A Stereocontrolled Synthesis of *dl*-Biflora-4,10(19),15-triene[1]

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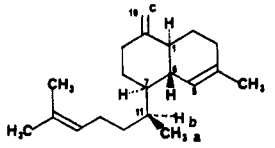
The stereoselective synthesis of *dl*-biflora-4,10(19),15-triene (1), a bicyclic diterpene component of the defense secretion of termite soldiers (*Cubitermes umbratus*), makes use of the regioselective Ireland–Claisen rearrangement of the *Z*-enolates of esters of 2,5-disubstituted 1,4-dien-3-ols. The synthetic scheme links the dienol Ireland–Clasisen rearrangement with an intramolecular Diels–Alder closure; this strategy allows introduction of the four contiguous chiral centers with the desired relative stereochemistry.

The defense system of the termite colony is based on a strategically constructed nest fortified by members of the soldier caste.[2] The soldiers exhibit genus-specific attack behavior; in many genera, glandula secretions are used to repel or disable invaders. The secretions act as irritants, entangling agents, and highly specific insecticides. Their chemical constituents include long-chain functionalized and nonfunctionalized alkanes, terpenoids, and macrocycles.[3]

Cubitermes is one of the biting/injecting genera. In defending the nest against the most common predator, the ant, the soldiers discharge a diterpene mixture from glands situated above saber-like mandibles; the secretions coats the mandibles and is thus applied to wounds of the victims.[4] Although the function of the defense secretion is unknown for *Cubitermes*, it has been suggested that its components[5] may interfere with coagulation of the hemolymph or with cuticle repair.[4]

Of six species of *Cubitermes* studied to date, five produce secretions which contain the diterpene biflora-4,10(19),15-triene (1).[4,6] In *Cubitermes umbratus*, the secretion contains 29% of this compound.

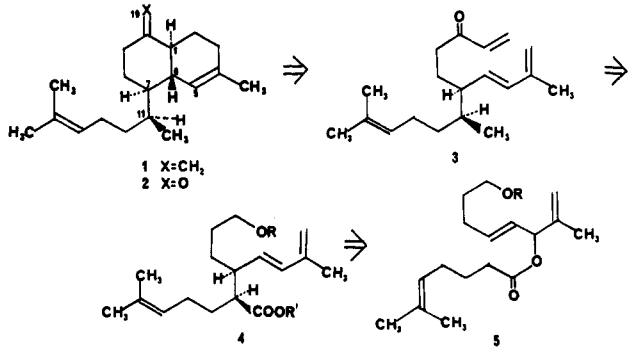


1

The structure of bifloratriene 1 was established by an X-ray crystallographic study of a derivative.[5c] Mori and Waku have now shown the absolute configuration of 1 to be 1*S*,6*R*,7*R*,11*S*.[m]

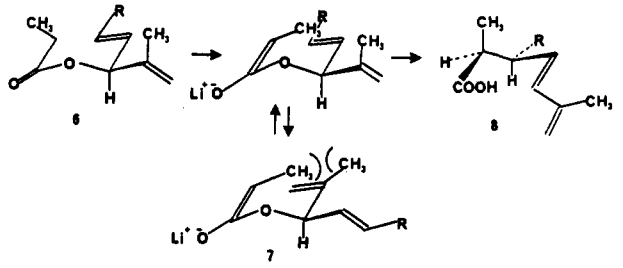
Strategy

Structure 1, which contains four contiguous chiral centers, two of them at the ring juncture positions, seemed a prime target for construction by our new cyclization strategy.[8] In this approach to bicyclic systems, two chiral centers are fixed by Ireland–Claisen rearrangement[9] and one of these is used to induce one (or conceivably both) of the chiral centers at the ring juncture in a subsequent intramolecular Diels–Alder closure. (Concurrent with our explorations, two other Diels–Alder preparations of 1 were developed; however, these were otherwise stereorandom[10]). The retrosynthetic analysis applied to structure 1 is shown below.



1 X=CH$_2$
2 X=O
3
4
5

Unlike our previous use of this strategy, this application requires regioselectivity in the Ireland–Claisen rearrangement of an ester of a dienol. Model studies have now shown that *Z*-enolates 7 (from dienol esters 6 with substitution patterns similar to that of 5) undergo rearrangement to acids 8 with regioselectivity (i.e., to the substituted terminus rather than to the methylene of the isopropenyl group) as well as with the expected stereoselectivity.[1]



6
7
8

(1) For model studies which form the basis for the key step of this synthesis see: Parker, K. A.; Farmar, J. G. *Tetrahedron Lett.* **1985**, *26*, 3655.

(2) Deligne, J.; Pasteels, J. M. In *The Biology of Social Insects*; Breed, M. D., Michener, C. D., Evans, H. E., Eds.; Westview Press: Boulder, CO; 1982; pp 288–289.

(3) The genus-specific defense mechanisms of termites are discussed in the following (a) Prestwich, G. D. *Sci. Am.* **1983**, *249*, 78. (b) Deligne, J.; Quennedey, A.; Blum, M. S. In Hermann, H. R. *Social Insects*, Vol. II, Academic Press: New York, 1981; pp 1–76.

(4) Prestwich, G. D. *J. Chem. Ecol.* **1984**, *10*, 1219.

(5) (a) Prestwich, G. D.; Wiemer, D. F.; Meinwald, J.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 2560. (b) Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Miura, I. *J. Org. Chem.* **1979**, *44*, 3950. (c) Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Solheim, B.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 191.

(6) Bifloratriene 1 is also present in the defense secretion of the *Cubitermes* guest species *Cubitermes mixtus*. According to ref 4, the GC traces of the defense secretions afford a species-specific fingerprint for *Cubitermes*.

(7) Mori, K.; Waku, M. *Tetrahedron* **1984**, *40*, 305.

(8) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1982**, *47*, 337.

(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(10) While our work was in progress, two groups reported syntheses of bifloratrienes: (a) Mori (ref 7) prepared four of the eight possible stereoisomers of (11*S*)-bifloratriene by a nonstereoselective route based on the intramolecular Diels–Alder closure of a mixture of ketone 3 and its C-7 epimer. (b) Vig has also reported two routes to biflora-4,10(19),15-trienes in which the same intramolecular Diels–Alder closure (of *dl*-3 and its diastereomer) was used. As no effort was made to control stereochemistry in either route, Vig's products presumably consisted of mixtures of the enantiomeric pairs of the four stereoisomers obtained by Mori: Vig, O. P.; Sharma, M. L.; Kiran, S.; Singh, J. *Ind. J. Chem.* **1983**, *22B*, 746. Vig, O. P.; Vig, R.; Kaur, U. J.; Jindal, R. T. *J. Ind. Chem. Soc.* **1983**, *60*, 757.

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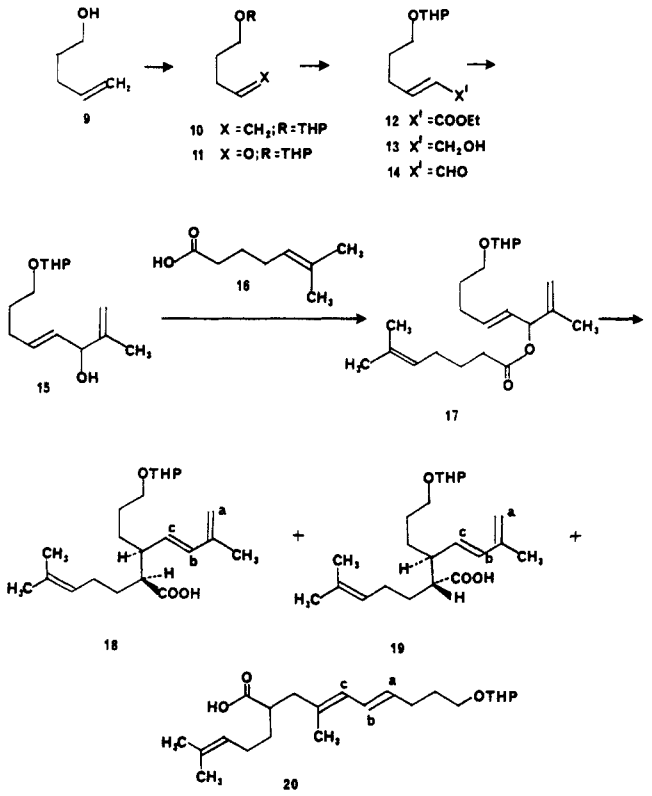
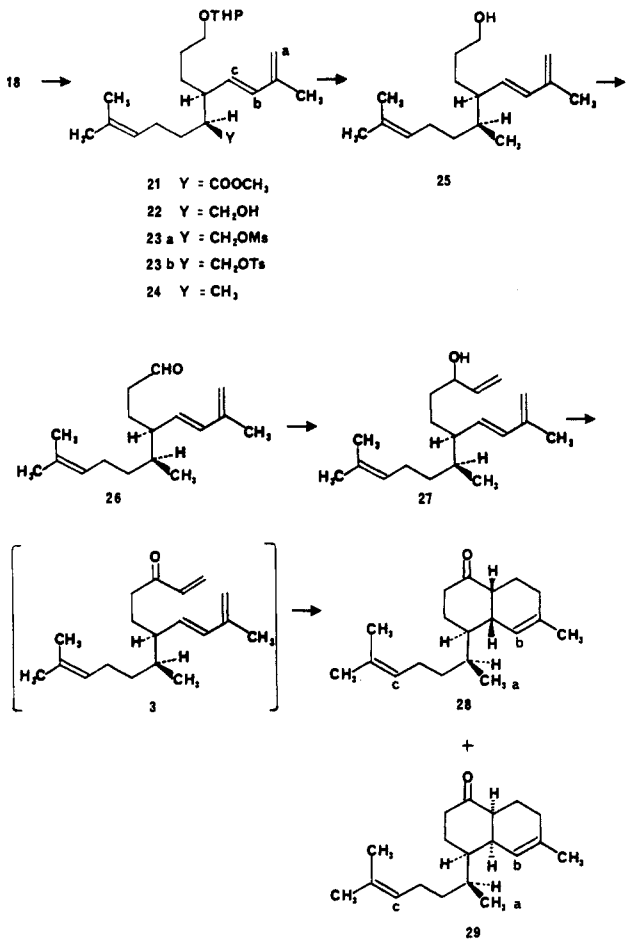
Scheme I



Scheme II



Thus, it seemed assured that we could prepare the Diels–Alder substrate **3** in a straightforward fashion. Furthermore, studies of Taber with the Diels–Alder closure of a related trienone[11] led us to believe that we would obtain predominantly the C-1 epimer of bicyclic ketone **2** from the cyclization. Additional studies by Taber[11] suggested that this cis octalone (see **28** below) could be epimerized to a mixture which contained the desired trans octalone. Then Wittig reaction would complete our synthesis. The known selectivity of the key reactions (Claisen rearrangement and Diels–Alder closure) should control relative stereochemistry at three chiral centers (C-11, C-7, and C-6); we were hopeful that by adjusting conditions in the Wittig reaction, we might also control stereochemistry at C-1.

Results

In the event, the bis-allylic alcohol required for the key Claisen rearrangement (**15**) was prepared by a strightforward sequence. Commercially available 4-penten-1-ol was converted to its tetrahydropyranyl ether **10** by the standard procedure;[12] ozonolysis of the olefinic bond of **10** at −78 °C, followed by treatment of the ozonide with dimethyl sulfide, afforded aldehyde **11**.[13] Homologation to aldehyde **14** was achieved by Wittig reaction (**11** → **12**). DIBAH reduction (**12** → **13**), and oxidation (**13** → **14**). Treatment of aldehyde **14** with 2-lithiopropene gave alcohol **15** (Scheme I).

Esterification of the bis-allylic alcohol with the known acid **16**[14] was best effected by a modification of the procedure of Neises and Steglich.[15] This involved treatment of **15** with the carboxylic acid in the presence of 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride,[16] (dimethylamino)pyridine, and triethyl amine.

When ester **17** was subjected to Irelands's *Z*-enolate-forming conditions (LDA, THF, −78 °C → 25 °C), a mixture of carboxylic acids was isolated in 80% yield. Careful analysis of the 250-MHz NMR spectrum (see Experimental Section) led us to believe that this mixture consisted mainly of the desired diastereomer **18** (approximately 90%) contaminated by small amounts of its stereoisomer **19** (approximately 5%) and the regioisomeric Claisen product **20** (approximately 5%). The principal absorptions in the olefinic region were a singlet at 4.90 ppm (terminal methylene), a doublet of doublets (J = 9, 16 Hz) at 5.29 ppm, and a doublet (J = 16 Hz) at 6.14 ppm. Clearly, the rearrangement had afforded almost exclusively **18** and/or **19**; by analogy to the original experiments of Ireland we expected to obtain mostly **18**.

Inspection of the minor absorptions in the olefinic region revealed a signal at 5.52 ppm; in an experiment where the reaction was quenched after stirring at room temperature for an increased reaction time, this signal, a doublet of doublets (J = 9, 16 Hz), had grown at the expense of the 5.29 absorption. Presumably, under these conditions, the initially formed diastereomer **18** is epimerized to **19**. Thus, the signal at 5.29 ppm may be assigned to Hc of **18** and the signal at 5.52 may be assigned to Hc of **19**. Minor

(11) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.
(12) Woods, G. F.; Kramer, D. N. *J. Am. Chem. Soc.* **1947**, *69*, 2246.
(13) Aldehyde **11** has been prepared by an alternative procedure, see: Bestman, H. J.; Koschatky, K. H.; Schatzke, W.; Sub, J.; Vostrowsky, O. *Liebigs Ann. Chem.* **1981**, 1705.
(14) Mori, K.; Matsui, M. *Tetrahedron* **1969**, *25*, 5013.
(15) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(16) Aldrich Chemical Company. This compound was first described by Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

signals due to the olefinic protons of **20** were easily distinguished by chemical shifts and coupling constants.

The carboxylic moiety of **18** was fully reduced by a sequence of four reactions (Scheme II). Methylation with CH_2N_2 gave a quantitative yield of ester **21**. DIBAH reduction gave alcohol **22** in 85% yield. Conversion of **22** to mesylate **23a** was followed by $LiEt_3BH$ reduction to give ether **24**. Alternately, the tosylate **23b** could be prepared and reduced by lithium aluminum hydride to **24**.

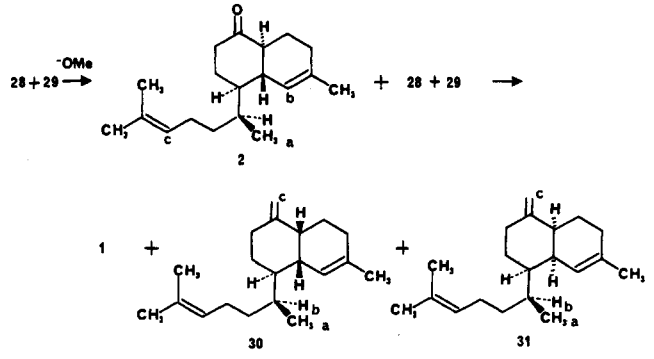
Deprotection of the THP ether **24** was accomplished in refluxing ethanol containing a catalytic amount of pyridinium *p*-toluenesulfonate to afford alcohol **25**. Pyridinium dichromate oxidized the alcohol to aldehyde **26** and vinylmagnesium bromide added to **26** to give allylic alcohol **27**.

The eight-step sequence from ester **17** to alcohol **27** could be carried out without purification of intermediates in 51% overall yield.

Oxidation of **27** at 0 °C by MnO_2 or by chromic acid resulted in spontaneous [4 + 2] cyclization. The 250-MHz NMR spectrum of the product showed two upfield doublets (0.88 ppm and 1.01 ppm, total integral 3 H) in a ratio of 9:1. By analogy to Taber's case,[11] we assigned structure **28** to the major component and structure **29** to the minor component. (Note that **28** is Mori's ketone **11a**;[7] Mori does not report the minor product **29**).

When this material was subjected to 3.5 equiv of triphenylphosphonium methylide (from methyltriphenylphosphonium bromide and *n*-BuLi in THF),[7] a product with one prominent upfield doublet δ (0.78 ppm) was obtained. The olefinic region contained a broad singlet at 5.53 ppm, a triplet (J = 6 Hz) at 5.10 ppm, and two doublets (J = 2 Hz) at 4.65 and 4.59 ppm. The major olefination product then is **30** (Mori's **1a**);[7] the presence of a minor olefination product was inferred from the observation that the signal at 0.90 ppm appeared to include a second methyl doublet and from the presence of ketone **29** in the starting material.

Treatment of the cyclization product (**28** + **29**) with sodium methoxide in refluxing methanol led to a new mixture of ketones. The 250-MHz NMR spectrum exhibited three doublets (0.78, 0.87, and 1.00 ppm, total integral 3 H) in a ratio of approximately 45:45:10 and two broad singlets in the olefinic region (5.40 and 5.54 ppm) in a ratio of approximately 45:55. By deduction and again by analogy to Taber's case, we assigned the new doublet at 0.78 ppm to the methyl group of the desired trans ketone **2** and the new olefinic signal at 5.40 ppm to the C-5 proton of **2**.



Treatment of the epimerized ketone mixture with triphenylphosphonium methylide (from methyltriphenylphosphonium bromide and NaH) in Me_2SO according to Mori[7] gave a mixture of olefins **30** and the desired **1** (these are Mori's **1a** and **1c**, respectively). The ratio of **30** to **1** (approximately 1:1) was determined by comparing the signals at 4.58 and 4.54 ppm (one of the C-1 protons in **30** and one of the C-1 protons in **1**) and the doublets at 0.78 and 0.74 (methyl groups in **30** and **1**). Bifloratriene **1** was isolated from the mixture by flash chromatography; the ^1H and ^{13}C NMR spectra of this synthetic material were identical with those obtained from natural bifloratriene.[18]

Surprisingly, treatment of the ketone mixture **2** and **28** (derived from NaOMe equilibration, approximately 1:1) with triphenylphosphonium methylide (from butyllithium and methyltriphenylphosphonium bromide in THF) gave material which had been enriched in the trans series. Reaction of the ketone mixture with 3 equiv of methylene ylide for 4 h gave a 90% yield of a mixture of bifloratrienes **1** and **30** (ratio 80:20). In a second run, treatment with 6 equiv of methylene ylide for 24 h gave a 59% yield of bifloratrienes **1** and **30** (ratio 90:10). As above, the ratio of **1** to **30** from these experiments was determined by comparison of the signals at 4.58 and 4.54 ppm and those at 0.78 and 0.74 ppm.

The fortuitous improvement in the ratio of the trans-fused to cis-fused ring system was unexpected but reproducible. One possible explanation for the improved ratio is that the cis-fused product or its precursor is being selectively destroyed during the reaction; however, as cis ketone **28** was converted to the cis-fused olefin **30** (ref 7 and our experiment described above) in excellent yield under what would seem to be identical conditions, this seems unlikely.

The alternative explanation for the improvement in ratio is that the cis ketone is equilibrated to the trans ketone under the reaction conditions and the trans ketone is selectively converted to product. Indeed, this takes place in the Wittig reaction of **28** in Me_2SO (see above; also see ref 19 for related cases). As ketone **28** was converted to olefin **30** without epimerization when the reaction was run in THF, it would seem, at first sight, as if this explanation needs some qualification. We are forced to conclude that the reaction conditions for the transformation of **28** to **30** are actually different from those used for the transformation of **28** + **2** to **30** + **1**, i.e., that epimerization of the cis ketone **28** in the mixture of ketones **28** and **2** is catalyzed by residual oxygen base from the previous step (or possibly by the enolate of trans ketone **2**).

This Wittig procedure completes the synthesis, each step of which is selective for the desired ratio- and stereoisomer.

Experimental Section

^1H NMR spectra (samples in $CDCl_3$) were recorded on a Varian EM360 (60 MHz) or a Bruker WM250 (250 MHz) spectrometer. Chemical shifts (δ in ppm) are reported relative to tetramethylsilane using the following abbrevations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Mass spectra were measured by using ion bombardment or chemical ionization (CI); for the latter, M^+ and (M^+ + 1) peaks are listed. All reactions were performed under a nitrogen atmosphere in dry solvents: THF distilled from sodium/benzophenone, amines distilled from CaH_2 onto molecular sieves, other solvents according to Burfield and Smithers.[20] Flash chromatography was peformed according to Still's method;[17] i.d. = inner diameter of the column. TLC was performed on Merck glass-backed silica gel 60 plates.

4-Penten-1-ol, Tetrahydropyranyl Ether (10). Dihydropyran (8.94 g, 106 mmol) was added to 8.34 g (96.8 mmol) of 4-penten-1-ol. One drop of concentrated HCl was added. After 5 h, two pellets of NaOH were added and distillation was begun. The fraction collected between 140 °C and 210 °C was redistilled

(18) Spectra of material derived from the natural source were supplied by Professor David F. Wiemer.

(19) (a) Marshall, J. A.; Pike, M. T.; Carroll, R. D. *J. Org. Chem.* **1966**, *31*, 2933. (b) Soffer, M. D.; Burk, L. A. *Tetrahedron Lett.* **1970**, 211.

(20) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2420.

(150 °C) to give 16.1 g (quantitative yield) of a clear oil: IR 2930, 1635, 1125 cm^{-1}; NMR δ 1.65 (m, 8 H), 2.10 (m, 2 H), 3.54 (m, 4 H), 4.54 (s, 1 H), 5.00 (m, 2 H), 5.75 (m, 1 H). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.34; H, 10.92.

4-[(Tetrahydropyranyl)oxy]butanal (11). Olefin **10** (5.55 g, 32.8 mmol) was dissolved in 50 mL of methanol and cooled to −78 °C. Ozone (26 min at 1.32 mmol/min, 34.3 mmol) was then bubbled through the solution. Ozone was replaced by oxygen and then nitrogen; dimethyl sulfide (2.79 g, 44.6 mmol) was added slowly to the solution. After 15 min the reaction mixture was warmed to 0 °C, stirred for 1 h, brought to room temperature, and stirred for 2 h. The reaction mixture was concentrated and extracted with petroleum ether. This solution was dried and concentrated to give 3.70 g (71%) of a clear oil: IR 2940, 2770, 1720, 1200 cm^{-1}; NMR δ 1.30–2.10 (m, 8 H), 2.57 (m, 2 H), 3.60 (m, 4 H), 4.56 (s, 1 H), 9.84 (t, J = 2 Hz, 1 H); MS (CI) calcd for $C_9H_{16}O_3$ 172.1099, found 172.1084 and 173.1156.

Ethyl 6-[(Tetrahydropyranyl)oxy]-2-hexenoate (12). To aldehyde **11** (3.97 g, 23.2 mmol) dissolved in 50 mL of dry benzene was added (carbethoxymethylene)triphenylphosphorane (8.07 g, 23.2 mmol). The mixture was stirred overnight, heated to reflux for 2 h, cooled, and concentrated. The residue was extracted (5×) with pentane. The combined pentane solution was concentrated and the residue distilled (140 °C, 0.1 mm) to give 4.58 g (82%) of a colorless oil: IR= 2930, 1715, 1650, 1260 cm^{-1}; NMR δ 1.28 (t, J = 7 Hz, 3 H), 1.65 (m, 8 H), 2.32 (m, 2 H), 3.57 (m, 4 H), 4.15 (q, J = 7 Hz, 2 H), 4.55 (s, 1 H), 5.80 (d, J = 16 Hz, 1 H), 7.00 (dt, J = 7, 16 Hz, 1 H); MS (CI) calcd for $C_{13}H_{22}O_4$ 242.1518, found 242.1597 and 243.1597.

Ethyl 6-[(Tetrahydropranyl)oxy]-2-hexenoate (12), Directly from Olefin 10. A solution of olefin **10** (5.55 g, 32.8 mmol) in 40 mL of dichloromethane and 50 mL of methanol was cooled to −78 °C. Ozone was bubbled through the solution for 40 min (1.32 mmol/min, 52.8 mmol). After a nitrogen purge, 4.23 g (68.1 mmol) of dimethyl sulfide was added. After 30 min, the reaction mixture was stirred at 0° for 5 h and at room temperature overnight, concentrated and extracted with petroleum ether. The petroleum ether solution was dried and concentrated. The residue was added to a solution of (carbethoxymethylene)triphenylphosphorane (11.5 g, 32.8 mmol) in 50 mL of dry benzene. The mixture was stirred overnight and heated for 7 h (with 1 g of ylide added after 2.5 h). After cooling, the reaction mixture was concentrated, extracted with pentane, and filtered. Concentration and distillation (140 °C, 0.1 mm) afforded 6.70 g (85%) of a clear oil. This material was identical with that previously obtained.

6-[(Tetrahydropyranyl)oxy]-2-hexen-1-ol (13). Ester **12** (3.17 g, 13.1 mmol) was dissolved in 60 mL of dry benzene. DIBAH (26.3 mL, 1.5 M in toluene, 39.4 mmol) was added over 30 min. The reaction mixture was stirred for 2.5 h and carefully quenched with 3 mL of water. The heterogeneous mixture was filtered through a glass frit (C) and the precipitate was washed with 200 mL of dichloromethane. Concentration afforded a cloudy oil which distilled (140 °C, 0.1 mm) to give 2.24 g (86%) of a clear oil: IR 3400, 2930, 2860, 1665 cm^{-1}; NMR δ 1.65 (m, 8 H), 2.10 (m, 2 H), 2.50 (s, 1 H), 3.57 (m, 4 H), 4.10 (s, 2 H), 4.57 (s, 1 H), 5.68 (m, 2 H); MS (CI) calcd for $C_{11}H_{20}O_3$ 200.1413, found 200.1390 and 201.1413.

6-[(Tetrahydropyranyl)oxy]-2-hexenal (14). A 6-g sample of MnO_2 (activated overnight at 120 °C) was suspended in 15 mL of dry dichloromethane. The reaction mixture was vigorously stirred and a solution of alcohol **13** (860 mg, 4.34 mmol) in 5 mL of dichloromethane was added. After 24 h the reaction mixture was diluted with dichloromethane, filtered through Celite, and concentrated. Distillation at 120 °C (0.2 mm) gave 702 mg (82%) of a clear oil: IR 2930, 2710, 1690, 1635 cm^{-1}; NMR δ 1.65 (m, 8 H), 2.50 (q, J = 7 Hz, 2 H), 3.62 (m, 4 H), 4.57 (s, 1 H), 6.13 (dd, J = 8, 16 Hz, 1 H), 6.94 (dt, J = 7, 16 Hz, 1 H), 9.54 (d, J = 8 Hz, 1 H); MS (CI) calcd for $C_{11}H_{18}O_3$ 198.1255, found 198.1171 and 199.1324.

7-Methyl-1-[(tetrahydropyranyl)oxy]-4(*E*),7-octadien-6-ol (15). Lithium (0.0423 g/cm, 5.96 cm in 0.5-cm pieces, 252 mg, 36.6 mmol, washed in pentane) was placed under argon and 25 mL of ether added. An ethereal solution (10 mL) of 2-bromopropene (1.34 g, 11.1 mmol) was added to the cooled flask (0 °C) over 10 min and the reaction mixture stirred for 3 h. The mixture was filtered into another cooled, dry flask under argon and an ethereal solution (10 mL) of aldehyde **14** (1.46 g, 7.41 mmol) was added dropwise. After 3 h at 0 °C, 10 mL of 20% NH_4Cl was added followed by 10 mL of water. The aqueous layer was extracted with ether. The combined ethereal solution was washed with 1 N HCl and water, dried, and concentrated. Distillation (150 °C, 0.1 mm) gave 1.60 g (90%) of a clear oil: IR 3380, 2930, 2850, 1645 cm^{-1}; NMR δ 1.10–2.40 (11 H), 1.72 (s, 3 H), 3.30–4.20 (m, 5 H), 4.50–6.10 (m, 5 H); MS (CI) calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1705 and 241.1821.

7-Methyl-6-*O*-(6-methyl-5-heptenoyl)-1-[(tetrahydropyranyl)oxy]-4(*E*),7-octadien-6-ol (17). Carboxylic acid **16** (192 mg, 1.35 mmol), alcohol **15** (322 mg, 1.35 mmol), and a large crystal of (dimethylamino)pyridine were dissolved in 4 mL of dry dichloromethane. The reaction mixture was cooled 0 °C and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (258 mg, 1.35 mmol) and triethylamine (138 mg, 136 mmol) were added. After 20 min the bath was removed. After 2 h, 50 mg (0.35 mmol) of carboxylic acid **16**, the diimide (26 mg, 0.21 mmol), and triethylamine (35 mg, 34 mmol) were added. The mixture was stirred for 3 h and diluted with ether. The ethereal solution was washed with water, 5% NaOH, 1 N HCl, and again with water, dried, and concentrated. The residue was subjected to flash chromatography (20 mm i.d.; hexanes/ether, 4/1) to give 410 mg (84%) of a clear oil: IR 2930, 1735, 1665, 1650 cm^{-1}; NMR δ 1.58 (s, 3 H), 1.65 (11 H), 1.68 (s, 3 H), 1.72 (s, 3 H), 2.02 (m, 2 H), 2.15 (m, 2 H), 3.45 (m, 2 H), 3.80 (m, 2 H), 4.56 (s, 1 H), 4.88 (s, 1 H), 4.99 (s, 1 H), 5.09 (t, J = 7 Hz, 1 H), 5.65 (m, 2 H). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.37; H, 10.33.

5-Carboxy-9-methyl-4-(3-methyl-1,3-butadienyl)-1-[(tetrahydropyranyl)oxy]-8-decene [Erythro (18) and Threo (19)] and 4-Methyl-2-(4-methyl-3-pentenyl)-10-[(tetrahydropyranyl)oxy]-4,6-decadienoic Acid (20). A solution of dry diisopropylamine (383 mg, 3.80 mmol) in 20 mL of dry THF was cooled to 0 °C under argon. To this was added 1.70 mL of *n*-butyllithium (1.5 M in hexane, 2.55 mmol). After 10 min the reaction mixture was cooled to −78 °C. Ester **9** (410 mg, 1.13 mmol) in 2 mL of dry THF was added to the vigorously stirred solution over 4 min. After 6 min the flask was brought to room temperature and the solution was stirred for 2 h. The reaction mixture was poured into water and the aqueous layer washed with pentane. The aqueous layer was acidified in the presence of dichloromethane; further extraction with dichloromethane afforded 326 mg (80%) of a slightly yellow oil: IR 2940, 1730, 1695, 1640, 1605 cm^{-1}; NMR δ 1.20–2.40 (16 H), 1.56 (s, 3 H), 1.67 (s, 3 H), 1.83 (s, 3 H), 3.30–3.90 (m, 4 H), 4.57 (br s, 1 H), 4.90 (s, 1.9 H, 18_a and 19_a), 5.05 (br t, J = 6 Hz, 1 H), 5.29 (dd, J = 9, 16 Hz, 0.90H, 18_c), 5.52 (dd, J = 9, 16 Hz, 0.05 H, 19_c), 5.58 (m, 0.05 H, 20_a), 5.83 (br d, J = 12 Hz, 0.05 H, 20_c), 6.14 (d, J = 16 Hz, 0.95 H, 18_b and 19_b), 6.23 (m, 0.05 H, 20_b), 9.15 (br s, 1 H).

Esterification of 18, 19, and 20. An ethereal solution of diazomethane at 0 °C (generated by addition of *N*-nitrosomethylurea to 40% KOH and ether at 0 °C) was added in excess to an ethereal solution of **18**, **19**, and **20** (326 mg) at 0 °C. After 5 min, 10% acetic acid was added. The aqueous layer was extracted with ether several times. The combined ethereal layer was washed with saturated $NaHCO_3$ and water and dried to give a quantitative yield (330 mg) of a slightly yellow oil. An 86-mg portion of the esters was subjected to flash chromatography (20 mm i.d.; hexanes/ether, 2/1) to afford 65.2 (55%) of a mixture of **21** and the methyl ester of **19**: IR 1730 cm^{-1}. Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.63. Found: C, 73.11; H, 10.32.

5-(Hydroxymethyl)-9-methyl-4-(3-methyl-1,3-butadienyl)-1-[(tetrahydropyranyl)oxy]-8-decene (22). Methyl ester **21** (79.6 mg, 0.211 mmol) was dissolved in 7 mL of dry benzene. DIBAH (0.42 mL, 1.5 M in toluene, 0.63 mmol) was added to the vigorously stirred solution. After 1 h, water was added dropwise and the reaction mixture stirred for 30 min. The solution was filtered through a glass frit (M) with dichloromethane and the precipitate was washed with dichloromethane. The combined organic solution was concentrated. Flash chromatography (10 mm i.d.; hexanes/ether, 1/1) afforded 62.4 mg (85%) of a clear oil: IR 3440, 2900, 1640, 1605 cm^{-1}; NMR δ 1.60 (17 H), 1.64 (s, 3 H), 1.72 (s, 3 H), 1.87 (s, 3 H), 3.60 (m, 6 H), 4.58 (br s, 1 H), 4.88 (s, 2 H), 5.10 (m, 1 H), 5.40 (m, 1 H), 6.18 (d, J = 16 Hz, 1 H). Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.16; H, 11.19.

5-(Hydroxymethyl)-9-methyl-4-(3-methyl-1,3-butadienyl)-1-[(tetrahydropyranyl)oxy]-8-decene 5-Mesylate (23a). Alcohol **22** (51.3 mg, 0.147 mmol) was cooled to 0 °C and 0.40 mL of dry pyridine was added. Methanesulfonyl chloride (16.8 mg, 0.191 mmol) was added to the stirred solution. The flask was transferred to a refrigerator (−4 °C) where it stood for 24 h. While still at 0 °C, 1 mL of water was added. After being stirred for 0.5 h, the reaction mixture was diluted with dichloromethane and the organic solution was washed with 1 N HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated to give a cloudy oil (54.2 mg, 86%): IR 2920, 1640, 1605, 1170 cm^{-1}; NMR δ 1.60 (16 H), 1.68 (s, 3 H), 1.73 (s, 3 H), 1.86 (s, 3 H), 3.03 (s, 3 H), 3.60 (m, 4 H), 4.15 (m, 2 H), 4.54 (s, 1 H), 4.90 (s, 2 H), 5.20 (m, 1 H), 5.40 (m, 1 H), 6.17 (d, J = 16 Hz, 1 H).

5-(Hydroxymethyl)-9-methyl-4-(3-methyl-1,3-butadienyl)-1-[(tetrahydropyranyl)oxy]-8-decene 5-Tosylate (23b). Alcohol **22** (80.3 mg, 230 mmol) was cooled to 0 °C and 3 mL of dry pyridine added. TsCl (recrystallized, 70.0 mg, 0.367 mmol) was added and the mixture allowed to stand overnight in a refrigerator (−4 °C). Water was added to the cooled (0 °C) flask. After 15 min the reaction mixture was extracted 3× with ether. The combined ethereal solution was washed with 0.5 N HCl, water, and saturated $NaHCO_3$. After drying, concentration afforded a quantitative recovery of a cloudy oil. Flash chromatography (20 mm i.d.; hexane/ether, 1/1) gave 70.9 mg (61%) of a clear oil: IR 2930, 1640, 1605, 1595 cm^{-1}; NMR δ 1.20–2.30 (16 H), 1.57 (s, 3 H), 1.67 (s, 3 H), 1.76 (s, 3 H), 2.46 (s, 3 H), 3.30–4.15 (6 H), 4.53 (br s, 1 H), 4.80–5.50 (5 H), 5.94 (d, J = 16 Hz, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H).

5,9-Dimethyl-4-(3-methyl-1,3-butadienyl)-1-[(tetrahydropyranyl)oxy]-8-decene (24) from 23a. Dry THF (1 mL) was added to mesylate **23a** (54.2 mg, 0.127 mmol). A 1.0 M solution of $LiEt_3BH$ in THF (0.24 mL, 0.24 mmol) was added dropwise. After 1 h another 0.24 mL of the $LiEt_3BH$ solution was added. The reaction mixture stirred overnight and was quenched with 3 mL of water. The aqueous layer was extracted 3× with pentane and the combined pentane solution was washed with water, dried, and concentrated. Flash chromatography of the residue (10 mm i.e.; hexane/ether, 10/1) afforded 29.8 mg (67%) of a clear oil: IR 2920, 1635, 1605, 1195 cm^{-1}; NMR δ 0.87 (d, J = 7 Hz, 3 H), 1.20–2.10 (16 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.83 (s, 3 H), 3.37 (m, 1 H), 3.50 (m, 1 H), 3.72 (m, 1 H), 3.87 (m, 1 H), 4.57 (br s, 1 H), 4.85 (s, 2 H), 5.09 (br t, J = 6 Hz, 1 H), 5.43 (dd, J = 9, 16 Hz, 1 H), 6.08 (d, J = 16 Hz, 1 H); MS calcd for $C_{22}H_{38}O_2$ 334.2872, found 334.2872.

5,9-Dimethyl-4-(3-methyl-1,3-butadienyl)-1-[(tetrahydropyranyl)oxy]-8-decene (24) from 23b. LAH (5.3 mg, 0.14 mmol) was dissolved in 4 mL of dry THF. A 2-mL THF solution of tosylate **23b** (70.0 mg, 0.139 mmol) was added. The reaction mixture was stirred at reflux. After 6 and 10 h the reaction mixture was cooled to room temperature and 5 mg of LAH was added. After reflux overnight the reaction mixture was quenched with water, 5% NaOH, and more water. The aqueous layer was extracted 4× with ether. The combined ethereal layer was washed with 5% NaOH, 1 N HCl, and saturated $NaHCO_3$ solution. Drying and concentration afforded 45.7 mg (99%) of a clear oil, one spot by TLC.

This material was identical with that obtained from reduction of mesylate **23a**.

5,9-Dimethyl-4-(3-methyl-1,3-butadienyl)-8-decen-1-ol (25). The tetrahydropyranyl ether **24** (29.8 mg, 0.89 mmol) was dissolved in 5 mL of absolute ethanol. A catalytic amount of pyridinium *p*-toluenesulfonate was added and the solution was stirred at reflux for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was subjected to flash chromatography (10 mm i.d.; hexane/ether, 1/1) to afford 13.4 mg (63%) of a clear oil: IR 3350, 2920, 1640, 1605 cm^{-1}; NMR δ 0.88 (d, J = 7 Hz, 3 H), 1.20–2.10 (11 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.83 (s, 3 H), 3.64 (m, 2 H), 4.86 (s, 2 H), 5.09 (br t, J = 7 Hz, 1 H), 5.43 (dd, J = 9, 16 Hz, 1 H), 6.08 (d, J = 16 Hz, 1 H); MS calcd for $C_{17}H_{30}O$ 250.2297, found 250.2297.

5,9-Dimethyl-4-(3-methyl-1,3-butadienyl)-8-decenal (26). To a vigorously stirred solution of 109 mg (0.256 mmol) of pyridinium dichromate in 3 mL of dry dichloromethane was added 42.5 mg (0.170 mmol) of alcohol **25** in 1.5 mL of dry dichloromethane. After being stirred overnight, the heterogeneous mixture was diluted with anhydrous ether and filtered through $MgSO_4$. Concentration and another similar filtration afforded 25.8 mg (85%) of a clear oil: IR 2900, 2710, 1720, 1650, 1605 cm^{-1}; NMR δ 0.89 (d, J = 6 Hz, 3 H), 1.10–2.30 (10 H), 1.65 (s, 3 H), 1.72 (s, 3 H), 1.87 (s, 3 H), 4.88 (s, 2 H), 5.12 (m, 1 H), 5.36 (m, 1 H), 6.10 (d, J = 16 Hz, 1 H), 9.77 (m, 1 H).

7,11-Dimethyl-6-(3-methyl-1,3-butadienyl)-1,10-dodecadien-3-ol (27). To an ethereal solution (5 mL) of vinylmagnesium bromide (0.41 mL, 1.0 M in THF, 0.41 mmol) was added a 1-mL ethereal solution of aldehyde **26** (20.6 mg, 0.083 mmol). After 25 min the reaction was quenched by addition of 20% NH_4Cl. The aqueous layer was extracted with ether and the combined ethereal solution was washed with water, dried, and concentrated. Flash chromatography (10 mm i.d.; hexane/ether, 2/1) gave 20.3 mg (89%) of a colorless oil: IR 3350, 2910, 1630, 1605 cm^{-1}; NMR δ 0.87 (d, J = 7 Hz, 3 H), 1.10–2.10 (11 H), 1.59 (s, 3 H), 1.68 (s, 3 H), 1.83 (s, 3 H), 4.07 (m, 1 H), 4.86 (s, 3 H), 5.10 (m, 2 H), 5.21 (d, J = 17 Hz, 1 H), 5.42 (dd, J = 9, 16 Hz, 1 H), 5.85 (m, 1 H), 6.08 (d, J = 16 Hz, 1 H).

19-Norbiflora-4,15-dien-10-ones 28 and 29 from Chromic Acid Oxidation. Chromic acid (0.10 mL, 1 M, 0.1 mmol) was added dropwise to a 2.5-mL ethereal solution of alcohol **27** (23.3 mg, 0.085 mmol) at 0 °C. After 0.5 h an additional 0.05 mL of chromic acid was added. After 5 min the reaction mixture was diluted with ether. The ethereal solution was washed with water and saturated $NaHCO_3$, dried, and concentrated. Flash chromatography (10 mm i.d.; hexane/ether, 4/1) afforded 21.1 mg (91%) of a colorless oil: IR 2920, 1695, 1445 cm^{-1}; NMR δ 0.88 (d, J = 7 Hz, 2.7 H, 28_a), 1.01 (d, J = 7 Hz, 0.3 H, 29_a), 1.25–1.80 (6 H), 1.61 (s, 3 H), 1.66 (s, 3 H), 1.69 (s, 3 H), 1.83 (m, 2 H), 2.00 (m, 4 H), 2.33 (m, 2 H), 2.46 (m, 2 H), 5.10 (br t, J = 8 Hz, 1 H), 5.38 (br s, 1 H): ^{13}C NMR BB 14.7, 17.7, 23.1, 23.6, 23.8, 25.6, 26.1, 29.0, 32.0, 35.7, 38.5, 38.8, 43.4, 47.7, 123.8, 124.7, 131.3, 134.8, 214.4.

19-Norbiflora-4,15-dien-10-ones 28 and 29 from MnO_2 Oxidation. Alcohol **27** (10.2 mg, 0.037 mmol) in 1 mL of dry dichloromethane was cooled to 0 °C and 100 mg (1.15 mmol) of MnO_2 (activated at 110 °C for 4 h) was added. After 3 h the reaction mixture was diluted with dichloromethane and filtered through Celite. Concentration afforded 9.5 mg (94%) of a clear oil. This material was identical with that obtained from the chromic acid oxidation of **27**.

Biflora-4,10(19),15-trienes 30 and 31 from Ketones 28 and 29 in THF. *n*-Butyllithium (0.17 mL, 1.5 M in hexane, 0.26 mmol) was added to 91.4 mg (0.256 mmol) of methyltriphenylphosphonium bromide in 5 mL of dry THF. After 30 min, a 1.4-mL aliquot of this reaction mixture was added to a solution of ketones **28** and **29** (9.5 mg, 0.04 mmol) in 1 mL of dry THF. The bath was removed and after 45 min another 0.80 mL of the ylide solution was added. After 3 h, water was added and the reaction mixture was extracted with hexane. The organic solution was dried, concentrated, and subjected to flash chromatography (10 mm i.d., pentane only) to give 8.5 mg (95%) of a clear oil: IR 3040, 2950, 1640 cm^{-1}; NMRδ 0.78 (d, J = 7 Hz, 2.7H, 30_a), 0.90 (br d, J = 7 Hz, 1.3 H, 30_b, 31_b, and 31_a), 1.10–1.80 (6 H), 1.61 (s, 3 H), 1.69 (s, 6 H), 2.00 (m, 8 H), 2.39 (m, 1 H), 4.59 (d, J = 2 Hz, 1 H), 4.65 (d, J = 2 Hz, 1 H), 5.10 (br t, J = 6 Hz, 1 H), 5.52 (br s, 1 H).

Equilibration of 28 and 29 to 2, 28, and 29. A 4-mL methanol solution of ketones **28** and **29** (9.5 mg, 0.04 mmol) and a catalytic amount of NaOMe were stirred at reflux for 3 h. The mixture was acidified, concentrated, and partitioned between water and ether. The ether solution was dried and concentrated to afford 9.5 mg, (quantitative recovery) of a clear oil: IR 2920, 1695, 1665, 1050 cm^{-1}; NMR δ 0.78, 0.87, 1.00 (d, J = 7 Hz, 3 H, 2_a, 28_a, 29_a, respectively), 1.62 (s, 3 H), 1.70 (s, 6 H), 1.10–1.80 (8 H), 2.00 (m, 4 H), 2.40 (m, 3 H), 5.12 (m, 1 H, 28_c, 29_c, 2_c), 5.40 (br s, 0.5 H, 28_b and 29_b), 5.54 (br s, 0.5 H, 2_b).

Biflora-4,10(19),15-triene 1 and 30 (and 31) from 2 and 28 (and 29) in Me_2SO. NaH (9 mg, 0.2 mmol, 50% in oil, washed with pentane) was dissolved in 0.4 mL of dry Me_2SO and the heterogeneous mixture was stirred for 10 min. Next, 26 mg (.07 mmol) of $(C_6H_5)_3PCH_3Br$ was added. After 15 min, a solution of ketone **2** and **28** (9.9 mg, 0.04 mmol) in 0.6 mL of dry THF was added dropwise. After 3 h the reaction mixture was poured

into water and extracted several times with pentane. The combined pentane solution was washed with water and dried. Concentration afforded 8.9 mg (91%) of a clear oil: IR 3040, 2950, 1640 cm^{-1}; NMR δ 0.74 and 0.78 (d, J = 7 Hz, 2.9 Hz, 1_a and 30_a), 0.90 (m, 1.1 H, 1_b, 30_b, 31_b, and 31_a), 1.10–1.80 (6 H), 1.61 (s, 3 H), 1.69 (s, 6 H), 2.00 (m, 8 H), 2.37 (m, 1 H), 4.55 (br s, 0.6 H, 1_c), 4.58 (br s, 0.4 H, 30_c and 31_c), 4.66 (br s, 1 H), 5.09 and 5.12 (two overlapping t, 1 H), 5.52 (br s, 1 H).

Separation of 1 from 30 and 31. A mixture of **1**, **30**, and **31** from several experiments was subjected to flash chromatography (hexane).

More mobile fractions, **30** and **31**: NMR δ 0.78 (d, J = 7 Hz, 2.7 H, 30_a), 0.90 (br d, J = 7 Hz, 1.3 H, 30_b, 31_b, and 31_a), 1.10–2.10 (6 H), 1.60 (s, 3 H), 1.69 (s, 6 H), 2.00 (m, 8 H), 2.39 (m, 1 H), 4.58 (br s, 1 H), 4.65 (br s, 1 H), 5.09 (br t, J = 6 Hz, 1 H), 5.53 (br s, 1 H); ^{13}C NMR BB 13.6, 17.6, 23.8, 25.5, 25.7, 26.3, 26.4, 31.0, 31.6, 31.7, 36.0, 39.6, 43.0, 43.8, 106.5, 124.5, 125.1, 130.9, 133.8, 154.3. This material also contained approximately 20% of the natural product (**1**) as determined by 250-MHz ^1H and ^{13}C NMR.

Less mobile fraction, **1**: NMR δ 0.74 (d, J = 7 Hz, 3 H, 1_a), 0.89 (m, 1 H, 1_b), 1.10–1.80 (6 H), 1.61 (s, 3 H), 1.69 (s, 6 H), 2.00 (m, 8 H), 2.36 (m, 1 H), 4.55 (s, 1 H), 4.66 (s, 1 H), 5.12 (br t, J = 7 Hz, 1 H), 5.53 (br s, 1 H); ^{13}C NMR BB 13.4, 17.7, 23.8, 25.7, 25.9, 26.4, 27.0, 30.6, 31.3, 36.0, 36.5, 44.4, 45.0, 45.3, 103.2, 122.5, 125.0, 131.1, 134.7, 153.3.

Biflora-4,10(19),15-trienes 1 and 30 (9:1) from 2 and 28 in THF. Methyltriphenylphosphonium bromide (65.3 mg, 0.18 mmol) was added to 5.0 mL of dry THF and cooled to 0 °C. *n*-Butyllithium (0.12 mL, 1.5 M in hexanes, 0.18 mmol) was added and then the reaction mixture was stirred at 25 °C for 45 min. To 9.0 mg (0.03 mmol) of ketones **2**, **28**, **29** (from equilibration) in 1 mL of THF was added 2.5 mL of the cloudy, yellow ylide solution. After 1 h the reaction mixture was brought to 25 °C and after 2 h the remainder of the ylide solution was added to the reaction mixture. After being stirred overnight, the reaction mixture was quenched with water and extracted 5× with pentane. The combined organic solution was washed with water, dried, and concentrated. The residue was subjected to flash chromatography (10 mm i.d., pentane only) and afforded 5.3 mg (59%) of a clear oil: IR 3040, 2950, 1640 cm^{-1}; NMR δ 0.74 (d, J = 7 Hz, approximately 2.7 H) and 0.78 (d, J = 7 Hz, approximately 0.3 H), 0.90 (m, 1 H), 1.20–1.80 (6 H), 1.61 (s, 3 H), 1.69 (s, 6 H), 2.00 (m, 8 H), 2.37 (m, 1 H), 4.54 (br s, 0.9 H, 1_c), 4.58 (br s, 0.1 H, 30_c), 4.65 (br s, 1 H), 5.12 (br t, J = 6 Hz, 1 H), 5.53 (br s, 1 H).

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Registry No. (±)-**1**, 95910-64-8; (±)-**2**, 104195-69-9; **10**, 64841-44-7; **11**, 54911-85-2; **12**, 104155-98-8; **13**, 66084-36-4; **14**, 98076-79-0; **15**, 104155-99-9; **16**, 24286-45-1; **17**, 104156-00-5; (±)-**18**, 104156-01-6; (±)-**19**, 104195-63-3; (±)-**19** (methyl ester), 104195-64-4; **20**, 104156-02-7; **20** (methyl ester), 104156-04-9; (±)-**21**, 104156-03-8; (±)-**22**, 104156-05-0; (±)-**23a**, 104156-06-1; (±)-**23b**, 104156-07-2; (±)-**24**, 104156-08-3; (±)-**25**, 104195-65-5; (±)-**26**, 104195-66-6; **27**, 89272-53-7; (±)-**28**, 104195-67-7; (±)-**29**, 104195-68-8; (±)-**30**, 104195-70-2; (±)-**31**, 104195-71-3; 4-penten-1-ol, 821-09-0; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; 2-lithiopropene, 6386-71-6.

Supplementary Material Available: Proton NMR spectra (250-MHz) for **1**, **30**, and the 1:1 mixture of **1** and **30**; 62.8-MHz carbon-13 NMR spectrum for **1**; 250-MHz proton NMR spectrum for Claisen rearrangement product mixture, **18** containing 5% **19** and 5% **20** (6 pages). Ordering information is given on any current masthead page.

Synthesis of Allylic Alcohol Single-Chain PGH Analogues. A Synthetic Application of the Argon Laser

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Hydroformylation of either the diethyl azodicarboxylate or *N*-phenyltriazolinedione–cyclopentadiene Diels–Alder adducts provides ready access to 5-substituted-2,3-diazabicyclo[2.2.1]hept-2-enes. Single-chain azo prostaglandin analogues have been prepared by this route and their argon laser initiated, sensitized photodecomposition affords substituted cyclopenta-1,3-diyls which are easily trapped by molecular oxygen to form single-chain prostaglandin endoperoxide analogues. In the case of the allylic alcohol single-chain endoperoxide analogue, both the natural exo side chain and the unnatural endo side chain configuration are obtained by this method in quantities which are useful for the study of their chemistry.

The prostaglandin endoperoxide PGH_2 (**1**) plays a pivotal role in the biosynthesis of the prostaglandins, prostacyclin (PGI_2, **2**)[1] and thromboxane A_2 (TXA_2, **3**),[2] as shown in Scheme I. In view of the strategic biosynthetic importance of PGH_2 (**1**), it is surprising that so little is known about the chemical factors which influence its partitioning between these various pathways. Several studies seem to indicate that the side chains of PGH_2 may play an important role in governing the mode of endoperoxide decomposition. The parent unsubstituted endoperoxide **4** undergoes β-scission of the one-carbon bridge to the exclusion of the alternative β-scission of the two-carbon bridge, pathways a and b in Scheme II, respec-

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