pentacosadiene (14 and 20). The mesylate **13** (410 mg, 0.92 mmol) dissolved in 5 mL of THF was added dropwise to a solution of NaCN (196 mg, 4 mmol) in Me_2SO (5 mL) at 65 °C and stirred for 3 h. The usual workup and chromatography on silica gel with hexane–ether (1:1) as the eluent gave the cyanide **14** in 90% yield (311 mg): IR (neat) 3006 (CH=CH), 2240 (CN), 966 (CH=CH trans); ^1H NMR (300 MHz) δ 0.890 (3 H, t, J = 5.5 Hz), 2.605 (2 H, t, J = 6 Hz, 2-CH_2), 5.433 (4 H, br m, olefinic protons); mass spectrum, m/z (relative intensity) 373 (M^+, 0.3), 218 (0.3), 190 (0.6), 176 (1.5), 97 (12.0), 83 (31.2), 55 (67.1), 41 (100).

Similarly, the mesylate **19** was converted to the cyanide **20** whose spectroscopic data were identical with those of **14**.

(5*E*,9*Z*)- and (5*E*,9*E*)-5,9-Hexacosadienoic Acid (15 and 21). The cyanide **14** (290 mg, 0.77 mmol) was hydrolyzed in 2 N KOH/ethanol for 48 h under refluxing conditions to give the acid **15a** (159 mg). Similarly, the cyanide **20** afforded the 5*E*,9*E* acid **21a**. The spectroscopic data of **15b** and **21b** were identical with those of **9b**.

Acknowledgment. Financial support was provided by NIH grant GM 06840. We thank Dr. Lois J. Durham for the ^{13}C NMR spectra. Use of the NMR center at the Stanford 500-MHz and 300-MHz facility (NSF Grant GP 23633) is gratefully acknowledged. P.L.M. and O.P. thank the Swiss National Science Foundation for postdoctoral fellowships.

Registry No. **1**, 1552-12-1; **2a**, 72195-80-3; **2b**, 82861-01-6; **3**, 90913-48-7; **4**, 90913-49-8; **5a**, 52715-55-6; **5b**, 90913-50-1; **6**, 90913-51-2; **7**, 90913-52-3; **8**, 90913-53-4; **9a**, 90913-54-5; **9b**, 90913-55-6; **10**, 90913-56-7; **11**, 90913-57-8; **12**, 90913-58-9; **13**, 90913-59-0; **14**, 90913-60-3; **15a**, 90913-61-4; **15b**, 90913-62-5; **16**, 90913-63-6; **17**, 90913-64-7; **18**, 90913-65-8; **19**, 90913-66-9; **20**, 90913-67-0; **21a**, 90913-68-1; **21b**, 90913-69-2; (4-carboxybutyl)-triphenylphosphonium bromide, 17814-85-6; vinylbromide, 593-60-2; trimethyl orthoacetate, 1445-45-0.

A Synthetic Approach to the Quassinoids

Clayton H. Heathcock,* Cyril Mahaim,[1] Matthew F. Schlecht,[2] and Thanin Utawanit[3]

Department of Chemistry, University of California, Berkeley, California 94720

Received February 1, 1984

A synthetic route to the quassinoids has been developed. Two-stage annelation of 2-methylcyclohexanone with 1-chloro-3-pentanone gives tricyclic dienone **9** (60%), which is oxidized by acetyl chromate in acetic acid to give dienedione **27** (80%). Bisketalization of this material followed by hydrolysis of the conjugated enone ketals provides monoketal **30** (77%), along with recovered **27**. Ring C of **30** is functionalized by the Stiles and Reich methods to obtain the unsaturated keto ester **33** (73%). The latter material reacts with ketene acetal **35** at 5–6 kbar and room temperature to give an adduct that is desilylated by treatment with aqueous KF; keto diester **39** is produced in 95% yield. Epoxidation of **39** occurs smoothly with *m*-CPBA to give **46** (88%), which is converted into allylic alcohol **40** by the two-step Sharpless procedure (78%). Finally, pyridinium chlorochromate induces solvolytic cyclization of **40**, affording **41** in 55% yield. In the course of the investigation, it was also discovered that β-keto ester **46** is oxidized by *m*-CPBA to **47** in quantitative yield.

The quassinoids are a group of diterpenoids that occur in genera of the family Simaroubaceae.[4] Those members of the group that have been obtained from the genus *Brucea* are known as bruceolides.[5-9] In 1973, S. M.

(1) Current address: Sandoz Ltd., Pharmaceutical Division, Chemical Research, CH-4002 Basel, Switzerland.

(2) Current address: Department of Chemistry, Polytechnic Institute of New York, Brooklyn, NY 11201.

0022-3263/84/1949-3264$01.50/0