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DIELS–ALDER CYCLIZATION OF 2,8,10-UNDECATRIENALS AS A ROUTE TO 1,2,3,4,4a,5,6,8a-OCTAHYDRONAPHTHALENES

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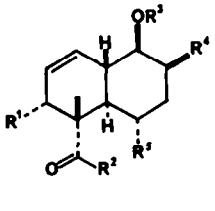
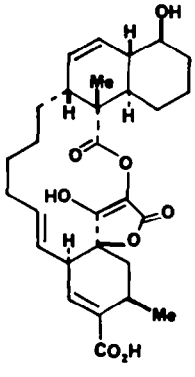
Abstract—2,8,10-Undecatrienals have been found to undergo facile Diels–Alder cyclization upon treatment with alkylaluminum chlorides in methylene chloride at low temperature. The reaction is highly *endo*-selective. Protected alcohol substituents at the C-4 and C-7 positions are fully accommodated and TBDMS protected alcohols show a strong axial preference. The methodology has been applied to a hydronaphthalenecarboxylic acid of possible use in a projected total synthesis of the macrocyclic antitumor antibiotic, chlorothricolide.

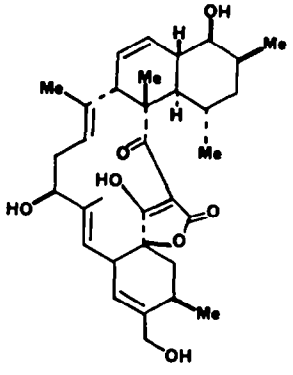
The macrocyclic antitumor antibiotics chlorothricin[1] and kijanimicin[2] share a number of interesting and unusual structural features. Both possess a substituted 1,2,3,4,4a,5,6,8a-octahydronaphthalene nucleus (I) fused to a macrocyclic lactone or a carbocyclic ring incorporating an additional fused cyclohexene ring and a spirocyclic tetronic acid moiety as a bridging unit. In recent years a number of reports describing synthetic approaches to the hydronaphthalene, spirolactone, and macrocyclic subunits of chlorothricolide, the aglycone of chlorothricin, have appeared.[3,4] A favored strategy for the hydronaphthalene system has been the intramolecular Diels–Alder bicyclization of an appropriate 2,8,10-undecatrienoate such as II.[3e–f] Unfortunately, such cyclizations show poor *endo*-selectivity and lead to mixtures of *cis* and *trans* fused products. Attempts to promote *endo*-selectivity through Lewis acid catalysis causes extensive decomposition of the sensitive allylic alcohol functionality.



I



Chlorothricolide

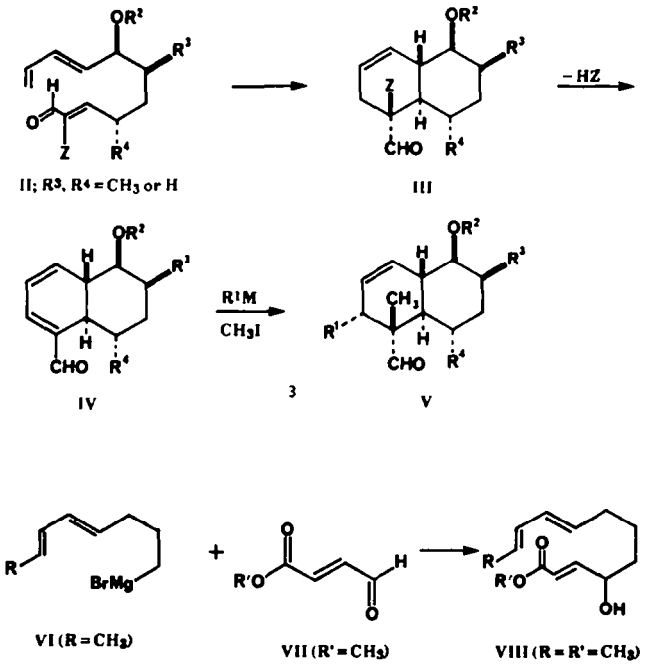


Kijanolide

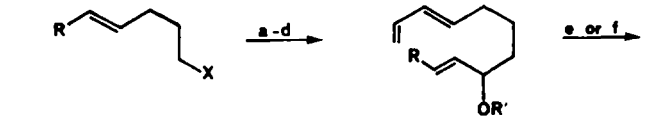
We were interested in examining an approach to the hydronaphthalene subunit V involving 1,4-addition of an appropriate side chain R^1 to a cyclohexadienal such as IV followed by *in situ* methylation of the resulting enolate. In considering possible routes to dienal IV we were drawn to the intramolecular Diels–Alder cyclization strategy as applied to a trienal such as II. While this strategy might be considered unwise in light of the unsuccessful attempts by others to effect similar cycloadditions, there were several considerations that encouraged us to persevere. To begin with, conjugated aldehydes have rarely been employed in such cyclizations and never under Lewis acid catalysis. The only examples known to us were thermal reactions leading to substituted hydrindanes.[5] Furthermore, conjugative effects should appreciably enhance the dienophilic reactivity of a Lewis acid–enal complex.[6] An additional, though possibly less important consideration, was the placement of an electron-withdrawing substituent Z as in II to enhance the dienophilicity of the enal further. Finally, by deferring introduction of the contiguous R^1 and CH_3 groupings, potentially adverse steric effects that might disfavor a cyclization leading directly to V would be minimized.

Our initial aim was to test the feasibility of a Lewis-acid promoted cyclization on a simple trienal. Funk and Zeller described a straightforward approach to the undecatrienoic ester VIII via selective addition of 4,6-heptadienylmagnesium bromide to ester aldehyde VII.[7] Ester VIII and various hydroxyl protected derivatives were found to cyclize both thermally and under Lewis acid catalysis. The catalyzed cyclizations showed high *endo*-stereo-selectivity. These promising observations prompted our selection of the unsubstituted analog, trienal 11, as a test system (Scheme 1).

Addition of formaldehyde to the tetrahydropyranyl ether of 4-pentynol followed by reduction of the triple

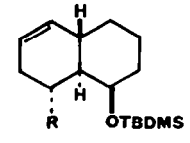


bond with Red-Al, oxidation of the allylic alcohol to the corresponding aldehyde **2**, and Wittig methylenation afforded diene **3**. Hydrolysis of the tetrahydropyranyl grouping with Dowex acidic ion exchange resin in methanol gave the alcohol **4**. Conversion to the bromide **6** was effected via treatment of the mesylate derivative **5** with lithium bromide in tetrahydrofuran. The Grignard reagent **7**, prepared via ultrasonication of the bromide **6** and magnesium turnings in tetrahydrofuran at 0°, added selectively to isopropyl



1 R = CH_2OH, X = OTHP
2 R = CHO, X = OTHP
3 R = $CH=CH_2$, X = OTHP
4 R = $CH=CH_2$, X = OH
5 R = $CH=CH_2$, X = OMs
6 R = $CH=CH_2$, X = Br
7 R = $CH=CH_2$, X = MgBr

8 R = CO_2i-Pr, R' = H
9 R = CO_2i-Pr, R' = TBDMS
10 R = CH_2OH, R' = TBDMS
11 R = CHO, R' = TBDMS
12 R = $CH(OH)C_2H_5$, R' = TBDMS



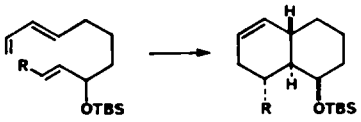
13 R = CO_2i-Pr
14 R = CHO
15 R = $CH(OH)C_2H_5$

(a) a) i-$PrO_2CCH=CHCHO$, Et_2O b) TBDMSCl, DMF, imidazole c) DIBAH, Et_2O, -78°C d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 e) MnO_2, CH_2Cl_2, 25°C f) $EtAlCl_2$, CH_2Cl_2, -78°C

(b) THP =  TBDMS = t-Bu$(Me)_2$Si

Scheme 1.[a,b]

Table 1. Comparative cyclizations of 2,8,10-undecatrienes



R	Conditions	Temp (°)	Time	Yield (%)	R
CH_2OH	MnO_2, CH_2Cl_2	25	30 h	64	CHO
CHO	$EtAlCl_2$,[a] CH_2Cl_2	−78	1 min	62	CHO
CO_2i-Pr	$EtAlCl_2$,[b] CH_2Cl_2	8	18 h	60	CO_2i-Pr

[a] 0.2 equiv.
[b] 1.0 equiv.

(*E*)-3-formylpropenoate (**VII**, R′ = i-Pr) to give the hydroxy ester **8** in high yield. The formylpropionate **VII** (R′ = i-Pr) was secured by selective ozonolysis of isopropyl sorbate as reported by Funk for the methyl ester.[7] We found the isopropyl ester easier to handle and more selective in reactions with Grignard reagents.

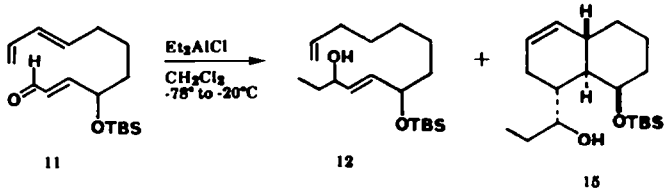
The hydroxy ester **8** was protected as the t-butyldimethylsilyl (TBDMS) ether, then reduced with bis-isobutylaluminum hydride (DIBAH) to the allylic alcohol **10**. Oxidation with MnO_2 in methylene chloride proceeded surprisingly slowly and unexpectedly afforded aldehyde **14**, the Diels–Alder cycloadduct, as the sole product. Oxidation of alcohol **10** via the Swern method gave the conjugated aldehyde **11**. This aldehyde was recovered unchanged upon treatment with MnO_2 in methylene chloride even after several days. Apparently the observed oxidation–cyclization of alcohol **10** to the bicyclic aldehyde **14** is promoted by a reduction product of MnO_2 rather than MnO_2 itself.[8] Aldehyde **11** was found to cyclize readily in the presence of a catalytic amount of ethylaluminum dichloride (Table 1). In contrast, the ester **9** required a full equivalent of the catalyst at an appreciably higher temperature and considerably longer time to achieve a comparable degree of cyclization. The aldehyde grouping thus imparts a profound rate enhancement to the catalyzed Diels–Alder cyclization. The stereochemistry of the bicyclic ester **13** and aldehyde **14** was readily deduced from the ^{1}H-NMR spectra. The observed high *endo*-selectivity and the nearly complete axial preference of the OTBDMS substituent parallel previous findings with the methyl analog of **9**.[7]

Seeking even milder cyclization conditions we subjected aldehyde **11** to diethylaluminum chloride in methylene chloride at low temperature. The sole product was a 3:1 mixture of alcohols **12** and **15** resulting from ethyl addition to the aldehydes **11** and **14**. Such additions have been previously noted in connection with catalyzed ene reactions of aldehydes.[9]

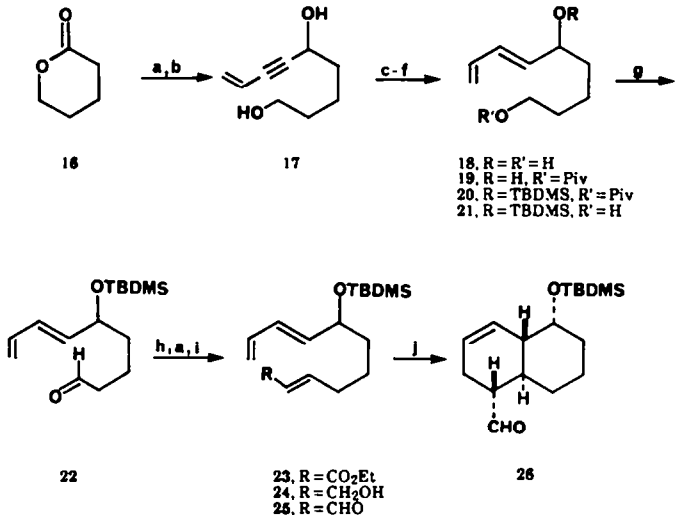
Our findings with trienal **11** indicated that conjugated aldehydes can be highly effective dienophiles, especially under Lewis acid catalysis. However, it should be recognized that the strategic placement of the alcohol function in trienal **11** effectively precludes acid-promoted dissociative side reactions which could undermine the intended application of the cyclization as a route to bicyclic alcohols such as **III**. It remained to be seen whether the cyclization of an enal such as **25** could be effected under conditions mild enough to allow survival of the sensitive allylic alcohol functionality.

Our route to enal **25** is outlined in Scheme 2. Partial reduction of δ-valerolactone (**16**) with DIBAH followed by addition of vinylacetylene afforded the diol **17**. Reduction of the acetylene with Red-Al proceeded with high stereoselectivity to give the *trans*-diene diol **18**. Conversion to the silyl protected diol **21** was effected via a three-step procedure involving selective esterification of the primary alcohol with pivaloyl chloride, silylation of the remaining secondary alcohol with t-butyldimethylsilyl chloride and then cleavage of the pivalate with lithium aluminum hydride. The alcohol **21** was oxidized and the derived aldehyde was treated with (carbethoxymethyl)triphenylphosphorane to give the *trans*-enoate **23**, which was smoothly reduced to the allylic alcohol **24** by DIBAH. This alcohol was readily oxidized to the aldehyde **25** by MnO_2 in methylene chloride. In this case, none of the bicyclic aldehyde **26** was observed, even when the reaction was allowed to proceed for 3 days at room temperature. The "reduced MnO_2" catalysis of intramolecular Diels–Alder additions thus appears to be somewhat substrate-dependent.

Enal **25** could be smoothly cyclized with dimethylaluminum chloride at −78° to −23° to give bicyclic aldehyde **26**. The ^{1}H-NMR spectrum of **26** confirmed the assigned stereochemistry. Thus both trienals **11** and **25** cyclize with high *endo*-selectivity and



11 12 15



(a) a) DIBAH, THF, -78°C b) $CH_2=CHC\equiv CMgBr$, THF, -78° to 25°C c) Red-Al, Et_2O, 0° to 25°C d) $(CH_3)_3CCOCl$, C_5H_5N, -40°C e) TBDMSCl, DMF, imidazole f) $LiAlH_4$, Et_2O, 0°C g) PDC, CH_2Cl_2, 3Å molecular sieves h) $Ph_3P=CHCO_2Et$, CH_2Cl_2 i) MnO_2, CH_2Cl_2 j) Me_2AlCl, CH_2Cl_2, -78° to -23°C

(b) Piv = $(CH_3)_3CCO$, TBDMS = t-Bu(Me)$_2$Si

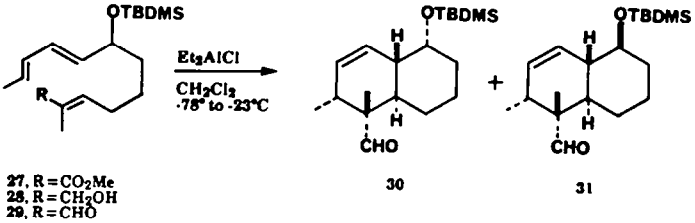
Scheme 2.[a,b]

both show a strong preference for axial orientation of the OTBDMS grouping. Whereas the observed *endo*-specificity is typical of Lewis acid promoted Diels–Alder additions, the preference for axial OTBDMS is indicative of a subtle transition-state conformational effect. The phenomenon is clearly relevant to asymmetric syntheses of intermediates such as **III**.

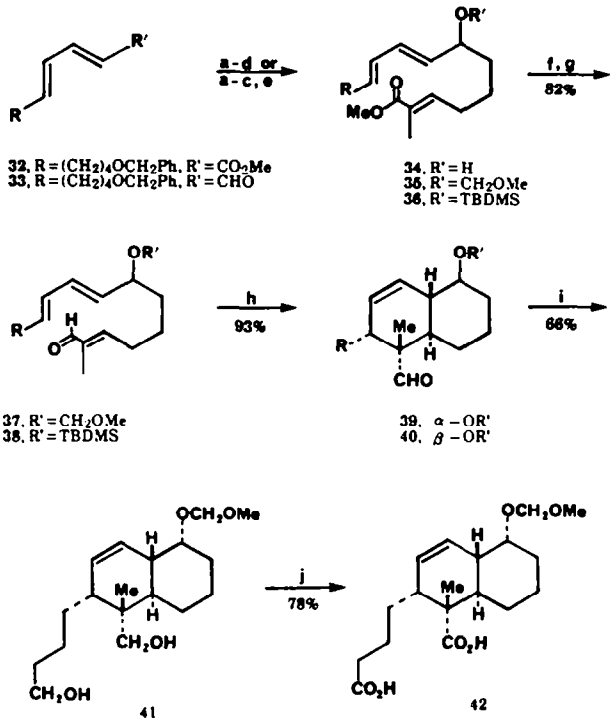
Interestingly, in the cyclization leading to **26** there was no sign of methyl addition to either the product or the starting aldehyde. The contrasting behavior of dimethyl vs diethylaluminum chloride with aldehydes **11** and **25** reflects the differing nucleophilicities of these two reagents.[9]

Our success with Lewis acid promoted Diels–Alder cyclizations of even acid-labile trienals such as **25** encouraged further applications to more substituted trienals as a possible route to hydronaphthalenes such as **V**. For preliminary studies the Roush ester **27** seemed well suited.[3a] Accordingly, the published route to this material starting with sorbic aldehyde and γ-bromobutanal diethyl acetal was repeated. Reduction of ester **27** with DIBAH afforded the alcohol **28** which was converted to the aldehyde **29** via Swern oxidation. Attempted cyclization of this aldehyde with ethylaluminum dichloride as the catalyst led to extensive decomposition even at low temperature as had been reported for the ester **27**.[3a] However, with the milder Lewis acid, diethylaluminum chloride, the cyclization proceeded readily in methylene chloride at −78° to −23° with high *endo*-selectivity to give a 75:15:10 mixture of the carbinyl epimers **30**, **31** and the *cis* fused counterpart of **30** in 84% yield (Scheme 3). In contrast to our findings with trienal **11**, no products of ethyl addition could be detected in this reaction. Evidently the α-methyl substituent decreases the carbonyl reactivity of aldehydes **29–31** sufficiently to block this reaction.

Since cyclization of the methyl substituted 2,8,10-undecatrienal **29** actually proceeded in higher yield than the unsubstituted case it was of interest to explore further applications of the methodology to systems of possible value for natural product synthesis. A likely target was the diacid **42** prepared by Ireland and Thompson[10] in some 17 steps from the Diels–Alder adduct of 2-methylcycloheptenone and Danishefsky's diene. Our route to this diacid started with 5-(benzyloxy)pentanal, obtained via oxidation of 5-(benzyloxy)pentanol with pyridinium chlorochromate in methylene chloride (Scheme 4). Condensation with methyl (*E*)-(4-diethylphosphono)-2-butenoate in THF



Scheme 3.



(a) a) $BrMg(CH_2)_3CH(OEt)_2$, THF, 0°C b) $(CO_2H)_2$, H_2O, 25°C, 18 h c) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, 25°C d) $MeOCH_2Cl$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0° to 25°C e) TBDMSCl, DMF, imidazole f) $i\text{-}Bu_2AlH$, Et_2O, -78°C g) MnO_2, CH_2Cl_2, 25°C, 6 h h) Et_2AlCl, CH_2Cl_2, -78° to -23°C, 14 h i) Na, NH_3 j) CrO_3, H_2SO_4, acetone, 0°C

(b) TBDMS = *tert*-BuMe$_2$Si

Scheme 4.[a,b]

afforded the ester **32** of greater than 95% stereochemical purity according to high-field ^{1}H-NMR analysis. Reduction with DIBAH at −78° followed by Swern oxidation gave the aldehyde **33**. From this point the route was patterned after Roush's preparation of the triene ester **27**.[3e] Thus addition of 4,4-diethoxybutylmagnesium bromide followed by hydrolysis of the acetal with 50% aqueous oxalic acid and treatment of the resultant δ-lactol with (carbomethoxy)triphenylphosphorane afforded the triene ester **34**. The hydroxyl grouping of this ester was protected both as the methoxymethyl **35** and the TBDMS ether **36**. Reduction of ester **35** and subsequent oxidation with MnO_2 gave the trienal **37** in 92% yield. High-field ^{1}H-NMR analysis indicated an isomeric purity of over 90%. Cyclization of **37** was effected with diethylaluminum chloride at −78° to −23° to afford a separable 45:55 mixture of the bicyclic aldehydes **39** and **40** (R′ = CH_2OMe) in 93% yield. The TBDMS protected trienal **38**, on the other hand, gave a 95:5 mixture of the corresponding aldehydes **39** and **40** (R′ = TBDMS) when treated analogously. In each case a small (*ca* 10%) peak at 9.3 ppm in the ^{1}H-NMR spectrum could be attributed to *cis* fused cyclization products. Thus both trienals show high *endo*-selectivity but the directing effects of the ether substituents differ markedly.† The origin of these effects is a matter of interest which we are currently examining in connection with directed asymmetric synthesis of more substituted hydronaphthalene systems such as **I** and **III**.

Aldehydes **39** and **40** (R′ = CH_2OMe) were easily distinguished through high-field ^{1}H-NMR analysis. After separation, the α-epimer **39** was treated with sodium in ammonia to cleave the benzyl ether. The resultant diol **41** upon oxidation with excess Jones reagent afforded the Ireland diacid **42**.[10] Comparison by TLC, mixed melting point and high-field ^{1}H-NMR analysis established the identity of the two samples.

EXPERIMENTAL

The apparatus and methods described by Kramer *et al.*[12] were used to maintain an argon or nitrogen atmosphere in the reaction flask. IR absorption maxima are reported in wavenumbers (cm^{-1}) and are standardized by reference to the 1601 cm^{-1} peak of polystyrene. ^{1}H-NMR spectra were recorded on Varian EM-390 and Bruker WH-400 spectrometers. Chemical shifts (δ) are reported downfield from TMS (Me_4Si) in ppm of the applied field. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; envelope, e; multiplet, m. Combustion microanalyses were performed by Atlantic Laboratories, Atlanta, GA. Column chromatography was performed on E. Merck silica gel 60 (230–400 ASTM mesh) according to the procedure of Still *et al.*[13] In the interest of brevity, experimental details for the conversion of alcohol **34** to diol **41** are only provided for the methoxymethyl protected derivatives. The analogous TBDMS derivatives were treated identically.

† The preference for the α(axial)-epimer in a similar situation has been attributed to a stereoelectronic effect.[11] The effect appears to be absent in methoxymethyl and other alkyl ethers we are currently investigating.

(E)-6-Tetrahydropyranyloxy-2-hexene-1-ol (**1**)

The procedure of Denmark[14] was modified. To a stirred, cooled (0°) soln of 4.3 ml (30.7 mmol) of sodium bis-methoxyethoxyaluminum hydride (Red-Al) in 25 ml of Et_2O was added 1.95 g (9.6 mmol) of 6-tetrahydropyranyloxy-2-hexyn-1-ol in 10 ml of Et_2O over 1 h. The soln was warmed to room temp and stirred for 12 h. The mixture was again cooled to 0° and cautiously quenched with H_2O. The aq layer was saturated with NaCl and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$). Solvent was removed and the residue was purified by chromatography on silica gel eluting with 25% EtOAc in hexanes to afford 1.85 g (95%) of (*E*)-allylic alcohol **1** as a colorless oil.

IR (film) ν 3380, 2920, 2805, 1650, 1460, 1355 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 1.70–1.30 (8H, br m, CH_2), 2.3–2.1 (2H, m, allylic CH_2), 3.80–3.30 (4H, m, CH_2O), 4.0 (2H, br s, allylic CH_2O), 4.5 (1H, br s, acetal H), 5.85–5.60 (2H, m, vinyl H). (Found: C, 66.04; H, 10.09. Calc for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.)

(E)-6-Tetrahydropyranyloxy-2-hexenal (**2**)

The procedure of Corey[15] was modified. To a stirred, cooled (−10°) soln of 180 g (478 mmol) of pyridinium dichromate in 1.0 l of dimethylformamide was added 79.6 g (398 mmol) of allylic alcohol **1** over 15 min. The mixture was warmed to 0° and stirred for 2 h. The mixture was poured into 1 l of H_2O and was extracted 4 times with Et_2O–pentane. The combined organic layers were washed with H_2O, sat $CuSO_4$ aq and brine, and dried ($MgSO_4$). Distillation under reduced pressure afforded 67 g (85%) of aldehyde as a colorless liquid. IR (film) ν 2920, 2850, 2710, 1690, 1640, 1440, 1360 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 2.0–1.40 (8H, br m, CH_2), 2.6–2.3 (2H, dt, J = 6 Hz, H4), 4.0–3.3 (4H, m, CH_2O), 4.55 (1H, br s, acetal H), 6.10 (1H, dd, J = 8, 15 Hz, H2), 6.80 (1H, dt, J = 15, 6 Hz, H3), 9.50 (1H, d, J = 8 Hz, H1). (Found: C, 66.54; H, 9.19. Calc for $C_{11}H_{18}O_3$: C, 66.64; H, 9.17%.)

(E)-4,6-Heptadien-1-ol (**4**)

To a stirred, cooled (−78°) suspension of 151 g (422 mmol) of methyltriphenylphosphonium bromide in 600 ml of dry THF was added 150 ml (420 mmol) of n-BuLi (2.8 M in hexanes). The mixture was stirred at −78° for 30 min and 66 g (333 mmol) of aldehyde **2** was added in 50 ml of dry THF. After stirring at −78° for 1 h and warming to room temp the mixture was poured into 400 ml of H_2O and was extracted 3 times with Et_2O–pentane. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was suspended in pentane and filtered through 100 g of silica gel. The filtrate was concentrated and dissolved in 150 ml of MeOH whereupon 1.0 g of activated Dowex AG 50W acidic ion exchange resin was added and the mixture was heated to 40° for 3 h, cooled to room temp and filtered. Distillation (105°, 47 mmHg) afforded 24.7 g (66%) of heptadienol **4** as a colorless liquid. IR (film) ν 3320, 2930, 2860, 1650, 1610, 1440 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 1.64–1.59 (2H, m, H2), 2.11 (2H, dt, J = 7.2 Hz, H3), 2.57 (1H, br s, OH), 3.56 (2H, t, J = 6.5 Hz, H1), 5.06–4.91 (2H, 4 lines, H7), 5.69–5.60 (1H, m, H4), 6.06–5.99 (1H, m, H5), 6.30–6.20 (1H, m, H6). (Found: C, 75.01; H, 10.73. Calc for $C_7H_{12}O$: C, 74.95; H, 10.78%.)

(E)-1-Bromo-4,6-heptadiene (**6**)

To a stirred, cooled (0°) soln of 770 mg (6.86 mmol) of alcohol **4** in 15 ml of dry CH_2Cl_2 was added 2.35 ml (16.9 mmol) of Et_3N followed by 0.95 ml (12.3 mmol) of freshly distilled methanesulfonyl chloride. The turbid mixture was stirred at 0° for 1 h, poured into ice water, and extracted with Et_2O (2 ×). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Crude mesylate **5** was dissolved in 10 ml of dry THF containing 1.47 g (16.9 mmol) of anhydrous LiBr. The soln was heated to reflux for 18 h, cooled, poured into H_2O and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and solvent was removed to afford 1.06 g (90%) of crude bromide, which was suitable at this point for preparation of the Grignard reagent **7**.

IR (film) ν 3000, 2950, 1605, 1445, 1250, 1010 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 1.90 (2H, t, J = 7 Hz, H2), 2.25 (2H, dt, J = 7 Hz, H3), 3.45 (2H, t, J = 6.3 Hz, H1), 5.2–4.9 (2H, m, H7), 5.7–5.6 (1H, m, H4), 6.15–6.05 (1H, m, H5), 6.35–6.25 (1H, m, H6).

(E)-4,6-Heptadienylmagnesium bromide (**7**)

A cooled (0°) suspension of 195 mg (8.0 mmol) of Mg metal (50 mesh, oven dried) in 2 ml of dry THF was treated for 5 min in an ultrasound bath. While sonication was maintained, 1.06 g (6.0 mmol) of bromide **6** in 3 ml of dry THF was added over 1 h. The sonication was discontinued and the supernatant was decanted from the excess Mg metal. The soln was found to be 0.85 M in Grignard reagent by titration with 1.0 M 2-propanol in xylene using 1,10-phenanthrolene as the end-point indicator.

Isopropyl (E,E)-4-hydroxyundeca-2,8,10-trienoate (**8**)

To a stirred, cooled (−78°) soln of 2.13 g (15.0 mmol) of isopropyl (*E*)-3-formylpropenoate[16] in 100 ml of dry THF was added a soln of 17.6 ml (15.0 mmol) of 0.85 M 4,6-heptadienylmagnesium bromide in 15 ml of dry THF over 1 h. The mixture was stirred at −78° for 1 h and was poured into 100 ml of Et_2O and 100 ml of sat NH_4Cl. The organic layer was washed with sat NH_4Cl and the combined aq washes were extracted with Et_2O. The organic layers were dried (Na_2SO_4–K_2CO_3) and the solvent was removed under reduced pressure to afford 4.0 g (> 100% crude) of an orange oil which was purified by chromatography on triethylamine-deactivated silica gel, eluting with 15% EtOAc in hexanes to afford 3.2 g (90%) of product as a colorless oil. IR (film) ν 3400, 3100, 2950, 2900, 1705, 1660, 1460 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 1.25 (6H, d, J = 6.2 Hz, $CH(C\underline{H}_3)_2$), 1.40–1.80 (4H, m, CH_2), 2.0–2.2 (2H, m, allylic CH_2), 4.28 (1H, m, C<u>H</u>OH), 4.90–5.10 (2H, m, C=CH_2), 5.05 (1H, sept., J = 6.2 Hz, C<u>H</u>$(CH_3)_2$), 5.62–5.69 (1H, 5 lines, C=CH), 5.98 (1H, dd, J = 15.7, 1.6 Hz, H2), 5.95–6.07 (1H, m, C=CH), 6.23–6.32 (1H, 6 lines, C=CH), 6.87 (1H, dd, J = 15.7, 5.0 Hz, H3). (Found: C, 70.49; H, 9.28. Calc for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%.)

Isopropyl (E,E)-4-(t-butyldimethylsilyloxy)undeca-2,8,10-trienoate (**9**)

To a stirred soln of 3.0 g (12.6 mmol) of **8** in 25 ml of dry DMF was added 2.18 g (3.0 mmol) of imidazole followed by 2.41 g (16.0 mmol) of t-butyldimethylchlorosilane in a single portion. The mixture was stirred at 25° for 18 h, then diluted with 100 ml of Et_2O and washed twice with H_2O. The organic layer was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 2% EtOAc in hexanes to afford 4.27 g (96%) of silyl ether **9** as a colorless oil. IR (film) ν 2940, 2860, 1715, 1660, 1610, 1480, 1380 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.02, 0.04 (6H, 2s, $SiCH_3$), 0.90 (9H, s, $C(CH_3)_3$), 1.26 (6H, d, J = 6.2 Hz, $CH(C\underline{H}_3)_2$), 1.40–1.80 (4H, m, CH_2), 2.07 (2H, 5 lines, allylic CH_2), 4.30 (1H, m, C<u>H</u>OH), 4.90–5.10 (2H, m, C=CH_2), 5.05 (1H, sept., J = 6.2 Hz, C<u>H</u>$(CH_3)_2$), 5.56–5.63 (1H, 5 lines, C=CH), 5.92 (1H, dd, J = 15.5, 1.7 Hz, H2), 5.95–6.08 (1H, m, C=CH), 6.24–6.34 (1H, m, C=CH), 6.87 (1H, dd, J = 15.5, 4.7 Hz, H3). (Found: C, 68.28; H, 10.33. Calc for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29%.)

(E,E)-4-(t-Butyldimethylsilyloxy)undeca-2,8,10-trienol (**10**)

To a stirred, cooled (−78°) soln of 2.16 g (6.1 mmol) of **9** in 100 ml of Et_2O was added 12.4 ml (12.4 mmol) of 1.0 M DIBAH in hexanes. The soln was stirred at −78° for 1 h. The reaction was quenched by addition of sat sodium potassium tartrate soln. The mixture was extracted with Et_2O and the organic layer was dried (Na_2SO_4 and K_2CO_3). Solvent was removed under reduced pressure and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 10% EtOAc in hexanes to afford 1.83 g (99%) of **10** as a colorless oil. IR (film) ν 3300, 3020, 2910, 2840, 1600, 1460, 1365, 1255 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 0.04, 0.06 (6H, 2s, $SiCH_3$), 0.90

(9H, s, $C(CH_3)_3$), 1.2–1.8 (4H, m, CH_2), 1.95–2.25 (2H, m, allylic CH_2), 4.15 (3H, m, $C\underline{H}_2OH$, CHOSi), 4.85–5.75 (2H, m, $C{=}CH_2$), 5.5–6.5 (5H, m, C=CH). (Found: C, 68.99; H, 10.92. Calc for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88%.)

(E,E) - 4 - (t-*Butyldimethylsilyloxy*)*undeca* - 2,8,10 - *trienal* (**11**)

To a stirred, cooled (−78°) soln of 184 mg (1.42 mmol) of oxalyl chloride in 10 ml of dry CH_2Cl_2 was added 227 mg (2.9 mmol) of DMSO over 5 min. The soln was stirred at −78° for 3 min and 300 mg (1.01 mmol) of **10** was added in 3 ml of CH_2Cl_2. The soln was stirred at −78° for 1 h then 1.4 ml (10.0 mmol) of Et_3N was added and the mixture was warmed to room temp for 1 h. The mixture was poured into H_2O and was extracted with CH_2Cl_2. The combined organic layers were washed with cold dilute HCl and were dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 10% EtOAc in hexanes to afford 262 mg (68%) of aldehyde **11** as a pale yellow oil. IR (film) ν 3070, 2930, 2840, 2700, 1685, 1640, 1600, 1460, 1370, 1260 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.0, 0.03 (6H, 2s, $SiCH_3$), 0.90 (9H, s, $C(CH_3)_3$), 1.20–1.80 (4H, m, CH_2), 1.95–2.25 (2H, m, allylic CH_2), 4.30–4.50 (1H, m, CHOSi), 4.85–5.25 (2H, m, $C{=}CH_2$), 5.4–6.5 (4H, m, C=CH), 6.80 (1H, dd, J = 5, 15 Hz, H3), 9.64 (1H, d, J = 7.5 Hz, CHO). (Found: C, 69.10; H, 10.32. Calc for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27%.)

Isopropyl 1,2,4aβ,5,6,7,8,8aα - *octahydro* - 8β - (t - *butyldimethylsilyloxy*)*naphthalene* - 1α - *carboxylate* (**13**)

To a stirred, cooled (0°) soln of 300 mg (1.02 mmol) of **9** in 15.0 ml of dry CH_2Cl_2 was added 1.02 ml (1.02 mmol) of 1.0 M ethylaluminum dichloride in hexanes. The mixture was stirred at 8° for 18 h then quenched by rapid addition of sat $NaHCO_3$ aq, and extracted twice with CH_2Cl_2. The organic layer was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel eluting with 5% EtOAc in hexanes to afford 240 mg (60%) of **13** as a colorless oil. IR (film) ν 3000, 2920, 2840, 1720, 1460, 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.02, 0.04 (6H, 2s, $SiCH_3$), 0.93 (9H, s, $C(CH_3)_3$), 1.24, 1.27 (6H, 2d, J = 6.2 Hz, $CH(C\underline{H}_3)_2$), 2.09–2.20 (1H, m, H2α), 2.30–2.41 (2H, m, H2β, H4α), 2.60 (1H, dt, J = 11.2, 5.3 Hz, H1), 4.10 (1H, br s, H8), 5.05 (1H, sept., J = 6.2 Hz, $C\underline{H}(CH_3)_2$), 5.46 (1H, dd, J = 8.0, 1.8 Hz, H4), 5.55 (1H, m, H3). (Found: C, 68.24; H, 10.63. Calc for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29%.)

1,2,4aβ,5,6,7,8,8aα - *Octahydro* - 8β - (t-*butyldimethylsilyloxy*)*naphthalene* - 1α - *carboxaldehyde* (**14**)

A. *From alcohol* **10**. To a stirred soln of 183 mg (0.62 mmol) of **10** in 10 ml of dry CH_2Cl_2 was added 1.6 g of freshly prepared active gamma-manganese dioxide.[17] The mixture was stirred at room temp for 36 h. Celite was added and the mixture was filtered and concentrated. The residue was chromatographed on silica gel eluting with 5% EtOAc in hexanes to afford 117 mg (64%) of **14** as a colorless oil.

B. *From aldehyde* **11**. To a stirred, cooled (−78°) soln of 300 mg (1.02 mmol) of **11** in 15 ml of dry CH_2Cl_2 was added 1.02 ml (1.02 mmol) of 1.0 M ethylaluminum dichloride in hexanes.[18] The soln was warmed to −40° then immediately quenched by rapid addition of sat $NaHCO_3$ aq and processed as described for **13** to afford 187 mg (62%) of chromatographed aldehyde **14** as a colorless oil. IR (film) ν 3010, 2920, 2845, 1720, 1460, 1440, 1370, 1265 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.02, 0.06 (6H, 2s, $SiCH_3$), 0.90 (9H, s, $C(CH_3)_3$), 2.10–2.20 (2H, m, H2), 2.41 (1H, br t, J = 12.0 Hz, H4a), 2.74 (1H, ddt, J = 3.0, 6.5, 10.75 Hz, H1), 4.10 (1H, br s, H8), 5.45 (1H, dd, J = 8.5, 1.7 Hz, H4), 5.57 (1H, ddd, J = 1.4, 3.4, 8.5 Hz, H3), 9.74 (1H, d, J = 3.0 Hz, CHO). (Found: C, 69.22; H, 10.30. Calc for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27%.)

Non-6-yn-8-ene-1,5-*diol* (**17**)

To a stirred, cooled (−78°) soln of 2.0 ml (21.6 mmol) of valerolactone in 50 ml of dry THF was added 21.6 ml (21.6 mmol) of 1.0 M DIBAH in hexanes. The mixture was stirred at −78° for 1 h. In a separate flask, 17.9 ml (50 mmol) of 2.8 M EtMgBr in THF was added to a stirred soln of 6.7 ml (50 mmol) of a 50% xylene soln of vinylacetylene in 20 ml of refluxing THF. (This flask was equipped with a dry ice–Me_2CO condenser.) After 1 h at reflux, the soln of bromomagnesium enyne was cooled to 0° and transferred via cannula to the valerolactone reduction mixture. The mixture was warmed to room temp and stirred for 3 h, then poured into sat NH_4Cl aq and extracted three times with Et_2O. The combined organic extracts were washed with brine and dried (Na_2SO_4). Solvent was removed to afford 3.06 g (92%) of diol **17** which was used without further purification.

(E)-Nona-6,8-*diene*-1,5-*diol* (**18**)

To a stirred, cooled (0°) soln of 40 ml (135 mmol) of Red-Al in 550 ml of Et_2O was added a soln of 8.5 g (54 mmol) of crude ynol **17** in 250 ml of Et_2O over 4 h. The mixture was warmed to room temp and stirred for 18 h, then again cooled to 0° and 150 ml of a sat soln of sodium potassium tartrate was added over 2 h. After an additional 1 h, the product was isolated by extraction with EtOAc and chromatography on silica gel eluting with 50% EtOAc in hexanes to afford 6.4 g (76%) of **18** as a viscous oil. IR (film) ν 3300, 2930, 2850, 1610, 1420, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.70–1.30 (6H, m, CH_2), 3.7–3.5 (2H, m, CH_2O), 4.2–4.0 (1H, m, allylic C$\underline{H}$OH), 5.3–5.0 (2H, m, H9), 5.60 (1H, dd, J = 15, 6.5 Hz, H6), 6.50–6.0 (2H, m, H7, H8). (Found: C, 68.86; H, 10.41. Calc for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.)

(E) - 5 - *Hydroxy* - 6,8 - *nonadienyl* 1,1,1 - *trimethylacetate* (**19**)

To a rapidly stirred, cooled (−40°) soln of 6.4 g (41.0 mmol) of **18** in 90 ml of pyridine and 20 ml of CH_2Cl_2 was added 5.3 ml (43.1 mmol) of trimethylacetyl chloride via syringe over 4 h. The mixture was warmed to room temp, diluted with 200 ml of Et_2O, and poured into H_2O. The organic layer was washed with sat $CuSO_4$ aq, the combined aq washes were extracted with Et_2O and the combined organic layers were washed with H_2O and brine and dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 10% EtOAc in hexanes to afford 8.2 g (85%) of **19** as a colorless oil. IR (film) ν 3400, 2950, 2850, 1725, 1605, 1480, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.17 (9H, s, $C(CH_3)_3$), 4.04 (2H, t, J = 6.5 Hz, H1), 4.13 (1H, dt, J = 6.5 Hz, H5), 5.2–5.1 (2H, 8 lines, H9), 5.68 (1H, dd, J = 15.1, 6.5 Hz, H6), 6.3–6.2 (2H, m, H7, H8). (Found: C, 69.82; H, 10.09. Calc for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.)

(E) - 5 - (t-*Butyldimethylsilyloxy*) - 6,8 - *nonadienyl* 1,1,1 - *trimethylacetate* (**20**)

To a stirred soln of 715 mg (2.98 mmol) of **19** in 10 ml of dry DMF was added 580 mg (8.5 mmol) of imidazole followed by 628 mg (4.16 mmol) of t-butyldimethylsilyl chloride. The soln was stirred at room temp for 10 h, then processed as described for **9** to afford 951 mg (91%) of chromatographed silyl ether **20** as a colorless oil. IR (film) ν 2950, 2930, 2850, 1725, 1605, 1480, 1465 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.05, 0.09 (6H, 2s, $SiC\underline{H}_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.15 (9H, s, $C(CH_3)_3$), 4.20–4.0 (1H, br q, J = 6 Hz, allylic CHOSi), 5.3–5.0 (2H, m, H9), 5.65 (1H, dd, J = 6, 15 Hz, H6), 6.6–6.0 (2H, m, H8, H9). (Found: C, 67.86; H, 10.85. Calc for $C_{20}H_{38}O_3Si$: C, 67.74; H, 10.80%.)

(E)-5-(t-*Butyldimethylsilyloxy*)*nona*-6,8-*dien*-1-*ol* (**21**)

To a stirred, cooled (0°) suspension of 108 mg (2.7 mmol) of $LiAlH_4$ in 50 ml of Et_2O was added a soln of 951 mg (2.7 mmol) of **20** in 5 ml of Et_2O. The mixture was stirred for 1 h at 0°, warmed to room temp for 1 h and recooled to 0°. The hydride was quenched by addition of 108 μl of H_2O, 108 μl of 15% NaOH aq and 324 μl of H_2O. The mixture was filtered and the salts were washed with three 25 ml portions of Et_2O. The combined organic layers were concentrated under reduced pressure and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 15% EtOAc in hexanes to afford 657 mg (90%) of **21** as a colorless oil. IR (film)

ν 3350, 2930, 2850, 1605, 1460, 1265 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.0, 0.05 (6H, 2s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 3.64 (2H, t, J = 6.5 Hz, H1), 4.14 (1H, dt, J = 6.5 Hz, H5), 5.2–5.0 (2H, 8 lines, H9), 5.65 (1H, dd, J = 6.5, 15 Hz, H6), 6.10 (1H, dd, J = 12, 15 Hz, H7), 6.35–6.25 (1H, m, H8). (Found: C, 66.72; H, 11.15. Calc for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18%.)

(E)-5-(t-Butyldimethylsilyloxy)nona-6,8-dienal (**22**)

To a stirred, cooled (10°) soln of 657 mg (2.43 mmol) of **21** in 40 ml of dry CH_2Cl_2 was added 4 g of dry crushed 3 Å sieves.[19] To this mixture was added 1.37 g (3.6 mmol) of pyridinium dichromate in portions over 0.5 h. The mixture was warmed to room temp and stirred for 2 h, then diluted with 50 ml of pentane and 100 ml of Et_2O and filtered through Celite. The filter cake was washed with 3 additional 25 ml volumes of 50% ether in pentane. The organic washes were combined and concentrated under reduced pressure and the residue was chromatographed on triethylamine-deactivated silica gel to afford 485 mg (74%) of **22** as a pale oil. (Found: C, 66.99; H, 10.49. Calc for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51%.)

Ethyl (E,E) - 7 - (t-butyldimethylsilyloxy)undeca - 2,8,10 - trienoate (**23**)

To a stirred, cooled (0°) soln of 669 mg (2.0 mmol) of (carboethoxymethylene)triphenylphosphorane in 15 ml of dry CH_2Cl_2 was added a soln of 485 mg (1.8 mmol) of **22** in 5 ml of CH_2Cl_2. The soln was allowed to warm slowly to room temp and to stir for 18 h, then it was concentrated under reduced pressure. The residue was chromatographed on triethylamine-deactivated silica gel eluting with 2% EtOAc in hexanes to afford 545 mg (89%) of **23** as a pale oil. IR (film) ν 2920, 2850, 1715, 1630, 1465, 1440, 1270 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.01, 0.03 (6H, 2s, $SiCH_3$), 0.88 (9H, s, $C(CH_3)_3$), 2.25–2.15 (2H, dt, J = 6.8 Hz, H4), 4.16–4.10 (1H, m, H7), 5.20–5.05 (2H, m, H11), 5.62 (1H, dd, J = 6.5, 15.2 Hz), 5.80 (1H, br d, J = 15.5 Hz, H2), 6.16–6.08 (1H, m, H9), 6.52–6.25 (1H, m, H10), 6.94 (1H, dt, J = 15.5, 6.8 Hz, H3). (Found: C, 67.49; H, 10.24. Calc for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.25%.)

(E,E) - 7 - (t-Butyldimethylsilyloxy)undeca - 2,8,10 - trien - 1 - ol (**24**)

To a stirred, cooled (−78°) soln of 980 mg (2.89 mmol) of **23** in 40 ml of dry Et_2O was added 4.0 ml (6.0 mmol) of 1.5 M DIBAH in toluene. The soln was stirred at −78° for 1 h, 1.0 ml of MeOH was added to quench the excess hydride, and the mixture was warmed to room temp whereupon 100 ml of sat sodium potassium tartrate soln was added and stirring was continued for 1 h. The layers were separated and the organic phase was washed with 50 ml of sat sodium potassium tartrate soln. The combined aq washes were extracted with Et_2O; the combined organic layers were dried (Na_2SO_4) then concentrated under reduced pressure. The residue was chromatographed on triethylamine-deactivated silica gel to afford 8.5 g (96%) of **24** as a colorless liquid. IR (film) ν 3340, 2940, 2850, 1605, 1470, 1370 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.01, 0.03 (6H, 2s, $SiCH_3$), 0.86 (9H, s, $C(CH_3)_3$), 2.05–2.01 (2H, m, H4), 4.08 (2H, br s, H1), 4.15–4.10 (1H, m, H7), 5.20–5.00 (2H, m, H11), 5.70–5.55 (3H, m, H2, H3, H8), 6.15–6.08 (1H, m, H9), 5.35–5.25 (1H, m, H10). (Found: C, 68.91; H, 10.81. Calc for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88%.)

(E,E) - 7 - (t-Butyldimethylsilyloxy)undeca - 2,8,10 - trienal (**25**)

To a stirred soln of 457 mg (1.54 mmol) of **24** in 25 ml of dry CH_2Cl_2 was added 1.2 g of freshly prepared MnO_2.[17] The mixture was stirred at room temp for 6 h, Celite (5 g) was added and the mixture was filtered. The filter cake was washed with three 15 ml portions of CH_2Cl_2. The filtrate was concentrated to afford 418 mg (92%) of unstable **25** as a pale yellow oil. This aldehyde was carried on without further purification. IR (film) ν 2940, 2850, 2710, 1690, 1620, 1465, 1260 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 0.0, 0.05 (6H, 2s, $SiCH_3$), 0.90 (9H, s, $C(CH_3)_3$), 1.65–1.50 (4H, m, CH_2), 2.40–2.20 (2H, m, allylic CH_2), 4.30–4.10 (1H, m, allylic CHOSi), 5.30–5.0 (2H, m, H11), 5.60 (1H, dd, J = 6.5, 14 Hz, H8), 6.5–6.0 (3H, m, H9, H10, H2), 6.80 (1H, dt, J = 15, 6 Hz, H3), 9.50 (1H, d, J = 8.0 Hz, H1).

5α - (t-Butyldimethylsilyloxy) - 1,2,4aβ,5,6,7,8,8aα - octahydronaphthalene - 1α - carboxaldehyde (**26**)

To a stirred, cooled (−78°) soln of 120 mg (0.41 mmol) of **25** (dried azeotropically with C_6H_6) in 10 ml of dry CH_2Cl_2 was added 0.41 ml (0.41 mmol) of 1.0 M dimethylaluminum chloride as a soln in hexanes. The bright yellow soln was stirred at −78° for 1 h then warmed to −40°, immediately poured into sat $NaHCO_3$ aq and processed as described for **13** to afford 92 mg (77%) of chromatographed aldehyde **26** as a colorless oil. IR (film) ν 3050, 2930, 2850, 2700, 1730, 1470, 1260 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.01, 0.03 (6H, 2s, $SiCH_3$), 0.86 (9H, s, $C(CH_3)_3$), 4.0 (1H, m, CHOSi), 5.50 (1H, br d, J = 10.5 Hz, H4), 5.64 (H, ddd, J = 10.5, 4.9, 22.8 Hz, H3), 9.58 (1H, d, J = 4.5 Hz, CHO). (Found: C, 69.17; H, 10.33. Calc for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27%.)

(E,E,E)-2-Methyl-7 - (t-butyldimethylsilyloxy)dodeca - 2,8,10-trien-1-ol (**28**)

To a stirred, cooled (−78°) soln of 5.2 g (15.0 mmol) of **27**, prepared by the method of Roush,[3e] in 100 ml of Et_2O was added 30 ml (30 mmol) of 1.0 M DIBAH in hexanes. The soln was stirred at −78° for 1 h, then warmed to room temp, treated with 50 ml of sat sodium potassium tartrate soln, and processed as described for **10** to afford 4.8 g (98%) of chromatographed alcohol **28** as a colorless oil. IR (film) ν 3300, 2900, 2830, 1460, 1380, 1255 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.02, 0.03 (6H, 2s, $SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 1.63 (3H, br s, vinyl CH_3), 1.72 (3H, br d, J = 6.5 Hz, vinyl CH_3), 2.0 (2H, dt, J = 6.5 Hz, H4), 3.97 (2H, br s, H1), 4.07 (1H, dt, J = 6 Hz, H7), 5.37 (1H, dt, J = 1.1, 6.5 Hz, H3), 5.47 (1H, dd, J = 14.5, 6 Hz, H8), 5.70–5.60 (1H, m, H9), 6.1–5.90 (2H, m, H10, H11). (Found: C, 70.04; H, 11.23. Calc for $C_{19}H_{36}O_2Si$: C, 70.31; H, 11.18%.)

(E,E,E) - 2 - Methyl - 7 - (t-butyldimethylsilyloxy)dodeca - 2,8,10-trienal (**29**)

To a stirred, cooled (−78°) soln of 226 μl (2.6 mmol) of oxalyl chloride in 25 ml of dry CH_2Cl_2 was added 367 μl (5.18 mmol) of DMSO over 5 min. The mixture was stirred at −78° for 2 min and a soln of 600 mg (1.84 mmol) of **28** in 5 ml of CH_2Cl_2 was added. After 1 h, 3.48 ml (25 mmol) of Et_3N was added, and the mixture was warmed to room temp. H_2O was added to dissolve the solids and the mixture was processed as described for **11** to afford 460 mg (77%) of chromatographed enal diene **29** as a pale yellow oil. IR (film) ν 3000, 2920, 2840, 2700, 1685, 1645, 1470, 1370, 1260 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.01, 0.03 (6H, 2s, $SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 1.47–1.57 (4H, m, CH_2), 1.72 (3H, s, vinyl CH_3), 1.73 (3H, d, J = 8.5 Hz, C=CH—CH_3), 2.30–2.36 (2H, m, H4), 4.11 (1H, m, CHOSi), 5.44–5.50 (1H, m, C=CH), 5.62–5.69 (1H, m, C=CH), 5.97–6.09 (2H, m, C=CH), 6.46 (1H, br t, J = 7.4 Hz, H3). (Found: C, 70.67, H, 10.63. Calc for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.62%.)

1β,2α - Dimethyl - 5α - (t-butyldimethylsilyloxy) - 1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxaldehyde (**30**)

To a stirred, cooled (−78°) soln of 580 mg (1.8 mmol) of **29** (dried azeotropically with C_6H_6) in 50 ml of dry CH_2Cl_2 was added 1.8 ml (1.8 mmol) of 1 M diethylaluminum chloride in hexanes over 5 min. The bright yellow soln was stirred at −78° for 1 h then warmed to −23°, stirred for 6 h, and processed as described for **14** to afford 489 mg (84%) of aldehyde, a 75 : 15 : 10 mixture of **30** its carbinyl epimer **31** and the *cis* fused counterpart of **30**, according to glass capillary GC analysis. The latter aldehyde showed a characteristic signal at 9.3 ppm (CHO) in the ^1H-NMR spectrum. Aldehyde **30** could be separated by extremely careful chromatography. IR (film) ν 3000, 2910, 2840, 2670, 1720, 1460, 1375, 1260 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.03, 0.05 (6H, 2s, $SiCH_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.99 (3H, s, CH_3), 1.04 (3H, d, J = 7.1 Hz, CH_3), 2.45 (1H, dt, J = 2, 11.4 Hz, H8a), 4.06 (1H, br s, CHOSi), 5.36 (1H, br d, J = 10.2 Hz, C=CH), 5.53 (1H, ddd, J = 10.2, 4.9, 2.8 Hz, C=CH), 9.65 (1H, s, CHO). (Found: C, 70.82; H, 10.63. Calc for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.67%.)

Methyl (E,E)-9-(benzyloxy)nona-2,4-dienoate (**32**)

To a stirred, cooled (−40°) soln of 2.1 ml (15.0 mmol) of diisopropylamine in 150 ml of dry THF was added 9.4 ml (15.0 mmol) of 1.6 M n-BuLi in hexanes. The soln was stirred at −40° for 15 min then 3.54 g (15.0 mmol) of methyl diethylphosphonocrotonate[20] was added. The soln was stirred at −40° for 30 min and 2.36 g (12.3 mmol) of 5-(benzyloxy)pentanal[21] was added. The mixture was warmed to room temp over 1 h then poured into sat NH_4Cl aq and the product was isolated by extraction with Et_2O to afford 3.05 g (90%) of chromatographed ester **32** as a pale yellow oil. IR (film) ν 3010, 2930, 2840, 1720, 1660, 1435, 1270, 1250, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.30–2.10 (2H, m, allylic CH_2), 3.46 (2H, t, J = 6 Hz, OCH_2), 3.75 (3H, s, OCH_3), 4.50 (2H, s, $PhCH_2O$), 5.78 (1H, d, J = 15 Hz, C=C<u>H</u>CO_2CH_3), 6.00–6.20 (2H, m, C=CH), 7.25 (1H, m, C=CH), 7.42 (5H, m, aromatic H). (Found: C, 74.46; H, 8.11. Calc for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.)

(E,E)-9-(Benzyloxy)nona-2,4-dienal (**33**)

To a stirred, cooled (−78°) soln of 2.2 g (8.0 mmol) of **32** in 100 ml of Et_2O was added 18.0 ml (18.0 mmol) of 1.0 M DIBAH in hexanes. The soln was stirred at −78° for 1 h then the excess DIBAH was quenched by slow addition of 1.0 ml of MeOH, the mixture was warmed to room temp and processed as described for **10** to afford 2.0 g (100%) of alcohol which was used without further purification.

To a stirred, cooled (−78°) soln of 1.05 ml (12.0 mmol) of oxalyl chloride in 50 ml of dry CH_2Cl_2 was added 1.77 ml (25.0 mmol) of DMSO over 5 min. The mixture was stirred at −78° for 2 min and a soln of 2.0 g (8.0 mmol) of the above alcohol in 10 ml of CH_2Cl was added. The mixture was stirred at −78° for 1 h, 35 ml (250 mmol) of Et_3N was added, and the mixture was warmed to 0° and processed as described for **11** to afford 1.95 g of crude chromatographed aldehyde (97%) as a pale yellow oil which decomposed rapidly upon attempts at further purification.

Methyl (E,E,E)-2-methyl-7-hydroxy-15-(benzyloxy)pentadeca-2,8,10-trienoate (**34**)

To a stirred suspension of 1.6 g (65.8 mmol) of Mg powder in 30 ml of refluxing THF was added 5.0 g (22.2 mmol) of 4-bromobutyraldehyde diethyl acetal[3e] in 100 ml of dry THF over 3 h. The mixture was further heated at reflux for 1 h after complete addition of the bromoacetal soln. The soln was cooled to 0° and to it was added 1.95 g (8.0 mmol) of crude **33** in 10 ml of dry THF. The soln was stirred at 0° for 0.5 h, the excess organometallic was quenched with 2.0 ml of MeOH, and the mixture was filtered into a mixture of sat NH_4Cl aq and CH_2Cl_2. The aq layer was extracted twice with CH_2Cl_2 then the combined organic layers were washed with brine and concentrated under reduced pressure to afford 3.0 g (> 100%) of the hydroxyacetal as a pale orange oil. The oil was dissolved in 50 ml of THF and the soln was cooled to 0°. After stirring with 50 ml of 0.5 M aq oxalic acid at room temp for 18 h, the soln was poured into sat $NaHCO_3$ aq, and the product was isolated by extraction with CH_2Cl_2 to afford 2.85 g (> 100%) of the crude lactol as a pale orange oil. This oil was dissolved in 30 ml of dry CH_2Cl_2, cooled to 0° and 3.48 g (10.0 mmol) of (carbomethoxymethylene)triphenylphosphorane was added in small portions over 0.5 h. The mixture was stirred at room temp for 18 h, concentrated under reduced pressure, and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 15% EtOAc in hexanes to afford 1.76 g (57% from ester **32**) of hydroxy ester **34** as a colorless oil. IR (film) ν 3410, 3010, 2930, 2850, 1718, 1655, 1450, 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.82 (3H, br s, vinyl CH_3), 2.10 (2H, m, allylic CH_2), 2.20 (2H, m, allylic CH_2), 3.46 (2H, t, J = 6.5 Hz, CH_2OC), 3.72 (3H, s, OCH_3), 4.11 (1H, m, allylic C<u>H</u>OH), 4.49 (2H, s, $PhCH_2O$), 5.52–5.57 (1H, 4 lines, C=CH), 5.64–5.72 (1H, 5 lines, C=CH), 5.97–6.03 (1H, m, C=CH), 6.12–6.18 (1H, 4 lines, C=CH), 6.74 (1H, dt, J = 1.5, 7.4 Hz, C<u>H</u>=C(CH_3)CO_2CH_3), 7.30–7.34 (5H, m, aromatic H). (Found: C, 74.47; H, 8.92. Calc for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87%.)

Methyl (E,E,E)-2-methyl-7-(methoxymethoxy)-15-(benzyloxy)pentadeca-2,8,10-trienoate (**35**)

To a stirred, cooled (0°) soln of 1.38 g (3.6 mmol) of **34** in 10 ml of dry CH_2Cl_2 was added 683 μl (9.0 mmol) of chloromethyl methyl ether followed by 3.5 ml (20.0 mmol) of diisopropylethylamine. The soln was warmed to room temp and stirred for 18 h, then diluted with CH_2Cl_2 and washed with cold 1% HCl, water and brine. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc in hexanes to afford 912 mg (60%) of **35** as a colorless oil. IR (film) ν 2930, 2840, 1715, 1645, 1460, 1440, 1265 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.82 (3H, br s, vinyl CH_3), 2.08 (2H, m, allylic CH_2), 2.18 (2H, m, allylic CH_2), 3.35 (3H, s, OCH_3), 3.46 (2H, t, J = 6.5 Hz, CH_2OC), 3.72 (3H, s, OCH_3), 4.0 (1H, m, allylic CHOC), 4.49 (2H, s, $PhCH_2O$), 4.59 (2H, ABq, J = 6.7 Hz, $\Delta\nu_{AB}$ = 76.3 Hz, OCH_2O), 5.31–5.38 (1H, 4 lines, C=CH), 5.64–5.71 (1H, 5 lines, C=CH), 6.00–6.04 (1H, m, C=CH), 6.10–6.16 (1H, m, C=CH), 6.74 (1H, dd, J = 7.5, 1.5 Hz, C=CH), 7.32 (5H, m, aromatic H). (Found: C, 72.64; H, 8.91%. Calc for $C_{26}H_{38}O_5$: C, 72.53; H, 8.90%.)

(E,E,E)-2-Methyl-7-(methoxymethoxy)-15-(benzyloxy)pentadeca-2,8,10-trienal (**37**)

To a stirred, cooled (−78°) soln of 740 mg (1.72 mmol) of **35** in 15 ml of dry Et_2O was added 3.5 ml (3.5 mmol) of DIBAH as a 1.0 M soln in hexanes. The soln was stirred at −78° for 1 h, then 25 ml of sat aq sodium potassium tartrate soln was added and the mixture was processed as described for **10** to afford 665 mg (96%) of chromatographed alcohol as a colorless oil. IR (film) ν 3400, 2920, 2850, 1460, 1370 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.65 (3H, br s, vinyl CH_3), 2.12–2.02 (4H, m, allylic CH_2), 3.36 (3H, s, OCH_3), 3.46 (2H, t, J = 6.4 Hz, CH_2O), 4.00 (2H, br s, allylic CH_2O), 4.59 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 77.2 Hz, OCH_2O), 4.49 (2H, s, $PhCH_2O$), 5.41–5.34 (2H, m, H3, H8), 5.7–5.61 (1H, m, H9), 6.04–5.97 (1H, m, H10), 6.15–6.09 (1H, m, H11). (Found: C, 74.42; H, 9.55. Calc for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52%.)

To a stirred soln of 550 mg (1.36 mmol) of the above alcohol in 25 ml of dry CH_2Cl_2 was added 2.5 g of MnO_2. The mixture was stirred at room temp for 10 h and processed as described for **25** to afford 470 mg (85%) of chromatographed enal diene **37** as a colorless oil. IR (film) ν 3000, 2930, 2840, 2690, 1680, 1640, 1455, 1360 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.74 (3H, br s, vinyl CH_3), 2.09 (2H, m, allylic CH_2), 2.37 (2H, m, allylic CH_2), 3.36 (3H, s, OCH_3), 3.46 (2H, t, J = 6.4 Hz, CH_2OC), 4.02 (1H, m, allylic CHOC), 4.49 (2H, s, $PhCH_2O$), 4.59 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 77.2 Hz, OCH_2O), 5.32–5.38 (1H, 4 lines, C=CH), 5.65–5.70 (1H, 5 lines, C=CH), 5.98–6.05 (1H, m, C=CH), 6.11–6.17 (1H, m, C=CH), 6.47 (1H, dt, J = 7.4, 1.4 Hz, C=CH), 7.32 (5H, m, aromatic H), 9.39 (1H, s, CHO). (Found: C, 74.97; H, 9.08. Calc for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06%.)

1β-Methyl-2α-(4-benzyloxybutyl)-5-(methoxymethoxy)-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxaldehyde (**39**/**40**)

To a stirred, cooled (−78°) soln of 427 mg (1.1 mmol) of **37** (dried twice by C_6H_6 azeotrope) in 20 ml of dry CH_2Cl_2 was added 1.1 ml (1.1 mmol) of 1.0 M diethylaluminum chloride in hexanes dropwise over 1 min. The bright yellow soln was warmed to −23° over 1 h and stirred at −23° for 14 h. The reaction was processed as described for **26** to afford 400 mg (93%) of a chromatographed 1:1 mixture of carbinyl epimers **39** and **40** and *ca* 10% of the *cis* fused isomer (as determined by 400 MHz ^{1}H-NMR integration) as a colorless oil. IR (film) ν 3010, 2910, 2840, 2680, 1718, 1455, 1365 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.98, 1.02 (3H, 2s, CH_3), 3.30–3.21 (0.5 H, m, 5αH), 3.40, 3.34 (3H, 3s, 10:48:42, OCH_3), 3.94 (0.5 H, m, 5βH), 9.34, 9.60, 9.64 (1H, 2s, CHO). (Found: C, 75.05; H, 9.07. Calc for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06%.)

1β-Methyl-2α-(4-benzyloxybutyl)-5α-(methoxymethoxy)-1,2,4aβ,5,6,7,8,8aα-octahydro-1α-naphthylmethanol (**41**)

To a rapidly stirred soln of 108 mg (0.27 mmol) of a 1:1

mixture of **39** and **40** in 30 ml of refluxing dry NH_3 was added 31 mg (1.35 g atom) of Na metal in portions over 3 min. The blue soln was stirred for 10 min, then the reaction was rapidly quenched by addition of solid NH_4Cl. The NH_3 was evaporated and the residue was taken up in Et_2O. The organic layer was concentrated and the residue was chromatographed on silica gel eluting with 3% MeOH in CH_2Cl_2 to afford 38 mg (45%) of the desired axial **41** and 39 mg (46%) of its carbinyl epimer. IR (film) ν 3330, 2920, 2840, 1465, 1380 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.89 (3H, s, Cl, CH_3), 3.37 (3H, s, OCH_3), 3.55 (2H, ABq, J_{AB} = 9.91 Hz, $\Delta\nu_{AB}$ = 14.64 Hz, Cl, $C\underline{H}_2OH$), 3.66 (2H, t, J = 6.5 Hz, $C\underline{H}_2OH$), 3.80 (1H, m, H5), 4.63 (2H, ABq, J_{AB} = 6.0 Hz, $\Delta\nu_{AB}$ = 28.41 Hz, OCH_2O), 5.44 (1H, d, J = 10.5 Hz, H4), 5.85 (1H, ddd, J = 2.8, 5.0, 10.5 Hz, H3). (Found: C, 68.96; H, 10.30. Calc for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32%.)

1β - Methyl - 2α - (4 - carboxybutyl) - 5α - (methoxymethoxy) - 1,2,4aβ,5,6,7,8,8aα - octahydronaphthalene - 1α - carboxylic acid (**42**)

To a stirred, cooled (0°) soln of 20 mg (0.064 mmol) of **41** in 3 ml of Me_2CO was added 97 μl (0.26 mmol) of 2.67 M Jones reagent.[22] The mixture was stirred at 0° for 2 h, then it was extracted 3 times with 10% Na_2CO_3 aq. The basic extracts were acidified with 10% HCl and extracted 3 times with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with 50% EtOAc in hexanes containing 0.1% AcOH to afford 15 mg (69%) of **42** as a white solid (m.p. 144–145°; lit. m.p.[10] 149–150°; mixed m.p. 144–145°).

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