Conjugate Addition of Organocuprates to *trans*-4a,5,6,7,8,8a-Hexahydronaphthalene-1-carboxaldehydes. Synthesis of a Chlorothricin Degradation Product

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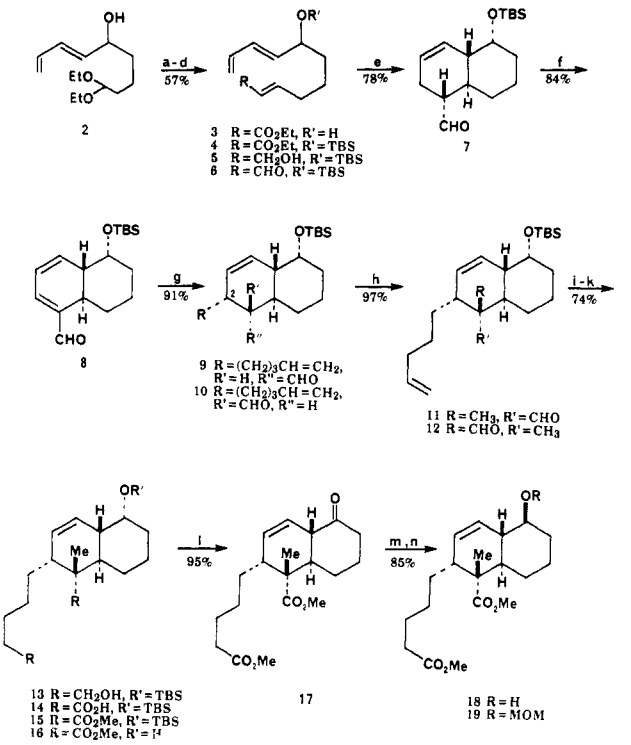
5-(*tert*-Butyldimethylsiloxy)-*trans*-4a,5,6,7,8,8a-hexahydronaphthalene-1-carboxaldehyde (8) undergoes highly stereo- and regioselective 1,4-addition of organocuprates to give the axially substituted adduct which can be methylated to the axial methyl derivative (e.g., 11) in high yield. Dienal 8 is available through Lewis acid catalyzed Diels–Alder cyclization of 7-(*tert*-butyldimethylsiloxy)-2,8,10-undecatrienal (6) followed by phenylselenation and regioselective selenoxide elimination. With lithium bis(4-pentenyl)cuprate as the organocopper reagent, a sequence was devised for the synthesis of diester 19, a degradation product of the antitumor antibiotic natural product chlorothricin. The 2-butenylcuprates also showed excellent stereo- and regioselectivity in additions to dienal 8.

The macrocyclic aglycon of the antitumor antibiotic chlorothricin[1] has been the subject of a number of recent synthetic endeavors.[2,3] In 1981, Ireland and coworkers described a degradation sequence for the conversion of chlorothricin via the aglycon methyl ester of *O*-methylchlorothricolide (I, R = Me) to the methoxymethyl-protected diester II (see Figure 1). Concurrent synthetic work by the Ireland group led to a racemic epimer of a homologue of diester II which was coupled with a "lower-half" tetronic acid prototype through an enolate Claisen rearrangement.[3] We recently prepared the Ireland synthetic diester by catalyzed Diels–Alder cyclization of a 2,8,10-undecatrienal (IV; R=$(CH_2)_4OCH_2Ph$,R'=Me, R''=CH_2OMe).[4] We now describe a synthesis of the degradation diester II, in racemic form, by a new route of potential applicability to the more complex members of the family.

The approach is based on the expectation that dienal III (Figure 2) should undergo both stereoselective and regioselective conjugate addition with cuprate reagents to give the axially substituted 1,4-adduct V whose subsequent methylation would be directed by the adjacent alkyl substituent giving rise to aldehyde VI. Models indicate that the cyclohexadiene ring of dienal III is rigidly held in a shallow bowl shaped conformation with a twisted diene orientation.[5] The consequences of this arrangement are twofold. (1) Attack should be favored on the convex face of the system and (2) conjugation with the remote double bond should be diminished, thereby favoring 1,4- over 1,6-addition. Steric factors should further augment this preference.[6]

Scheme I[a,b]



[a] (a) $(CO_2H)_2$, H_2O, THF; (b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0° to 25 °C (69%); (c) *tert*-$BuMe_2SiCl$, DMF, imidazole (98%); (d) *i*-Bu_2AlH, Et_2O, −78 °C (97%); MnO_2, CH_2Cl_2 (87%); (e) Me_2AlCl, CH_2Cl_2, −78° to −23 °C (78%); (f) piperidine, C_6H_6, Δ; PhSeCl, THF, −100° to −78 °C; $NaIO_4$, MeOH, H_2O, 25 °C (84%): (g) $[CH_2{=}CH(CH_2)_3]_2CuLi$, Et_2O, THF, Me_2S, −78 °C; Me_3SiCl; H_2O, HCl (91%); (h) $(Me_3Si)_2NK$, THF; MeI, −78 °C (97%); (i) $[Me_2CHCH(Me)]_2BH$, THF, −10 °C; H_2O_2, NaOH (89%); (j) H_2CrO_4, acetone, 0 to 25 °C; CH_2N_2, Et_2O, 0 °C (88%); (k) HF, CH_3CN (95%); (l) $(C_5H_5NH)_2Cr_2O_7$, DMF, 0 to 25 °C (95%); (m) $(i\text{-}Bu)_3Al$, $(C_6H_{11})_2NH$, CH_3Ph, Δ (94%); (n) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 0 to 25 °C (90%). [b] TBS = *tert*-$BuMe_2Si$.

Implementation of the foregoing strategy was facilitated by our discovery that 2,8,10-undecatrienals such as IV, in the presence of mild Lewis acids, undergo exceptionally facile Diels–Alder cyclizations to give trans-fused octahydronaphthalenes with excellent endo selectivity. The final link in the approach was forged by dehydrogenation of the Diels–Alder cyclization product to dienal III via phenyselenation of the enamine derivative.[7] The synthetic

(1) Keller-Schierlein, P. W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127. Muntwyler, R.; Widmer, J.; Keller-Schierlein, W. *Ibid.* **1970**, *53*, 1544. Muntwyler, R.; Keller-Schierlein, W. *Ibid.* **1972**, *55*, 2017. Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Ibid.* **1972**, *55*, 2094.

(2) (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200–5211. (b) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611–4621. (c) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825–4829. (d) Takeda, K.; Shinagawa, M.; Koizuma, T.; Yoshii, E. *Chem. Pharm. Bull.* **1982**, *30*, 4000–4005. (e) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370–4374. (f) Boeckman, R. K.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3423–3425.

(3) Ireland, R. E.; Thompson, W. J.; Srouji, G. H; Etter, R. *J. Org. Chem.* **1981**, *46*, 4963–4873. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.

(4) (a) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5279–5280. (b) Marshall, J. A; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron*, in press.

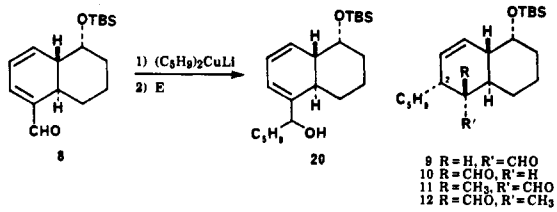
(5) Molecular modeling was carried out with the Still MODEL program on a VAX 11/780 computer. We are indebted to Dr. Lukasz Lebioda for providing the ORTEP program.

(6) For a comparison of 1,4 vs. 1,6-cuprate additions to conjugated dienones see: Marshall, J. A.; Ruden, R. A.; Hirsch, L. K.; Phillippe, M. *Tetrahedron* Lett. **1971**, 3795–3798.

(7) Williams, D. R.; Nishitani, K. *Tetrahedron Lett.* **1980**, *21*, 4417–4420.

0022-3263/86/1951-1730$01.50/0

Table I. 1,4-Additions of 4-Pentenylcuprates to Dienal 8



run	conditions	products, %[a] 8	20	9	10	11	12	other
1	2 RLi, CuI, Me_2S; 2:1 Et_2O–THF, 14 h; MeI	0	17	37	19	7	0	20
2	2 RLi, CuBr·Me_2S; 2:1 Et_2O–THF, 14 h; MeI	10	17	20	16	8	0	29
3	1.8 RLi, CuI, Me_2S; 1.6:1 Et_2O–THF, 14 h; MeI	0	0	30	22	33	0	12
4	1.8 RLi, CuI, Me_2S; 1.8:1 Et_2O–THF, 10 h; H_2O, H^+	0	0	65		–	–	35
5	1.6 RLi, CuI, Me_2S; 1.6:1 Et_2O–THF, 14 h; H_2O, H^+	92	0	0		–	–	8
6	1.8 RLi, CuI, Me_2S; 1.6:1 Et_2O–THF, 14 h; TMSCl; H_2O, H^+	0	0	91		–	–	9

[a] Analysis by glass capillary gas chromatography.

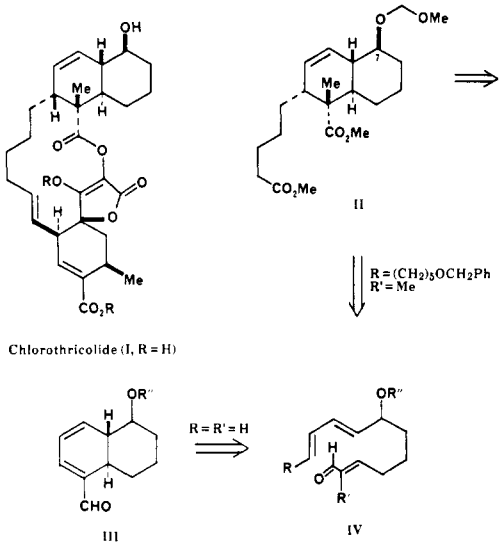


Figure 1. Synthetic analysis of a route to diester II, a degradation product of chlorothricolide.

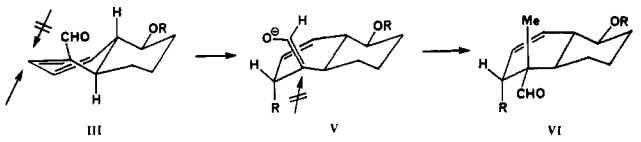


Figure 2. Stereochemical analysis of 1,4-addition–enolate alkylation of *trans*-4a,5,6,7,8,8a-hexahydronaphthalene-1-carboxaldehyde.

sequence is outlined in Scheme I.

Addition of 4,4-diethoxybutylmagnesium bromide[2a] to 2,4-pentadienal (1)[8] afforded the dienol **2**. Treatment with aqueous oxalic acid[2a] led to the cyclic hemiacetal (not pictured) which was directly treated with ethyl (triphenylphosphorylidene)acetate to give the trienyl ester **3** with complete trans stereoselectivity.[2a,4] Protection as the *tert*-butyldimethylsilyl ether **4** followed by reduction with DIBAH and oxidation with MnO_2 afforded trienal **6** in 78% overall yield. Diels–Alder cyclization at low temperature with catalytic Me_2AlCl gave the *anti,trans,syn*-octahydronaphthalene aldehyde **7** in 78% isolated yield. We have previously noted the strong axial preference of the OTBS grouping in similar Diels–Alder cyclizations.[4]

Dehydrogenation of aldehyde **7** was effected via in situ phenylselenation of the piperidine enamine (not shown) at low temperature[7] followed by immediate oxidation of the unstable α-seleno aldehyde with $NaIO_4$ at room temperature. Only the fully conjugated aldehyde **8** was obtained indicating a strong regiochemical preference in the selenoxide elimination step. Although the intermediate selenides were too unstable for accurate analysis, the ^1H NMR spectrum of the crude product indicated a mixture of stereoisomers was formed.[9] The observed regioselectivity must therefore reflect a preferred syn elimination of both selenoxide epimers toward the allylic position.

Attempted sequential addition of lithium bis(4-pentenyl)cuprate to dienal **8** followed by in situ methylation with methyl iodide led to mixtures of 1,2-adduct **20** and protonated 1,4-adducts **9** and **10** with only minor amounts of methylated product **11** (Table I, entries 1 and 2).[10] By using slightly less than a 2:1 ratio of 4-pentenyllithium to cuprous salt we were able to suppress 1,2-addition,[11] but the yield of methylated aldehyde **11** was still low (Table I, entry 3). Acidic quenching of the cuprate reaction was also not effective. Aldehydes **9** and **10** were obtained in only 65% yield (Table I, entry 4). With a lower ratio of alkenyllithium to cuprous salt (1.6:1), neither 1,2- nor 1,4-addition took place and starting dienal **8** was largely recovered (Table I, entry 5). The best conditions for 1,4-addition employed a 1.8:1 ratio of alkenyllithium to cuprous iodide in ether–THF[13] followed by addition of trimethylsilyl chloride (Me_3SiCl) to quench the intermediate enolate, thereby precluding subsequent reaction of the aldehyde product with excess organometallic reagents.[10] The intermediate Me_3Si enol ethers were directly hydrolyzed with mild acid (Table I, entry 6). In none of the foregoing reactions did we observe by products arising from 1,6-addition to dienal **8** within the limits of detection by high-field ^1H NMR and capillary gas chromatographic analysis. Furthermore, the C2 epimeric 1,4-adduct (cf. **9**, **10** with β-oriented C_5H_9) was likewise not detected.

(8) Woods, G. F.; Sanders, H. *J. Am. Chem. Soc.* **1946**, *68*, 2483–2485.

(9) The unstable α-phenylseleno aldehydes were isolated in 35–45% yield via chromatography on silica gel. Analysis by ^1H NMR indicated a roughly 2:1 mixture of epimers based on integration of the aldehyde signals at 9.6 and 9.4 ppm.

(10) For recent review of sequential 1,4-addition–enolate trapping of conjugated carbonyl compounds see: Taylor, R. J. K. *Synthesis*, **1985**, 364–392. Trimethylsilyl chloride has recently been found to dramaticaly accelerate 1,4-additions of organocuprates to conjugated aldehydes and ketones. Corey, E. J.; Boaz, N. W. *Tetrahedron* Lett. **1985**, *26*, 6015.

(11) The rationale is based on a presumed equilibrium between R_2CuLi and RCu + RLi.

(12) Cf. Chiut, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1981**, *37*, 1385. Clive, D. L. J.; Farina, V.; Beaulieu, P. L. *J. Org. Chem.* **1982**, *47*, 2572.

(13) Less polar solvents tend to favor 1,4-addition,[12] but, in the case at hand, the stereoselectivity was lower in ether than in THF.

Attempted methylation of aldehydes **9** and **10** with LDA as the base led to recovered starting material, even after prolonged reaction times and with added HMPA. With potassium hexamethyldisilazide (KHMDS), however, both deprotonation and alkylation were rapid and nearly quantitative. The derived aldehyde **11** was free of the isomer **12** according to high field ^1H NMR and capillary GC analysis. Hence the two-step conversion of dienal **8** to the methylated aldehyde **11** could be achieved cleanly and efficiently (88% overall yield). Interestingly, certain methyl ester analogues of aldehydes **9** and **10** were reportedly methylated with difficulty to a mixture of epimeric products.[14]

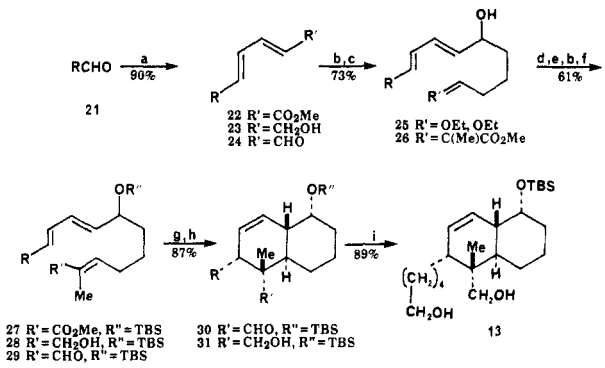
Elaboration of the pentenyl aldehyde **11** to hydroxy diester **16** proved straightforward. Thus, reduction–hydroboration with disiamylborane led to diol **13** which was oxidized to diacid **14** by Jones reagent.[15] Esterification with diazomethane gave the diester **15** which was smoothly desilylated with HF in acetonitrile to yield the hydroxy diester **16**.

At this point we note that owing to the high "axial" preference of the OTBS grouping in the Diels–Alder cyclization of trienal **6**[4] we must now invert the carbinyl center (C-7, chlorothricolide numbering) of hydroxy diester **16**. Ireland, et al.[3] alluded to "marginally successful" attempts at such an inversion in their synthetic homologue of diester **16**, but provided no details. Roush and Hall[2a] achieved partial success in a similar system (**16**, Me in place of $(CH_2)_4CO_2Me$) through oxidation to the ketone and reduction with $BH_3{\cdot}NH_3$ which led to a 2:1 mixture of the methyl counterparts of alcohols **18** and **16**. We explored the inversion of alcohol **16** via Mitsunobu DEAD chemistry[16] and nucleophilic displacement of the tosylate derivative, all to no avail.[17] In both cases, elimination to the conjugated diene resulted.[17] Such an elimination is of some interest in connection with possible approaches to the compactin family of natural products.[18]

Failing to find conditions for direct S_N2 inversion of alcohol **16** or its tosylate derivative, we turned to methodology based on ketone reduction. Here the procedure of Takegami[19] employing a complex of dicyclohexylamine and $(i\text{-}Bu)_3Al$ at elevated temperature worked admirably. A separable 9:1 mixture of alcohols **18** and **16** was obtained in 94% yield without contamination by double bond isomers. The derived methoxymethyl ether **19** was judged identical on the basis of infrared and ^1H NMR spectral comparison with those of the chlorothricin degradation product II kindly supplied by Professor Ireland.

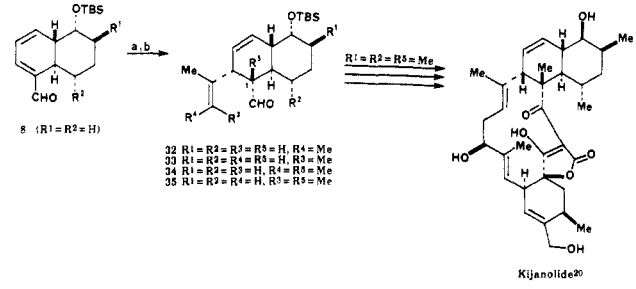
We recently described a synthesis of the side chain nor homologue of diester **15** [$(CH_2)_3CO_2Me$ in place of $(CH_2)_4CO_2Me$] via catalyzed Diels–Alder cyclization of the appropriate 2-methyl-11-alkyl-2,8,10-undecatrienal.[4b] As an additional structure confirmation and as a comparison of the complimentary strategies, the analogous sequence was adapted to diol **13** (Scheme II).[17] Thus addition of methyl γ-(diethylphosphono)crotonate to 6-benzyloxyhexanal (**21**) afforded the *trans,trans* dienoic ester **22** in high yield.[4] Reduction with DIBAH followed by Swern oxidation gave aldehyde **24**, which was treated with 4,4-diethoxybutylmagnesium bromide.[2a] The resulting δ-hydroxy acetal was hydrolyzed with aqueous oxalic acid to afford a δ-lactol whose direct treatment with methyl α-(triphenylphosphorylidene)acetate yielded the all-trans trienoate **26**. The *t*-$BuMe_2Si$-protected ester **27** was converted to the aldehyde **29** via sequential reduction and oxidation. Diels–Alder cyclization at −78° to −23 °C catalyzed by Et_2AlCl gave the bicyclic aldehyde **30** in 92% isolated yield. Reduction followed by debenzylation with sodium-in-ammonia afforded diol **13** in high overall yield. This material was identical with that prepared via Scheme I.

Scheme II[a,b,c]



[a] (a) $(EtO)_2POCH_2CH{=}CHCO_2Me$, LDA, THF, −45 °C (90%); (b) *i*-Bu_2AlH, hexane, −78 °C (97%): (c) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 °C; $BrMg(CH_2)_3CH(OEt)_2$, Et_2O (75%); (d) $(CO_2H)_2$, H_2O, THF, 0 to 25 °C; $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, 0 to 25 °C (80%); (e) *t*-$BuMe_2SiCl$, DMF, imidazole (97%); (f) MnO_2, CH_2Cl_2 (82%); (g) Et_2AlCl, CH_2Cl_2, −78 to 23 °C (92%); (h) *i*-Bu_2AlH, Et_2O, −78 °C (95%); (i) Na, NH_3, THF, −33 °C; NH_4Cl (89%). [b] R = $(CH_2)_5OCH_2Ph$, TBS = *t*-$BuMe_2Si$. [c] Experimental details for this Scheme may be found in the Ph.D. thesis of J. E. Audia.[17] The procedures employed are identical with those previously reported for an analogous sequence.[4]

Scheme III[a]



[a] (a) LiR_2Cu, Me_2S, THF, Et_2O, −78 °C, 10–14 h; Me_3SiCl, −78 to 25 °C; 10% HCl, 25 °C, 5 min; (b) $(TMS)_2NK$, THF, $PhCH_3$, 25 °C; CH_3I, −78 to 25 °C.

With the eventual aim of applying the sequential 1,4-addition–enolate methylation strategy to more complex aglycons such as kijanolide,[20] we briefly examined the reaction of dienal **8** with a prototype 2-butenylcuprate (Scheme III). The reagent derived from an 88:12 mixture of (*Z*)- and (*E*)-2-bromo-2-butene gave the 1,4-adducts **32**, **33** and their respective C1 epimers in 93% yield. Methylation afforded the aldehydes **34** and **35** nearly quantitatively. Interestingly, the ratio of **34** to **35** was found to be 35:65. Evidently, the (*E*)-2-butenyl moiety prefer-

(14) The ester analogue of aldehyde **10** with $(CH_2)_3O$*t*-$BuMe_2Si$ in place of C_5H_9 could not be deprotonated by LDA. Alkylation of the enolate derived from the epimeric ester related to aldehyde **9** led to a 56:13 mixture of β and α methylation products analogous to **11** and **12**.[2b]

(15) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem Soc.* **1946**, 39.

(16) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(17) For details of these studies see Audia, J. E. Ph.D. Dissertation, University, University of South Carolina, 1985.

(18) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.

(19) Suzuki, T.; Itoh, M.; Ogawa, S.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2664–2667.

(20) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; McFarlane, R. D; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 497–534. Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938–3940.

entially transfers to dienal 8 in the cuprate addition step, a consequence of its smaller steric requirements. Comparable steric fractionation should likewise be possible in projected applications of the methodology to kijanolide. Thus, the prospects for assembling such systems with complete steric control via the 1,4-addition–methylation sequence appear excellent.

Experimental Section

The apparatus and methods described by Kramer, Midland, and Levy[21] were used to maintain an argon or nitrogen atmosphere in the reaction flask. Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and dioxane), calcium hydride (hexamethylphosphoramide), phosphorus pentoxide (dichloromethane), or sodium (benzene and toluene). Infrared absorption maxima are reported in wavenumbers (cm^{-1}) and are standardized by reference to the 1601-cm^{-1} peak of polystyrene. Proton magnetic resonance spectra were recorded on Varian EM-390 and Bruker WH-400 spectrometers. Carbon-13 spectra were recorded at 20 MHz on an IBM NR-80 Fourier transform spectrometer. All samples were prepared as dilute solutions in deuteriochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane in parts per million of the applied field. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; envelope, e; multiplet, m. Coupling constants (J) are reported in hertz (Hz). Gas chromatography–mass spectral analysis (MS) was performed on a Finnigan 4021 instrument. Combustion microanalyses were performed by Atlantic Laboratories, Atlanta, GA. Analytical thin-layer chromatography was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F254 of 0.25-mm thickness, supplied by Brinkmann Instruments, were used. Column chromatography was performed by using E. Merck silica gel 60 (230–400 ASTM mesh) according to the procedure of Still, Kahn, and Mitra.[22]

(*E*)-5-Hydroxy-6,8-nonadienal Diethyl Acetal (2). To a stirred, cooled (0 °C) solution of (4,4-diethoxybutyl)magnesium bromide[2a] (65.7 mmol) in 248 mL of THF was added a solution of 4.6 g (56.7 mmol) of 2,4-pentadienal[8] in 20 mL of THF over a 15-min period. The mixture was stirred for 1 h, quenched with 1 mL of methanol, and poured through a plug of glass wool into saturated NH_4Cl solution. The mixture was extracted 3 times with Et_2O, and the combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4 and K_2CO_3. The solvent was removed under reduced pressure, and the residue was chromatographed on triethylamine-deactivated silica gel eluting with 1:2 Et_2O–hexane to afford 10.3 9.6, 14 (79%) of diethyl acetal **2** as a yellow oil: IR (film) ν 3375, 2950, 1380, 1130, 1065, 1010 cm^{-1}, ^1H NMR (400 MHz) δ 1.18 (6 H, t, J = 7 Hz, OCH_2CH_3), 3.46, 3.62 (4 H,m, OCH_2CH_3), 4.15 (1 H, m, H5), 4.45 (1 H, t, J = 6 Hz, H1), 5.07 (1 H, bd, J = 9.6 Hz, H9 cis), 5.18 (1 H, bd, J = 14 Hz, H9 trans), 5.68 (1 H, dd, J = 6.5, 14 Hz, H6), 6.20 (1 H, dd, J = 9.6, 14 Hz, H7), 6.3 (1 H, ddd, J = 9.6, 9.6, 14 Hz, H8). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.19; H, 10.64.

Ethyl (*E*,*E*)-7-Hydroxyundeca-2,8,10-trienoate (3). To a stirred solution of 70 mL of 5% aqueous oxalic acid in 70 mL of THF was added slowly a solution of 10.0 g (43.8 mmol) of diethyl acetal **2**. The solution was stirred for 12 h at room temperature under argon, then poured into 1:1 CH_2Cl_2–aqueous $NaHCO_3$ and the combined layers were extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and Na_2CO_3, filtered, and concentrated at reduced pressure to afford 6.58 g of crude lactol as a dark yellow oil which was used without further purification.

To a stirred solution of the foregoing lactol at 0 °C in 70 mL of dry CH_2Cl_2 was added 15.76 g (45.2 mmol) of ethyl α-(triphenylphosphorylidene)acetate in one portion. The mixture was allowed to warm to room temperature and stirred for an additional 20 h. Solvent was removed at reduced pressure and the resulting residue was chromatographed on silica gel deactivated with Et_3N. Elution with 15% EtOAc–hexane afforded 6.8 g (69%) of ester **3**. IR (film) ν 3400, 2925, 1720, 1650, 1370, 1275, 1200, 1010 cm^{-1}; ^1H NMR (400 MHz) δ 1.26 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 1.56 (4 H, m, H5 and H6), 2.21 (2 H, m, H4), 4.16 (2 H, q, J = 7.1 Hz, OCH_2CH_3 and 1 H, m, H7), 5.07 (1 H, d, J = 9.6 Hz, H11 cis), 5.18 (1 H, d, J = 15.6 Hz, H11 trans), 5.68 (1 H, dd, J = 7.1, 15.6 Hz, H8), 5.80 (1 H, dt, J = 1.6, 15.6 Hz, H9), 6.30 (1 H, ddd, J = 9.6, 9.6, 15.6 Hz, H10), 6.92 (1 H, dt, J = 7.1, 15.6 Hz, H3). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.46; H, 9.05.

Ethyl (*E*,*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]undeca-2,8,10-trienoate (4). To a stirred solution of 6.79 g (30.3 mmol) of alcohol **3** in 50 mL of DMF was added 6.37 g (93.5 mmol) of imidazole followed by 6.60 g (43.1 mmol) of *tert*-butyldimethylchlorosilane. The mixture was stirred for 36 h, poured into H_2O, and extracted with 1:1 Et_2O–hexane. The combined extracts were washed with saturated aqueous $CuSO_4$, and the combined aqueous layers were extracted twice with 1:1 Et_2O–hexane. The extracts were washed with H_2O and saturated brine, and dried over anhydrous Na_2SO_4 and Na_2CO_3. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel deactivated with Et_3N. Elution with 2.5% Et_2O–hexane afforded 10.10 g (98%) of silyl ether **4**. IR (film) ν 2925, 1720, 1630, 1470, 1260, 1010 cm–1; ^1H NMR (400 MHz) δ 0.01, 0.03 (6 H, 2 s, $Si(CH_3)_2$), 0.88 (9 H, $SiC(CH_3)_3$), 2.20 (2 H, dt, J = 6.8 Hz, H4), 4.16–4.10 (1 H, m, H7), 5.20–5.05 (2 H, m, H11), 5.62 (1 H, dd, J = 6.5, 15.2 Hz, H8), 5.80 (1 H, bd, J = 15.5 Hz, H2), 6.16–6.08 (1 H, m, H9), 6.35–6.25 (1 H, m, H10), 6.94 (1 H, dt, J = 15.5, 6.8 Hz, H3). Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.25. Found: C, 67.49; H, 10.24.

5α-[(*tert*-Butyldimethylsilyl)oxy]-4aβ,5,6,7,8,8aα-hexahydronaphthalene-1-carboxaldehyde (8). The procedure of Williams[7] was modified as follows. To a stirred solution of 1.38 g (4.7 mmol) of aldehyde **7** (prepared from trienoate **4** via reduction with DIBAH, oxidation with active MnO_2, and low-temperature cyclization with Me_2AlCl in CH_2Cl_2 as previously described[4b]) in 20 mL of dry benzene was added 0.70 mL (6.8 mmol) of freshly distilled piperidine. The solution was heated to reflux with azeotropic removal of H_2O for 14 h, cooled to 25 °C, and concentrated under reduced pressure. The crude enamine was dissolved in 20 mL of dry THF and cooled to –100 °C. A solution of 1.05 g (5.5 mmol) of benzeneselenyl chloride in 5 mL of dry THF was added over 5 min. The mixture was warmed to –78 °C and stirred for 10 min whereupon 2.0 mL of methanol, 1.28 g (6.0 mmol) of $NaIO_4$, and 2.0 mL of H_2O were sequentially added. After stirring at 25 °C for 14 h, the mixture was diluted with Et_2O and washed with saturated $Na_2S_2O_3$ solution, H_2O, and brine and then dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure, and the residue was chromatographed on silica gel eluting with 1% EtOAc in hexanes to afford 1.16 g (84%) of dienal **8** as a colorless oil. IR (film) ν 3020, 2935, 2920, 2840, 2680, 1675, 1555, 1460, 1260 cm^{-1}; ^1H NMR (400 MHz) δ 0.05 (6 H, s, $Si(CH_3)_2$), 0.86 (9 H, s, $SiC(CH_3)_3$), 2.20 (1 H, bd, J = 14 Hz, H8a), 2.95 (1 H, m, H4a), 4.17 (1 H, bd, J = 2.4 Hz, H5), 6.02 (1 H, bd, J = 9.4 Hz, H4), 6.13 (1 H, ddd, J = 3.0, 5.3, 9.4 Hz, H3), 6.66 (1 H, dd, J = 2.1, 5.3 Hz, H2). Anal. Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.92; H, 9.69.

2α-(4-Pentenyl)-5α-[(*tert*-butyldimethylsilyl)oxy]-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1-carboxaldehyde (9, 10). To a stirred, cooled (–45 °C) mixture of 571 mg (3.0 mmol) of CuI in 3.0 mL of dry THF and 3.0 mL of dry Me_2S was added 10.8 mL (5.4 mmol) of a 0.5 M solution of 1-lithio-4-pentene in Et_2O. The purple solution was stirred at –45 °C for 30 min and cooled to –78 °C whereupon a solution of 450 mg (1.54 mmol) of dienal **8** in 3.0 mL of dry THF precooled to –78 °C was transferred via cannula to the cuprate solution. The mixture was stirred at –78 °C for 14 h at which time 2.0 mL of chlorotrimethylsilane was added and the cooling bath was removed. After 2 h, 5 mL of 10% HCl was added and the mixture was stirred for 5 min, diluted with 25 mL of Et_2O, and washed with 10% NH_4OH solution. After back extraction of the aqueous phase with Et_2O, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 1% EtOAc in hexanes to afford 508 mg of a mixture of C1 epimers **9** and **10**; IR (film) ν 3000, 2910,

(21) Brown, H. C. "Organic Synthesis via Boranes"; Wiley: New York, 1975; pp 191–202.
(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

2840, 2690, 1725, 1640, 1465, 1445, 1260 cm^{-1}; ^1H NMR (400 MHz) δ 4.0 (1 H, bs, H5), 4.9–5.0 (2 H, m, vinyl Hs of C2 pentenyl), 5.44 (1 H, bd, J = 10.1 Hz, H4), 5.67 (1 H, ddd, J = 2.5, 4.8, 10.1 Hz, H3), 5.7–5.82 (1 H, m, vinyl H of C2 pentenyl), 9.40, 9.74 (1 H, 2d, J = 2.1, 3.3 Hz, CHO). Anal. Calcd for $C_{22}H_{38}O_2Si$: C, 72.87; H, 10.56. Found: C, 72.70; H, 10.63.

1β-Methyl-2a-(4-pentenyl)-5a-[(*tert*-butyldimethylsilyl)oxy]-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxaldehyde (11). To a stirred solution of 79 mg (0.22 mmol) of aldehydes **9** and **10** in 1.5 mL of dry THF was added 0.66 mL (0.44 mmol) of 0.67 M KHMDS in toluene. After stirring at 25 °C for 1 h, the yellow solution was cooled to −78 °C and was treated with 124 μL (2.0 mmol) of CH_3I. The mixture was allowed to warm to 25 °C over 2h, 5 mL of ether was added, and the solution was washed with saturated NH_4Cl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 1% EtOAc in hexanes to afford 80 mg (97%) of aldehyde **11** as the sole product; IR (film) ν 3000, 2910, 2830, 2680, 1720, 1635, 1460, 1370, 1260, cm^{-1}; ^1H NMR δ 0.0, 0.03 (6 H, 2 s, $Si(CH_3)_2$), 0.87 (9 H, s, $SiC(CH_3)_2$), 0.96 (3 H, s, C1 CH_3), 2.46 (1 H, dt, J = 2.6, 12.1 Hz, H8a), 4.05 (1 H, bs, H5), 4.88–4.98 (2 H, m, vinyl Hs of C2 pentenyl), 5.40 (1 H, bd, J = 10.4 Hz, H4), 5.66 (1 H, ddd, J = 2.6, 4.5, 10.4 Hz, H3), 5.68–5.74 (1 H, m, vinyl H of C-2 pentenyl), 9.66 (1 H, s, CHO); ^{13}C NMR ($CDCl_3$) (20 MHz) δ 209.5 (CHO), 138.5 (C4 of C2 pentenyl) 129.8, 128.5 (C3, 4), 114.6 (C5 of C2 pentenyl), 70.6 (C5), 49.9, 44.7, 44.0, 34.2, 34.0, 31.9, 31.4, 27.2, 26.9, 25.8 ($SiC(CH_3)_3$), 20.9, 18.1, 14.3, −4.4, −4.8 ($SiCH_3$); MS, base 319 (M-57, -*tert*-butyl). Anal. Calcd for $C_{23}H_{40}O_2Si$: C, 73.34; H, 10.70. Found: C, 73.00; H, 10.72.

[1β-Methyl-2α-(5-hydroxypentyl)-5α-[(*tert*-butyldimethylsilyl)oxy]-1,2,4aβ,5,6,7,8,8aα-octahydro-1α-naphthyl]methanol (13). To a stirred, cooled (−10 °C) solution of 79 μL (0.74 mmol) of 2-methyl-2-butene in 0.5 mL of THF was added 370 μL (0.37 mmol) of 1.0 M BH_3·THF in THF. The soultion was stirred at −10 °C for 3 h, then a solution of 56 mg (0.15 mmol) of aldehyde **11** in 0.5 mL of dry THF was added, and the mixture was warmed to 0 °C and stirred for 1 h. Several drops of H_2O were cautiously added followed by 130 μL (0.39 mmol) of 3 M NaOH and 130 μL (0.39 mmol) of 30% H_2O_2. After 15 min at room temperature the mixture was diluted with Et_2O, washed with H_2O and brine, and dried over $MgSO_4$. Removal of solvent at reduced pressure and chromatography afforded 42 mg of diol **13** as a colorless oil which crystallized upon standing; IR (film) ν 3340, 3000, 2930, 2845, 1460, 1375, 1260 cm^{-1}; ^1H NMR (400 MHz) δ 0.02, 0.01 (6 H, 2 s, $Si(CH_3)_2$), 0.86 (9 H, s, $SiC(CH_3)_3$), 0.87 (3 H, s, CH_3), 3.53 (2 H, ABq, J_{AB} = 10.7, $\Delta\nu_{AB}$ = 16.4 Hz, C1 CH_2OH), 3.63 (2 H, t, J = 6.6 Hz, side chain CH_2OH), 4.01 (1 H, m, H5), 5.34 (1 H, bd, J = 10.2 Hz, H4), 5.73 (1 H, ddd, J = 2.6, 5.3, 10.2 Hz, H3); ^{13}C NMR ($CDCl_3$) δ 130.1, 129.6 (C3, C4), 70.6, 68.5, 63.0 (C4, CH_2OH), 44.5, 42.4, 38.4, 33.9, 33.0, 32.8, 31.5, 27.2, 26.1, 25.8, 25.3, 20.8, 16.8, −4.4, −4.8. Anal. Calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18. Found: C, 69.50; H, 11.26.

Methyl 1β-Methyl-2α-[4-(carbomethoxy)butyl]-5α-[(*tert*-butyldimethylsilyl)oxy]-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxylate (15). To a stirred, cooled (0 °C) solution of 1.6 g (4.0 mmol) of diol **13** in 50 mL of acetone was added 6 mL (16.0 mmol) of Jones reagent[15] over 20 min. The mixture was warmed slowly to 25 °C, stirred for 3 h, diluted with brine, and extracted 3 times with Et_2O. The combined organic layers were washed with dilute HCl and brine and concentrated under reduced pressure. The crude diacid **14** was taken up in 20 mL of Et_2O, cooled to 0 °C, and treated with ethereal CH_2N_2 prepared at 0 °C by adding 4.60 g (46 mmol) of *N*-methyl-*N*-nitrosourea to a two-phase mixture of 10 mL of 50% aqueous KOH in 50 mL of Et_2O.[23] After 30 min the excess CH_2N_2 was quenched with HOAc and the mixture was washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The crude diester was purified by chromatography on silica gel eluting with 10% EtOAc in hexanes to afford 1.61 g (83%) of diester **15** as a colorless oil; IR (film) ν 3000, 2920, 2840, 1730, 1725, 1465, 1440, 1380, 1250 cm^{-1}; ^1H NMR (400 MHz) δ 0.01, 0.03 (6 H, 2 s, $Si(CH_3)_2$), 0.84 (9H, s, $SiC(CH_3)_3$), 1.10 (3 H, s, CH_3), 2.17–2.34 3 H, m, H8a, CH_2CO_2Me), 3.63, 3.64 (6 H, 2 s, OCH_3), 4.02 (1 H, bd, J = 2.2 Hz, H5), 5.33 (1 H, bd, J = 10.2 Hz, H4), 5.62 (1 H, ddd, J = 2.7, 5.1, 10.2 Hz, H3); ^{13}C NMR ($CDCl_3$) (20 MHz) δ 176.6, 174.0, 129.6, 128.2, 70.8, 51.3, 51.0, 48.2, 44.9, 44.7, 34.4, 34.0, 33.2, 28.0, 26.8, 25.8, 25.1, 21.2, 18.1, 17.3, −4.4, −4.8. Anal. Calcd for $C_{25}H_{44}O_5Si$: C, 66.33; H, 9.80. Found: C, 66.51; H,9.74.

Methyl 1β-Methyl-2α-[4-(carbomethoxy)butyl]-5α-hydroxy-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxylate (16). To a stirred solution of 220 mg (0.49 mmol) of silyl ether **15** in 5 mL of CH_3CN was added 1 drop of 48% HF. The solution was stirred at 25 °C for 18 h, diluted with Et_2O, and washed with saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the solution was concentrated and the residue was chromatographed on triethylamine-deactivated silica gel, eluting with 25% EtOAc in hexanes affording 150 mg (95%) of alcohol **16** as a colorless oil; IR (film) ν 3500, 3000, 2925, 2850, 1730, 1725, 1465, 1440, 1380, 1260 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (3 H, s, CH_3), 2.26 (2 H, t, J = 7 Hz, CH_2CO_2Me), 3.63, 3.64 (6 H, 2 s, OCH_3), 4.08 (1 H, m, H5), 5.44 (1 H, bd, J = 10.1 Hz, H4), 5.79 (1 H, ddd, J = 2.7, 5.0, 10.1 Hz, H 3). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C,67.24; H, 8.96.

Methyl 1β-Methyl-2α-[4-(carbomethoxy)butyl]-5-oxo-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxylate (17). To a stirred, cooled (0 °C) solution of 345 mg (1.02 mmol) of alcohol **16** in 5 mL of dry DMF was added 614 mg (1.63 mmol) of pyridinium dichromate in five portions over 0.5h.[24] The mixture was warmed to 25 °C, stirred for 14 h, and poured into H_2O. Extraction with three 25-mL portions of Et_2O, combination of the organic phases, drying over $MgSO_4$, and removal of solvent under reduced pressure afforded 520 mg (>100%) of a brown oil which, upon chromatography on silica gel eluting with 10% EtOAc in hexanes, afforded 328 mg (95%) of β,γ-unsaturated ketone **17** as a colorless oil; IR (film) ν 3000, 2925, 2840, 1720, 1460, 1430, 1380 cm^{-1}; ^1H NMR (400 MHz) δ 1.22 (3 H, s, CH_3), 2.26 (2 H, m, CH_2CO_2Me), 2.30–2.45 (2 H, m, H6), 2.76 (1 H, bd, J = 12.3 Hz, H4a), 3.64, 3.67 (6 H, 2 s, OCH_3), 5.78 (1 H, ddd, J = 2.5, 4.9, 10.2 Hz, H3), 5.90 (1 H, d, J = 10.2 Hz, H4); ^{13}C NMR (20 MHz) δ 210.2, 175.6, 173.9, 129.5, 121.7, 51.36, 50.9, 44.4, 41.3, 40.3, 33.1, 27.2, 26.7, 25.9, 25.0, 17.0. Anal. Calcd for $C_{19}H_{28}O_5$: C,67.83; H, 8.39. Found: C, 67.67; 8.44.

Methyl 1β-Methyl-2α-[4-(carbomethoxy)butyl]-5β-hydroxy-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxylate (18). The method of Takegami[19] was followed. To a stirred, cooled (0 °C) solution of 144 μL (0.72 mmol) of dicyclohexylamine in 7 mL of dry toluene was added 720 μL (0.72 mmol) of a 1.0 M solution of *i*-Bu_3Al in toluene. After the mixture had been stirred at 0 °C for 3 h, 240 mg (0.71 mmol) of ketone **17** in 2 mL of dry toluene was added. The solution was heated to 60 °C for 14 h, cooled to 0 °C, and hydrolyzed by cautious addition of 1 mL of H_2O. After dilution with Et_2O the mixture was washed with saturated Rochelle's salt solution and dried over $MgSO_4$. Removal of solvent under reduced pressure and rapid chromatography on triethylamine-deactivated silica gel afforded 228 mg (94%) of a 9:1 mixture of alcohols **18** and **16**. Careful chromatography on silica gel eluting with 5% EtOAc in hexanes afforded 196 mg (87%) of alcohol **18** and 20 mg (8%) of alcohol **16**; IR (film) ν 3420, 3020, 2925, 2850, 1735, 1720, 1460, 1440, 1380 cm^{-1}; ^1H NMR (400 MHz) δ 1.14 (3 H, s, CH_3), 2.26 (2 H, t, J = 7 Hz, $CH_2CO_2Me_3$), 3.34 (1 H, m, H5), 3.64 (6 H, s, OCH_3), 5.71 (1 H, ddd, J = 2.0, 5.1, 10.3 Hz, H3), 5.94 (1 H, d, J = 10.3 Hz, H4). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.24; H, 8.96.

Methyl 1β-Methyl-2α-[4-(carbomethoxy)butyl]-5β-(methoxymethyl)-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxylate (19). To a stirred, cooled (0 °C) solution of 114 mg (0.34 mmol) of alcohol **18** in 5 mL of CH_2Cl_2 was added 76 μL (1.0 mmol) of distilled chloromethyl methyl ether followed by 1.74 mL (10.0 mmol) of *i*-$PrNEt_2$. The mixture was warmed to 25 °C, stirred for 10 h, and diluted with 25 mL of Et_2O. After washing with H_2O, saturated $CuSO_4$ solution, H_2O, and brine, the organic layer was dried over $MgSO_4$ and concentrated under reduced

(23) Arndt, *Organic Syntheses*, Wiley: New York, 1943; Collect. Vol. 2, pp 165–167.

(24) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

pressure. Chromatography on silica gel eluting with 12% EtOAc in hexanes afforded 119 mg (90%) of methoxymethyl ether **19a**, a colorless oil. The ^1H NMR and infrared spectra of this material were identical with those of an authentic sample provided by Professor Ireland.[3]

1β-Methyl-2α-[(*E*)- and -(*Z*)-2-butenyl]-5α-[(*tert*-butyldimethylsilyl)oxy]-1,2,4aβ,5,6,7,8,8aα-octahydronaphthalene-1α-carboxaldehydes (34 and 35). To a stirred, cooled (−45 °C) solution of 191 mg (1.0 mmol) of CuI in 2 mL of dry THF and 1 mL of dry Me_2S was added 3.6 mL (1.80 mmol) of a 0.5 M solution of a 12:88 mixture of (*E*) and (*Z*)-2-butenyllithium in Et_2O. The mixture was stirred at −45 °C for 30 min and cooled to −78 °C whereupon 146 mg (0.5 mmol) of dienal **8** in 1 mL of dry THF was added. The mixture was stirred at −78 °C for 14 h, 1.0 mL (7.9 mmol) of Me_3SiCl was added and the reaction mixture was allowed to warm to 23 °C over 2 h. The mixture of silyl enol ethers was hydrolyzed at 23 °C by stirring for 10 min with 10 mL of 10% aqueous HCl. The mixture was diluted with Et_2O and washed with 10% NH_4OH, H_2O, and brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and chromatography on silica gel eluting with 5% EtOAc in hexanes afforded 162 mg (93%) of a mixture of four aldehydes (**32**/**33** and their C1 epimers); IR (film) ν 3000, 2940, 2900, 2690, 1720, 1460, 1440, 1375, 1255 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_2Si$: C, 72.36; H, 10.41. Found: C, 72.14; H, 10.48.

To a stirred solution of 50 mg (0.14 mmol) of the aldehyde mixture in 3 mL of dry THF at 23 °C was added 250 μL (0.16 mmol) of 1.64 M potassium hexamethyldisilazide in toluene. After stirring at 23 °C for 1 h, the solution was cooled to −78 °C and treated with 62 μL (1.0 mmol) of methyl iodide. The mixture was allowed to warm to 23 °C over 3 h, diluted with 15 mL of Et_2O, washed with saturated aqueous NH_4Cl, H_2O, and brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and chromatography on silica gel eluting with 1% EtOAc in hexanes afforded 18 mg (35%) of aldehyde **34** and 32 mg (63%) of aldehyde **35** as colorless oils.

34: IR (film) ν 3010, 2920, 2845, 2700, 1720, 1460, 1380, 1260 cm^{-1}; ^1H NMR (400 MHz) δ 1.01 (s, 3 H, C-1 CH_3), 1.45 (3H, dd, J = 1.5, 8.4 Hz, vinyl CH_3), 1.78 (3 H, bs, vinyl CH_3), 3.02 (1 H, m, H2), 4.11 (1 H, bs, H5), 5.35 (2 H, m, H3, butenyl H), 5.61 (1 H, bd, J = 10.0 Hz, H4), 9.34 (1 H, s, CHO). Anal. Calcd for $C_{22}H_{38}O_2Si$: C, 72.87; H, 10.56. Found: C, 72.60; H, 10.63.

35: IR (film) ν 3010, 2915, 2845, 2720, 1720, 1470, 1450, 1380, 1265 cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (3 H, s, C1 CH_3), 1.57 (6 H, m, vinyl CH_3's), 3.30 (1 H, m, H_2), 4.07 (1 H, bs, H5), 5.70–5.40 (3 H, m, vinyl H's), 10.0 (1 H, s, CHO). Anal. Calcd for $C_{22}H_{38}O_2Si$: C, 72.87; H, 10.56. Found: C, 72.72; H, 10.60.

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Registry No. (±)-**2**, 101492-67-5; **2** (lactol), 101492-68-6; (±)-**3**, 101492-69-7; (±)-**4**, 101492-70-0; (±)-**5**, 101492-71-1; (±)-**6**, 101492-72-2; (±)-**7**, 101492-73-3; (±)-**7** (piperidine enamine), 101492-74-4; (±)-**7** (phenylseleno deriv.) (isomer 1), 101492-75-5; (±)-**7** (phenylseleno deriv.) (isomer 2), 101627-02-5; (±)-**8**, 101492-76-6; (±)-**9**, 101492-77-7; (±)-**10**, 101627-03-6; (±)-**11**, 101492-78-8; (±)-**13**, 101492-79-9; (±)-**14**, 101492-80-2; (±)-**15**, 101492-81-3; (±)-**16**, 101492-82-4; (±)-**17**, 101492-83-5; (±)-**18**, 101492-84-6; (±)-**19**, 101627-04-7; **21**, 101492-91-5; **22**, 101492-92-6; **23**, 101492-93-7; **24**, 101492-94-8; (±)-**25**, 101492-95-9; **25** (lactol), 101492-96-0; (±)-**26**, 101492-97-1; (±)-**27**, 101492-98-2; (±)-**28**, 101492-99-3; (±)-**29**, 101493-00-9; (±)-**30**, 101493-01-0; (±)-**31**, 101493-02-1; (±)-**32** (isomer 1), 101492-85-7; (±)-**32** (isomer 2), 101492-87-9; (±)-**33** (isomer 1), 101492-86-8; (±)-**33** (isomer 2), 101492-88-0; (±)-**34**, 101492-89-1; (±)-**35**, 101492-90-4; $Ph_3PCHCOOEt$; 4-bromo-1,1-diethoxybutane, 78668-96-9; 2,4-pentadienal, 764-40-9; 1-lithio-4-pentene, 54313-25-6; methyl 4-(diethylphosphono)crotonate, 67629-62-3; chlorothricin, 34707-92-1.

Condensation of Long-Chain α-Phosphono Carboxylates with Aldehydes

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The condensation of several long-chain α-phosphono carboxylates with propanal was examined as a prototype route to trans and cis α-substituted conjugated esters. With the diisopropylphosphono and the dimethylphosphono bis-homogeranic esters A6 and A7, the trans product predominated by ca. 9:1. A similar trend was observed with the diisopropyl and dimethyl α-phosphono-ω-undecylenates B3 and B4. The bis(trifluoroethyl) α-phosphono-ω-undecylenate B5 afforded the cis product B11 as the major isomer with 8:1 stereoselectivity. Condensations of the α-(triphenylphosphorylidene)-ω-dodecenylate C3 with several representative aldehydes gave only trans products within the limits of detection. Thus, α-phosphorylidene esters show uniformly high trans stereoselectivity regardless of α-alkyl substitution. The phosphonates, on the other hand, show markedly diminished stereoselectivity when long-chain α-substituents are present.

Pursuant to synthetic investigations on cembranoid natural products we required both trans and cis conjugated esters such as A8 and A10 with long-chain functionalized α-substituents.[1] A simple route to both intermediates seemed possible on the basis of Nagaoka and Kishi's findings that Horner–Wadsworth–Emmons condensation of α-phenyl propionaldehyde with ethyl α-(diisopropylphosphono)propionate leads mainly to the trans conjugated ester whereas methyl or ethyl α-(dimethylphosphono)propionate afford primarily the cis isomers.[2] Ratios of 9:1 or better were reported with KO-*t*-Bu as the base in THF at −78 °C.

The requisite phosphonates A6 and A7 for our intended application were easily prepared starting with alcohol A1.[3] Oxidation with MnO_2 afforded aldehyde A2 whose homologation to alcohol A4 was effected via Wittig condensation and hydroboration–oxidation. Alkylation of sodio

(1) Marshall, J. A.; Cleary, D. G. *J. Org. Chem.*, in press. Cleary, D. G. *The Synthesis of 7(8)-Desoxyasperdiol and Related Studies*, PhD. Thesis, University of South Carolina, August 1985, pp 62–84. For a review of cembranolide natural products, see: Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 286.

(2) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(3) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.

0022-3263/86/1951-1735$01.50/0