2,2-Bis(4-acetylphenyl)-2′-acetonaphthone (5b): purification by PTLC; mp 139–141 °C (methylene chloride/*n*-hexane); NMR δ 2.58 (s, 6 H), 6.31 (s, 1 H), 7.43 (d, 4 H), 7.51–7.66 (m, 2 H), 7.83–8.05 (m, 8 H), 8.50 (s, 1 H); MS, *m/e* 406 (M^+), 208, 165, 155, 127.

4-Isopropoxy-6,7-dimethoxy-2,2′-binaphthalene (3c): irradiation time, 105 min; purification by repeated crystallization from methylene chloride/methanol; mp 154–155.5 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 4.00 (s, 3 H), 4.04 (s, 3 H), 4.95 (sept, 1 H), 7.22 (d, 1 H), 7.27 (s, 1 H), 7.54–7.62 (m, 2 H), 7.63 (s, 1 H), 7.70 (s, 1 H), 7.93–8.07 (m, 4 H), 8.21 (s, 1 H); MS, *m/e* 372 (M^+), 330. Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.65; H, 6.45. Found: C, 80.56; H, 6.67.

4-Isopropoxy-6,7,8-trimethoxy-2,2′-binaphthalene (3d): irradiation time, 120 min; purification by repeated recrystallization from methylene chloride/methanol; mp 97–99 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 3 H), 4.93 (sept, 1 H), 7.25 (d, 1 H), 7.47 (s, 1 H), 7.51–7.63 (m, 2 H), 7.91–8.04 (m, 5 H), 8.21 (s, 1 H); MS, *m/e* 402 (M^+), 360, 345. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.61; H, 6.47. Found: C, 77.56; H, 6.48.

4-Isopropoxy-6′-methoxy-2,2′-binaphthalene (3e): irradiation time, 75 min; purification by PTLC mp 143.5–144.5 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 3.98 (s, 1 H), 4.94 (sept, 1 H), 7.25–7.37 (m, 3 H), 7.48–7.65 (m, 2 H), 7.79 (s, 1 H), 7.89–8.01 (m, 4 H), 8.16 (s, 1 H), 8.41 (dd, 1 H); MS, *m/e* 342 (M^+), 300. Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.21; H, 6.43. Found: C, 84.11; H, 6.44.

1,4′-Diisopropoxy-2,2′-binaphthalene (3f): irradiation time, 120 min; purification by PTLC; mp 31–35 °C; NMR δ 1.06 (d, 6 H), 1.50 (d, 6 H), 4.09 (sept, 1 H), 4.89 (sept, 1 H), 7.36 (s, 1 H), 7.51–7.78 (m, 7 H), 7.92 (dd, 2 H), 8.40 (dd, 2 H); MS, *m/e* 370 (M^+), 328, 286. Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.32; H, 7.03. Found: C, 84.08; H, 7.12.

4-Isopropoxy-6,6′,7-trimethoxy-2,2′-binaphthalene (3g): irradiation time, 75 min; purification by repeated recrystallization from methylene chloride/methanol; mp 158–158.5 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 3.99 (s, 3 H), 4.06 (s, 3 H), 4.08 (s, 3 H), 4.92 (sept, 1 H), 7.19 (s, 1 H), 7.21–7.30 (m, 3 H), 7.63 (s, 1 H), 7.66 (s, 1 H), 7.85–7.97 (m, 3 H), 8.12 (s, 1 H); MS, *m/e* 402 (M^+), 360. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.61; H, 6.47. Found: C, 77.42; H, 6.68.

4-Isopropoxy-6,6′,7,8-tetramethoxy-2,2′-binaphthalene (3h): irradiation time, 100 min; purification by repeated recrystallization from methylene chloride/methanol; mp 149–150 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 3.97 (s, 3 H), 4.03 (s, 3 H), 4.07 (s, 3 H), 4.13 (s, 3 H), 4.90 (sept, 1 H), 7.19–7.28 (m, 3 H), 7.45 (s, 1 H), 7.85–7.93 (m, 3 H), 8.00 (s, 1 H), 8.14 (s, 1 H); MS, *m/e* 432 (M^+), 390, 375. Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.00; H, 6.48. Found: C, 74.78; H, 6.58.

1′,4-Diisopropoxy-6,7-dimethoxy-2,2′-binaphthalene (3i): irradiation time, 45 min; purification by PTLC; mp 71–73 °C (methanol/water); NMR δ 1.06 (d, 6 H), 1.49 (d, 6 H), 4.04 (s, 3 H), 4.08 (s, 3 H), 4.09 (sept, 1 H), 4.88 (sept, 1 H), 7.22 (s, 1 H), 7.27 (s, 1 H), 7.53–7.77 (m, 6 H), 7.92 (dd, 1 H), 8.40 (dd, 1 H); MS, *m/e* 430 (M^+), 388, 346, 345. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.14; H, 6.98. Found: C, 77.98; H, 6.85.

1′,4-Diisopropoxy-6,7,8-trimethoxy-2,2′-binaphthalene (3j): irradiation time, 75 min; purification by PTLC; mp 51–53 °C (methanol/water); NMR δ 1.08 (d, 6 H), 1.50 (d, 6 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 4.08 (sept, 1 H), 4.11 (s, 3 H), 4.88 (sept, 1 H), 7.35 (d, 1 H), 7.48 (s, 1 H), 7.53–7.78 (m, 4 H), 7.90–7.95 (m, 2 H), 8.40 (dd, 1 H); MS, *m/e* 460 (M^+), 418, 376, 375, 344. Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.65; H, 6.96. Found: C, 75.90; H, 7.11.

Registry No. **1a**, 93-08-3; **1b**, 3900-45-6; **1c**, 109124-52-9; **2a**, 2142-69-0; **2b**, 50777-64-5; **2d**, 99-90-1; **2e**, 591-50-4; **2f**, 74746-10-4; **2g**, 73252-59-2; **3a**, 109124-60-9; **3b**, 109124-61-0; **3c**, 109124-53-0; **3d**, 109124-54-1; **3e**, 109150-64-3; **3f**, 109124-55-2; **3g**, 109124-56-3; **3h**, 109124-57-4; **3i**, 109124-58-5; **3j**, 109124-59-6; **4b**, 1762-15-8; **5a**, 109124-62-1; **5b**, 109124-63-2; 1′-hydroxy-2′-acetonaphthone, 711-79-5; 2-bromo-4,5-dimethoxybenzaldehyde, 5392-10-9; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 2-bromo-3,4,5-trimethoxybenzaldehyde, 35274-53-4.

Stereoselective Total Synthesis of (±)-Aristolactone and (±)-Epiaristolactone via [2,3] Wittig Ring Contraction

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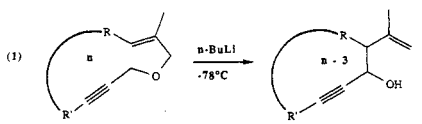
Received March 12, 1987

The germacranolide bridged lactone aristolactone (**16**) has been synthesized starting from geranyl acetate. Homologation of the derived chloride **5** via coupling with [(triisopropylsilyl)propargyl]magnesium bromide followed by deprotection, metalation, and addition of formaldehyde gave the chloro alcohol **9**. This was smoothly cyclized by treatment with ethylmagnesium bromide in THF–HMPA. The resulting 13-membered allylic propargylic ether **10** underwent facile [2,3] Wittig rearrangement to the cyclodecenyne **11** with trans-related vicinal OH and isopropenyl groupings. Mitsunobu inversion of this propargylic alcohol with benzoic acid followed by ester cleavage yielded the cis isomer **13**. Hydroalanation of the alkyne with Red-Al and trapping of the resulting alanate with *N*-iodosuccinimide afforded the unstable vinyl iodide **14**. Carbonylation over $Pd(Ph_3P)_4$ gave (±)-aristolactone. A more direct route to the cis alcohol **13** via [2,3] Wittig rearrangement of the macrocyclic *Z*-allylic propargylic ether **33** was also effected.

Pursuant to studies on the synthesis of medium-ring and macrocyclic natural products we developed a novel variant of the [2,3] Wittig rearrangement whereby cyclic allylic propargylic ethers were found to undergo a remarkably facile ring contraction to cycloalkynols.[1,2] In our initial application of this methodology to cembranoid natural products (n = 17), we were able to control the stereoselectivity of the rearrangement by changing the solvent from hexane–THF (trans product) to THF–HMPA (cis product).[1a,3] The cycloalkynol products proved well suited to



(1) Preliminary reports: (a) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316. (b) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *Tetrahedron Lett.* **1987**, *28*, 723.

(2) Takehashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

(3) Abbreviations: DEAD = diethyl azodicarboxylate; DIBAH = diisobutylaluminum hydride; DMAP = 4-(dimethylamino)pyridine; HMPA = hexamethylphosphoric triamide; KHMDS = potassium hexamethyldisilazide, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride; TBAF = tetra-*n*-butylammonium fluoride; TBHP = *tert*-butyl hydroperoxide; THF = tetrahydrofuran; TIPS = triisopropylsilyl; TLC = thin layer chromatography.

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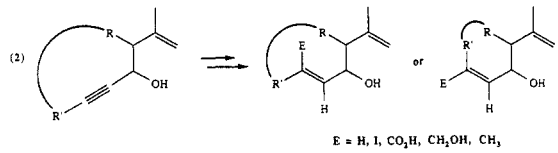
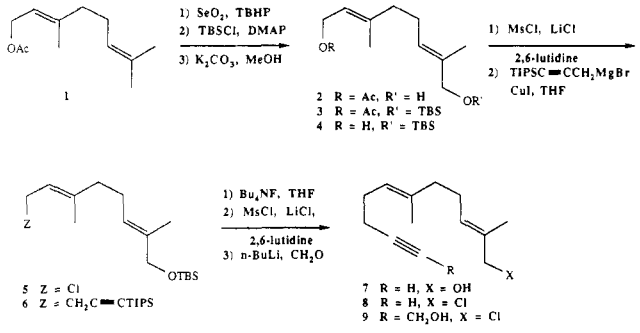
further synthetic elaboration through directed hydrometalation and subsequent electrophilic substitution.

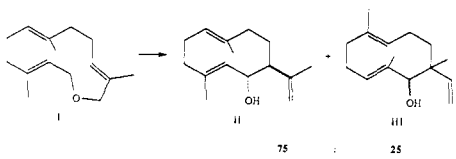


In parallel studies, we examined potential applications of the ring contraction methodology to medium-ring (germacranolide) natural products.[4] These have shown even higher selectivity than the larger ring systems. In this report we describe the first total synthesis of the interesting bridged germacranolide aristolactone (**16**)[5a] and its epimer **19** by a direct and completely stereoselective route that features stereochemically complimentary [2,3] Wittig ring contractions of the isomeric 13-membered allylic propargylic ethers **10** and **33**.[5b]

Geranyl acetate (**1**) served as the starting material for this work. Selective allylic oxidation with SeO_2–TBHP[3] followed by silylation and acetate cleavage yielded the alcohol **4**.[6] The derived allylic chloride **5**[7] underwent smooth coupling with TIPS[3]-protected propargylmagnesium bromide[8]–CuI in THF at −20 °C, giving the dienyne **6** in high yield. The silyl protecting groups were cleaved with TBAF[3] and the alcohol **7** converted to the allylic chloride **8**.[7] Addition of formaldehyde to the lithio acetylide derivative led to the cyclization precursor, chloro alcohol **9**.



(4) (a) For a recent review, see: Fischer, N. H.; Oliver, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47. (b) For representative synthetic work leading to germacranolides, see: Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736. Wender, P. A.; Lechleiter, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 267. Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717. Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984. Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373. Lange, G. L.; So, S.; Lautens, M.; Lohr, K. *Tetrahedron Lett.* **1981**, *22*, 311. Gopalan, A.; Magnus, P. *J. Org. Chem.* **1984**, *49*, 2317. (c) A related route involving [2,3] Wittig rearrangement of 13-membered diallylic ethers has been reported. The rearrangement proceeds in high yield with excellent stereoselectivity, but a 75:25 mixture of regioisomers is produced (i → ii + iii).[2] We thank Professor Takehashi for a preprint of this work.



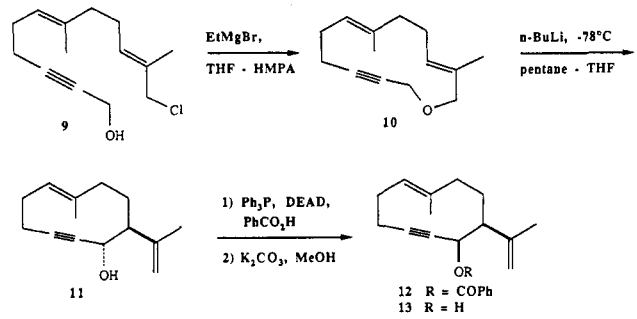
(5) (a) Lange, G. L.; Galatsis, P. *J. Org. Chem.* **1984**, *49*, 178. (b) All substances described in the present manuscript are racemic. A single enantiomer has been arbitrarily selected to depict relative configuration. The absolute configuration of natural aristolactone has not been determined.

(6) Umbreit, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. Marshall, J. A.; Andrews, R. C. *J. Org. Chem.* **1985**, *50*, 1602.

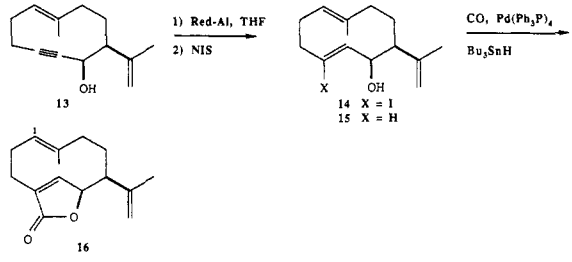
(7) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(8) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719.

Cyclization was effected by treatment of chloro alcohol **9** with EtMgBr at 0 °C followed by heating to reflux in THF–HMPA[3] at moderate dilution (0.02 M), affording the 13-membered ether **10** in 70% yield. Treatment of ether **10** with *n*-BuLi in 9:1 pentane–THF at −78 °C for 2.5 h resulted in facile [2,3] Wittig rearrangement giving the *trans*-isopropenylcyclodecynol **11** in 92% yield. The use of THF–HMPA[3] as solvent for the rearrangement caused decomposition of ether **10**. None of the cis product **13** could be detected in contrast to our previous findings with a homologous 17-membered allylic propargylic ether.[1] Fortunately, we were able to prepare the cis alcohol **13** in over 90% yield via Mitsunobu inversion[9] of the trans alcohol **11** with benzoic acid and cleavage of the inverted benzoate **12**.



Hydroalanation of the propargylic alcohol **13** with Red-Al[3] in THF[10] followed by addition of *N*-iodosuccinimide[11] afforded the unstable vinyl iodide **14** accompanied by varying amounts of the protonolysis product **15**. This mixture was subjected without purification to carbonylation with CO–$(Ph_3P)_4Pd$–*n*-Bu_3SnH in toluene[12] whereupon crystalline (±)-aristolactone (**16**), mp 87–88 °C, was secured in 18% yield for the three steps. The identity



of this material with natural aristolactone was confirmed through direct comparison of spectral properties and TLC behavior.[5b,13] When the foregoing hydroalanation of propargylic alcohol **13** was followed by an aqueous quench, the allylic alcohol **15** was obtained in 84% yield. We believe that the low yield of the three-step hydroalanation–iodination–carbonylation sequence results from the instability of vinyl iodide **14**. This intermediate did not survive column chromatography and decomposed upon solvent removal on a rotary evaporator.

Performing the analogous sequence on the trans propargylic alcohol **11**, we obtained in 30% overall yield crystalline butenolide **19** ("epiaristolactone"), mp 61–62

(9) Mitsunobu, O. *Synthesis* **1981**, 1.

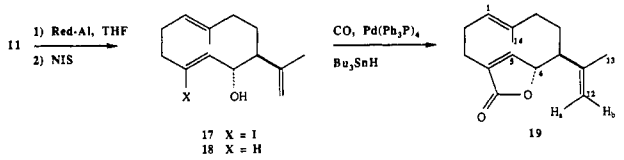
(10) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(11) The use of I_2 in this step led to additional byproducts, presumably arising from attack on the isolated double bond. We are indebted to Barry Shearer for experimental details of the NIS procedure.

(12) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

(13) A sample of natural aristolactone and copies of spectra were kindly provided by Professor G. L. Lange, Guelph, Ontario.

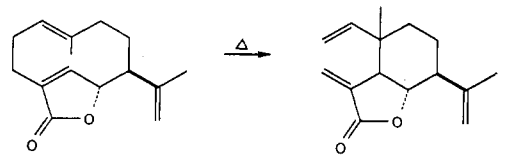
°C, clearly different from aristolactone in its physical properties. Although sharply melting and homogeneous by TLC[3] analysis, lactone **19** showed two sets of signals in the ^{1}H NMR spectrum. The composition was estimated as 70:30 by integration of the butenolide vinyl-H signals at 6.82 and 6.76 ppm. Aristolactone, on the other hand, displayed a single set of signals in its ^{1}H NMR spectrum.



17 X = I
18 X = H

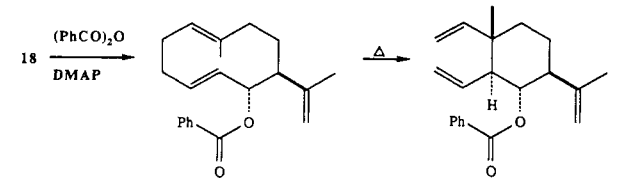
19

Suspecting conformational isomerism, we carried out variable temperature ^{1}H NMR studies on lactone **19**.[14,15] Indeed, the two vinylic H singlets coalesced at 72 °C and reappeared in the same 70:30 ratio upon cooling. At higher temperature (110 °C), a new set of signals, consistent with the Cope rearrangement product **20**, gradually appeared and remained after cooling of the sample. The apparent instability of this α-methylene lactone product precluded its isolation from preparative experiments. Aristolactone (**16**), on the other hand, showed no sign of rearranging, even after prolonged (12 h) heating at 110 °C. At higher temperature (refluxing xylene) multiple products were produced, possibly the result of double-bond isomerization as has been previously noted.[5a]



19 20

The related allylic alcohol benzoates behaved analogously. The benzoate of the cis alcohol **15** showed a single set of ^{1}H NMR signals and was recovered unchanged after being heated to 110 °C, whereas the trans isomer **21** gave rise to two sets of ^{1}H NMR signals and rearranged to the divinyl product **22** in refluxing toluene. Evidently the

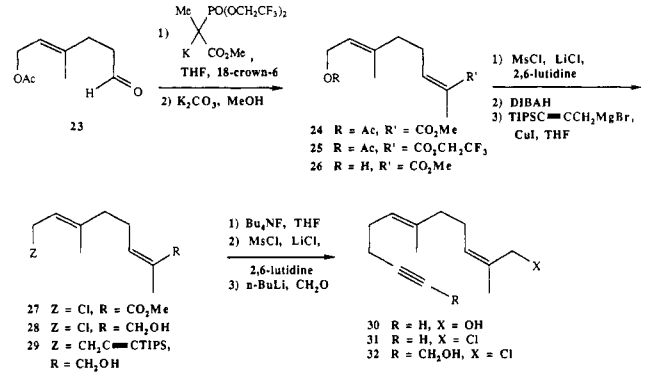


21 22

trans arrangement of isopropenyl and vicinal lactone or benzoate oxygen causes constraints on the jump-rope rotation of the trisubstituted double bond in **19** and **21**. Molecular models show that for the equatorial isopropenyl conformer the lactone oxygen of the cis isomer **16** assumes an axial orientation in a chairlike cyclodecadiene, thus enabling the ring to adopt a more open conformation in which jump-rope rotation is facilitated. In lactone **19**, the oxygen assumes a more equatorial orientation, thus placing the butenolide double bond in an interannular position where it blocks such rotation. The closer proximity of the transannular double bonds in this latter situation would account for the facile Cope rearrangement of the trans isomer in comparison to its cis counterpart.[14]

The [2,3] Wittig ring contraction step of the foregoing sequence, though efficient and completely stereoselective, leads to the undesired trans stereoisomer. Consequently, two additional steps must be employed to secure the cis alcohol **13** required for the synthesis of aristolactone. As noted above, the use of THF–HMPA[3] as solvent failed to alter the stereoselectivity of the rearrangement and caused extensive decomposition of the starting ether, unlike the analogous 17-membered allylic ether ring contraction.[1] Thus another approach was examined.

Nakai has shown that in acyclic [2,3] Wittig rearrangements, product stereochemistry usually depends upon the geometry of the allylic double bond.[16,17] Therefore, with a view toward a more direct synthesis of the cis alcohol **13** and a wish to further explore the scope of the ring contraction, we undertook the preparation of the *Z* allylic ether **33**. Geranyl acetate once again served as the starting material. Selective ozonolysis following the procedure of McMurry afforded the aldehyde **23**.[18] In our initial trials at Horner–Emmons condensation of aldehyde **23** with Still's methyl 2-[bis(trifluoroethyl)phosphono]propionate,[19] we obtained a 2:1 mixture of the methyl and trifluoroethyl esters **24** and **25**, as a consequence of contamination in the phosphonate reagent.[20] By modifying the experimental conditions for the preparation of the phosphonate, we were able to avoid the formation of ester **25**. Methanolysis of either the mixture or ester **24** alone led to a single hydroxy ester, **26**. Reduction of the derived chloro ester **27** with DIBAH[3] yielded the chloro alcohol **28**. This was converted to the homologous chloro alcohol **32** as described for the *E* isomer.



23

24 R = Ac, R' = CO_2Me
25 R = Ac, R' = $CO_2CH_2CF_3$
26 R = H, R' = CO_2Me

27 Z = Cl, R = CO_2Me
28 Z = Cl, R = CH_2OH
29 Z = $CH_2C{\equiv}CTIPS$, R = CH_2OH

30 R = H, X = OH
31 R = H, X = Cl
32 R = CH_2OH, X = Cl

Cyclization of chloro alcohol **32** to the 13-membered allylic ether **33** proceeded less efficiently (40% vs. 70%)

(14) The variable temperature ^{1}H NMR experiments and computer-assisted molecular modeling (Macromodel) were conducted by Dr. Stephen L. Crooks to whom we are grateful.

(15) For related observations, see: (a) Yoshioka, H.; Mabry, T. J. *Tetrahedron* **1969**, *25*, 4767. (b) Tori, K.; Horibe, Y.; Kuriyama, K.; Takeda, K. *J. Chem. Soc. D* **1970**, 952.

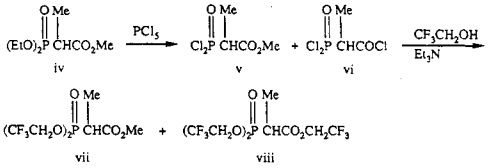
(16) Mikami, K.; Azuma, K.; Nakai, T. *Tetrahedron* **1984**, *40*, 2303. Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885 and references therein.

(17) For a nonselective [2,3] Wittig ring contraction of a *Z,E* diallylic ether, see ref 2.

(18) McMurry, J. E.; Erron, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712. Corey, E. J.; Achiva, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.

(19) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(20) The contamination arises as a result of the following series of reactions employed in the synthesis of the phosphonate vii: By carefully

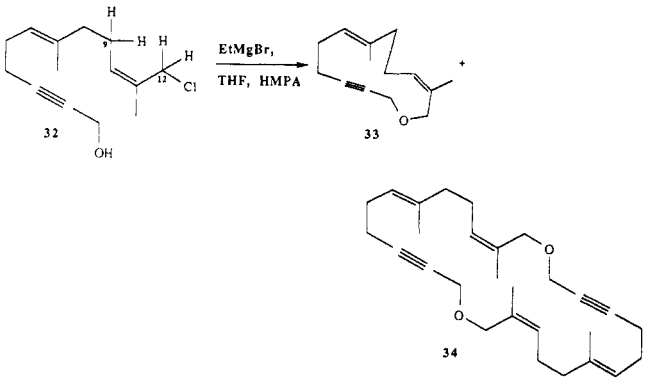


iv v vi

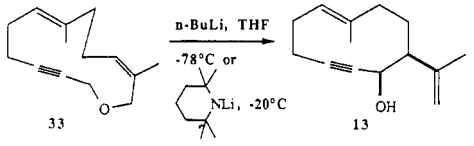
vii viii

monitoring the PCl_5 reaction we were able to minimize the production of the bis acid chloride vi to a negligible amount, thus essentially eliminating the formation of ester viii and, ultimately, the condensation product **25**.

compared to the *E* isomer **9**. In addition, a significant amount (25%) of a crystalline byproduct was isolated whose spectral properties and chromatographic behavior were consistent with the 26-membered diether **34**. No analogous product was observed in the cyclization of the *E* isomer **9**. This finding prompts our speculation that the transition-state conformation of the S_N2 cyclization is less favorable for the *Z* than for the *E* isomer, possibly as a result of repulsion between the 1,4-interannular allylic hydrogens (H9 and H12 in **32**). Thus intermolecular displacement of the allylic chloride competes with the intramolecular process to form a dimeric chloro alcohol. This longer chain chloro alcohol, being less constrained than its precursor **32**, is able to adopt a more favorable conformation for the ensuing intramolecular S_N2 displacement.



Ether **33** rearranged cleanly to the cis alcohol **13** upon treatment with *n*-BuLi in pentane–THF at −78 °C but at a slower rate (8 h vs. 2.5 h) than the *E* isomer **10**. The use of THF–HMPA as the solvent once again led to complete destruction of the ether.[1] Neither **13** nor the trans isomer **11** could be detected as reaction products. Best results were obtained by conducting the rearrangement at −20 °C with lithium 2,2,6,6-tetramethylpiperidide as the base. Under these conditions the reaction was complete within 10 min.



In summary, [2,3] Wittig ring contraction of the macrocyclic propargylic allylic ethers **10** and **33** proceeds with complete regio- and stereospecificity to afford the *trans*- and *cis*-isopropenylcyclodecynols **11** and **13**, respectively. Mitsunobu inversion of the former with benzoic acid followed by ester cleavage affords the latter in excellent yield. These alcohols are readily converted to the bridged butenolides **16** (aristolactone) and **19** (epiaristolactone) via carbonylation of the unstable vinyl iodides **14** and **17**.

Experimental Section

(2*E*,6*E*)-3,7-Dimethyl-8-[(*tert*-butyldimethylsilyl)oxy]-2,6-octadienyl Acetate (3). To a solution of 14.6 g (0.069 mol) of alcohol **2**[6] in 120 mL of CH_2Cl_2 were added 25 mL (0.018 mol) of triethylamine, 11.7 g (0.078 mol) of *tert*-butyldimethylsilyl chloride, and a catalytic amount of DMAP.[3] The resulting mixture was stirred for 2 h at room temperature and then poured into 100 mL of water and 100 mL of CH_2Cl_2. The organic layer was washed with water and the combined aqueous layers were extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $CuSO_4$, water, and brine. The resulting solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to 22.0 g (95%) of a yellow oil, which was used without further purification: IR (film) ν 2960, 2930, 2860, 1745, 1670, 1365, 1250, 1230, 1115, 1070, 1025, 960, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.35 (s, CH_3Si), 0.88 (s, *tert*-butyl), 1.57 (s, C7 vinyl CH_3), 1.69 (s, C3 vinyl CH_3), 2.0–2.2 (m, CH_2), 2.03 (s, CH_3CO), 3.98 (s, CH_2OTBS), 4.56 (d, J = 7 Hz, $-CO_2CH_2$), 5.33 (m, H2 and H6); MS, *m/e* 327 (M + 1), 269 (M − $(CH_3)_3C$), 267 (M − CH_3CO_2), 266 (M − 1 − CH_3CO_2). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.26; H, 10.43. Found: C, 66.30; H, 10.54.

(2*E*,6*E*)-3,7-Dimethyl-8-[(*tert*-butyldimethylsilyl)oxy]-2,6-octadien-1-ol (4). A solution of 22.0 g (0.067 mol) of crude acetate **3** was stirred in 100 mL of dry methanol as 1.5 g (0.011 mol) of anhydrous K_2CO_3 was added. After it was stirred under argon at 5 °C overnight, the mixture was diluted with an equal volume of water and extracted with three portions of ether. The combined extracts were washed with water and brine and were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (elution with 20% ethyl acetate–hexane) to give 14.6 g (76%) of the alcohol **4** as a colorless oil: IR (film) ν 3320, 2950, 2925, 2850, 1670, 1470, 1270, 1120, 1080, 1020, 850, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, CH_3Si), 0.89 (s, *tert*-butyl), 1.57 (s, C7 vinyl CH_3), 1.66 (s, C3 vinyl CH_3), 2.0–2.2 (m, $-CH_2$), 3.98 (s, CH_2OTBS), 4.13 (d, J = 7 Hz, CH_2OH), 5.30–5.49 (m, H2, H6); MS, *m/e* 284 (M), 283 (M − 1), 267 (M + 1 − H_2O), 171 (M + 1 − TBS). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 65.61; H, 11.27. Found: C, 65.70; H, 11.29.

(2*E*,6*E*)-1-Chloro-3,7-dimethyl-8-[(*tert*-butyldimethylsilyl)oxy]-2,6-octadiene (5). The procedure of Collington and Meyers was followed.[7] A solution of anhydrous LiCl (2.6 g, 0.061 mol) in 30 mL of DMF was cooled to 0 °C and a solution of 13.4 g (0.047 mol) of allylic alcohol **4** in 7.7 mL (0.066 mol) of 2,6-lutidine was added. After 45 min, 4.6 mL (0.059 mol) of methanesulfonyl chloride was added and the resulting slurry was stirred at 0 °C for 1.5 h. Then water and ether were added, the layers were separated, and the organic layer was washed twice with water. The combined aqueous layers were extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$, water, and brine and dried over anhydrous $MgSO_4$, and solvent was removed at reduced pressure to afford 13.6 g (95%) of chloride **5** as a yellow oil which was used without further purification: IR (film) ν 2925, 2850, 1660, 1470, 1390, 1370, 1270, 1110, 1080, 850, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.37 (s, CH_3Si), 0.88 (s, *tert*-butyl), 1.57 (s, C7 vinyl CH_3), 1.71 (s, C3 vinyl CH_3), 2.0–2.2 (m, CH_2), 3.98 (s, CH_2OTBS), 4.08 (d, J = 8 Hz, CH_2Cl), 5.33 (t, J = 6.5 Hz, H6), 5.43 (t, J = 7 Hz, H2); MS, *m/e* 302.5 (M), 266 (M − 1 − Cl), 251 (M − 1 − Cl − Me).

(2*E*,6*E*)-2,6-Dimethyl-2,6-undecadien-10-yn-1-ol (7). To a slurry of 2.0 g (0.010 mol) of CuI in 20 mL of THF at −78 °C was added 30.0 mL of 0.7 M [3-(triisopropylsilyl)-2-propynyl]-magnesium bromide dropwise. The resulting slurry was stirred at −78 °C for 30 min and the mixture was transferred to a cold bath at −23 °C. After 40 min, 3.70 g (0.012 mol) of chloride **5** in 5 mL of THF was added. The mixture was stirred for 3.5 h at −23 °C and then 30 mL of saturated aqueous NH_4Cl was added, the mixture was allowed to reach room temperature, and ether was added. The organic layer was washed with 3% NH_4OH until the washings were clear, the blue aqueous layers were extracted 2 times with ether, and the combined ether layers were washed with water and dried over $MgSO_4$. Removal of solvent left an oil (11.3 g) that was treated with 60.0 mL of 1 M tetra-*n*-butylammonium fluoride. The dark solution was stirred overnight, then poured into 50 mL of water, and extracted three times with ether. The combined extracts were washed with water and brine and dried over anhydrous $MgSO_4$. Removal of solvent left an oil that was purified by column chromatography on silica gel (15% EtOAc–hexanes), providing 2.2 g (96%) of acetylene **7**: IR (film) ν 3325, 2900, 2850, 1665, 1450, 1390, 1260, 1080, 1020, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, C6 vinyl CH_3), 1.53 (s, C2 vinyl CH_3), 1.92 (t, J = 2.5 Hz, acetylenic H), 1.98–2.24 (m, allylic, propargylic CH_2s), 3.95 (s, CH_2OH), 5.16 (m, H7), 5.36 (t, J = 7 Hz, H3); MS, *m/e* 192 (M), 191 (M − 1), 177 (M − CH_3), 161 (M − CH_2OH), 159 (M − H_2O − CH_3). Satisfactory analytical values could not be obtained for this compound.

(2*E*,6*E*)-1-Chloro-2,6-dimethyl-2,6-undecadien-10-yne (8). Following the procedure described for the preparation of allylic chloride **5**, 1.5 g (0.035 mol) of LiCl, 2.70 g (0.014 mol) of the allylic

alcohol **7**, 2.5 mL (0.021 mol) of 2,6-lutidine in 15 mL of DMF, and 1.6 mL (0.021 mol) of methanesulfonyl chloride afforded 3.02 g (100%) of chloride **8** as a yellow liquid: IR (film) ν 2925, 2850, 1660, 1450, 1400, 1280, 980, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, C6 vinyl CH_3), 1.71 (s, C2 vinyl CH_3), 1.92 (t, J = 2.5 Hz, acetylenic H), 2.00–2.25 (m, allylic, propargylic CH_2s), 3.99 (s, CH_2Cl), 5.17 (m, H7), 5.49 (t, J = 7 Hz, H3); MS, m/e 210.5 (M), 161 (M – CH_2Cl), 159 (M – HCl – CH_3).

(6*E*,10*E*)-12-Chloro-7,11-dimethyl-6,10-dodecadien-2-yn-1-ol (9). To a solution of 1.06 g (0.005 mol) of acetylene **8** in 7 mL of THF and 0.01 g of 1,10-phenanthroline at −78 °C was added 3.3 mL (0.0051 mol) of 1.55 M *n*-BuLi. The resulting dark solution was stirred at −78 °C for 1 h, and then 0.290 g (0.010 mol) of paraformaldehyde was added. The mixture was slowly warmed to 10 °C and stirred for 10 min. The reaction was quenched with saturated aqueous NH_4Cl and then diluted with water. The mixture was extracted twice with ether and the extracts were dried over anhydrous $MgSO_4$. Removal of solvent left an oil that was purified by column chromatography on silica gel (20% ethyl acetate–hexanes), affording 0.934 g (77%) of alcohol **9**: IR (film) ν 3450, 2980, 2870, 2290, 2230, 1650, 1450, 1030, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, OH), 1.59 (s, C7 vinyl CH_3), 1.72 (s, C11 vinyl CH_3), 1.95–2.22 (m, allylic, propargylic CH_2s), 4.00 (s, CH_2Cl), 4.24 (s, CH_2OH), 5.15 (m, H6), 5.43 (t, J = 7 Hz, H10); MS, m/e 240.5 (M), 205 (M – Cl).

(3*E*,7*E*)-3,7-Dimethyl-1-oxa-3,7-cyclotridecadien-11-yne (10). To a stirred, cooled (0 °C) solution of 920 mg (3.82 mmol) of the propargylic alcohol **9** and 0.02 g of 1,10-phenanthroline in 2.5 mL (15.2 mmol) of hexamethylphosphoramide and 200 mL of THF was added dropwise 1.6 mL (3.84 mmol) of 2.4 M ethylmagnesium bromide in THF, whereupon a persistent violet coloration appeared. After 5 min the cold bath was removed and the reaction solution was heated to reflux. After 4 h the mixture was cooled to room temperature, saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow liquid. Purification by column chromatography on silica gel (2% ethyl acetate–hexane) gave 600 mg (77%) of cyclic ether **10** as a colorless liquid: IR (film) ν 2975, 2900, 2830, 2275, 2225, 1670, 1440, 1370, 1140, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, vinyl CH_3), 1.60 (s, vinyl CH_3), 2.1–2.3 (m, allylic CH_2s), 3.9–4.1 (m, carbinyl CH_2s), 5.1 (t, J = 7 Hz, vinyl H), 5.4 (m, vinyl H); MS, m/e 203 (M – 1), 189 (M – CH_3), 174 (M – 2 CH_3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.25; H, 9.90.

***rel*-(1*S*,2*S*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-yn-1-ol (11).** To a stirred, cooled (−78 °C) solution of 513 mg (2.5 mmol) of the cyclic ether **10** in 40 mL of pentane and 5 mL of THF was added 4.1 mL (6.6 mmol) of 1.55 M *n*-BuLi in hexane. After 2.5 h water was added, the reaction mixture was warmed to room temperature, and the layers were separated. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford an oil. Purification by column chromatography on silica gel (15% ethyl acetate–hexane) gave 465 mg (92%) of the propargylic alcohol **11**: IR (film) ν 3450, 3050, 2900, 2895, 2250, 2200, 1640, 1440, 1025, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.4–2.4 (m, CH_2s), 1.68 (s, vinyl CH_3s), 4.05 (m, carbinyl H), 4.80 (s, vinyl Hs, 2 H), 5.08 (s, vinyl H); MS, m/e 204 (M), 189 (M – CH_3), 171 (M – CH_3 – H_2O). Anal. Calcd for $C_{19}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.31; H, 9.88.

***rel*-(1*S*,2*R*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-yn-1-ol (13). A. From Alcohol 11.** To a solution of 0.590 g (2.85 mmol) of alcohol **11** and 1.52 g (5.79 mmol) of triphenylphosphine in 5 mL of dry benzene was added over 4 h at room temperature a solution of 1.00 g (0.0057 mol) of DEAD[3] and 0.72 g (0.0059 mol) of benzoic acid in 4 mL of dry benzene. After 10 h, the reaction mixture was concentrated under reduced pressure to afford a viscous oil, which was stirred at room temperature with 30 mL of 1 M KOH in MeOH. After 30 min, saturated aqueous NaCl and ether were added, the layers were separated, and the aqueous layer was extracted with ether. The extracts were combined, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography on silica gel (8% ethyl acetate–hexanes) yielded 0.534 g (90%) of alcohol **13**: IR (film) ν 3450, 3050, 2950, 2900, 2230, 2200, 1640, 1440, 1380, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.6–2.5 (m, CH_2s), 1.69 (s, vinyl CH_3), 1.79 (s, vinyl CH_3), 4.3 (s, carbinyl H), 4.9 (s, vinyl Hs, 2 H), 5.1 (s, vinyl H). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.27; H, 9.91.

B. From Ether 33. To a stirred, cooled (−20 °C) solution of 44 mg (0.22 mmol) of the cyclic ether **33** in 2 mL of THF was added 2.5 mL (1.12 mmol) of 0.5 M lithium 2,2,6,6-tetramethylpiperidide in THF. After 10 min, water and ether were added, the reaction mixture was warmed to room temperature, and the layers were separated. The organic layer was washed with 2% HCl, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford an oil. Purification by column chromatography on silica gel (13% ethyl acetate–hexane) gave 27 mg (62%) of the propargylic alcohol **13** with spectral properties identical with those of a sample prepared as in part A above.

***rel*-(1*R*,2*R*)-(5*E*,9*E*)-2-Isopropenyl-5-methyl-5,9-cyclodecadien-1-ol (15).** To a stirred solution of 203 mg (1 mmol) of alcohol **13** in 3 mL of THF was added 0.47 mL (1.6 mmol) of 3.4 M Red-Al[3] in toluene. After being stirred overnight at room temperature, the reaction mixture was quenched with water followed by saturated aqueous Rochelle's salt. The product was isolated by ether extraction to afford 0.177 g (87%) of alcohol **15** as a clear oil: IR (film) ν 3450, 3075, 2940, 2860, 1650, 1480, 1390, 1110, 990, 910, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.3–2.5 (m, allylic CH_2s), 1.35 (s, vinyl CH_3), 1.78 (s, vinyl CH_3), 4.15–4.25 (m, carbinyl), 4.70–5.50 (m, vinyl H); MS, m/e 206 (M), 191 (M – CH_3), 173 (M – H_2O – CH_3). Anal. Calcd for $C_{14}H_{22}O$: C, 81.55; H, 10.68. Found: C, 81.39; H, 10.78.

***rel*-(1*R*,2*R*)-(5*E*,9*E*)-2-Isopropenyl-5-methyl-5,9-cyclodecadienyl Benzoate (Benzoate of Alcohol 15).** The procedure described for **21** was followed by using 105 mg (0.51 mmol) of alcohol **15**, 186 mg (0.82 mmol) of benzoic anhydride, and a catalytic amount of DMAP in 6 mL of THF. The mixture was heated for 2 days at reflux whereupon 104 mg (65%) of benzoate was isolated as a colorless oil: IR (film) ν 3080, 2940, 2875, 1720, 1645, 1450, 1175, 1115, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, C5 vinyl CH_3), 1.61 (s, isopropenyl CH_3), 1.65–2.50 (m, allylic CH_2), 4.64, 4.78 (isopropenyl CH_2), 4.80–5.00 (m, vinyl H), 5.20 (t, J = 10 Hz, carbinyl H), 5.4–5.6 (m, vinyl H), 7.3–8.1 (m, aromatic H); MS, m/e 310 (M), 295 (M – CH_3), 282 (M – C_2H_4), 188, (M – 1 – $PhCO_2$). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39. Found: C, 81.25; H, 8.49. The spectral properties of this material clearly differed from those of the trans isomer **21**.

(±)-Aristolactone (16). The procedure described for epiaristolactone (**19**) was followed by using 281 mg (1.37 mmol) of the propargylic alcohol **13** in 4 mL of THF and 0.65 mL (2.19 mmol) of 3.4 M Red-Al. Following quench with 500 mg (2.19 mmol) of *N*-iodosuccinimide in 4 mL of THF and workup, a solution of vinyl iodide in benzene was obtained. To this solution was added 80 mg (0.096 mmol) of $(Ph_3P)_4Pd$ under 1 atm of CO followed by 1.1 mL (4.09 mmol) of 3.7 M tributyltin hydride in 15 mL of benzene. After workup and purification, 57 mg (18%) of (±)-aristolactone was obtained, mp 86–87 °C (pentane): IR (KBr) ν 3090, 2980, 2930, 1735, 1640, 1430, 1375, 1205, 1060, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, C10 vinyl CH_3), 1.50–1.70 (m), 1.80 (s, isopropenyl CH_3), 1.85–2.65 (m, allylic CH_2s), 2.74 (dd, J = 12, 7 Hz, H2β), 4.57 (d, J = 12 Hz, H1), 4.69 (s, isopropenyl vinyl H), 4.81 (s, isopropenyl vinyl H), 4.97 (s, carbinyl H), 6.65 (s, H5) [The spectra were identical with those of an authentic sample.[13]]; MS, m/e 232 (M), 217 (M – CH_3), 204 (M – CO), 189 (M – CH_3 – C_2H_4). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.61; H, 8.68.

***rel*-(6*R*,7*R*)-(4*Z*,10*E*)-6-Hydroxy-7-isopropenyl-10-methyl-4,10-cyclodecadiene-4-carboxylic Acid Lactone; (±)-Epiaristolactone (19).** To a stirred solution of 210 mg (1.03 mmol) of the propargylic alcohol **11** in 3 mL of THF was added 0.48 mL (1.7 mmol) of 3.4 M Red-Al in toluene.[3] After being stirred at room temperature overnight, the reaction solution was cooled to −78 °C and 380 mg (1.7 mmol) of *N*-iodosuccinimide in 3 mL of THF was added dropwise. After 8 min, saturated aqueous Rochelle's salt was added followed by saturated aqueous Na_2SO_3. The aqueous layers were combined and extracted with ether. The combined extracts were washed with water and brine,

Table I. ^{1}H NMR Spectrum for Conformers of Lactone 19

H	major δ (pattern, coupling)	minor δ (pattern, coupling)
1	4.64 (d, 12)	4.64 (d, 12)
5	6.82 (s)	6.76 (s)
6	5.14 (d, 4)	5.05 (d, 6)
12a	4.94 (s)	4.87 (s)
12b	4.84 (s)	4.80 (s)
13	1.83 (s)	1.80 (s)
14	1.49 (s)	1.55 (s)

dried over anhydrous $MgSO_4$, and filtered. To this solution was added 20 mL of benzene, and the resulting mixture was concentrated to a volume of ca. 20 mL under reduced pressure at room temperature. To this colorless solution of vinyl iodide **17** and 60 mg (0.072 mmol) of $(Ph_3P)_4Pd$ under 1 atm of CO at 45–50 °C was added 0.8 mL of tributyltin hydride in 15 mL of benzene over 3 h. After the addition, the reaction solution was cooled to room temperature, diluted with water, and the resultant layers were separated. The organic layer was washed with 3% NH_4OH, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a black oil, which was filtered through a short column of silica gel (1% ethyl acetate–benzene). Purification by preparative TLC yielded 67 mg (30%) of epiaristolactone, mp 61–62 °C (pentane), and 30 mg (17%) of alcohol **18**: IR (KBr) ν 3090, 2995, 2950, 2880, 1745, 1645, 1440, 1385, 1355, 1210, 1105, 995, 895, 785 cm^{-1}. The ^{1}H NMR spectrum (300 MHz) in $CDCl_3$ indicated a 70:30 mixture of conformers. The principle peaks are summarized in the Table I. MS, *m/e* 232 (M), 217 (M – CH_3), 204 (M – CO), 189 (M – CH_3 – C_2H_4). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.56; H, 8.72.

***rel*-(1*R*,2*S*)-(5*E*,9*E*)-2-Isopropenyl-5-methyl-5,9-cyclodecadienyl Benzoate (21).** To a stirred solution of 230 mg (1.01 mmol) of benzoic anhydride in 5 mL of THF was added 160 mg (0.78 mmol) of alcohol **18** followed by 20 mg (0.2 mmol) of DMAP.[3] The resulting mixture was stirred at reflux for 12 h and then diluted with water and ether. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with saturated aqueous Na_2CO_3, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a light yellow oil. Purification by column chromatography on silica gel (2% ethyl acetate–hexane) yielded 174 mg (72%) of a white solid: mp 75–76 °C (pentane); IR (KBr) ν 3070, 2990, 2940, 1710, 1595, 1445, 1310, 1260, 1100, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, C5 vinyl CH_3), 1.62 (s, isopropenyl CH_3), 1.67–2.42 (m, allylic CH_2s), 4.6–5.0 (m, vinyl H), 5.20 (t, J = 10 Hz, carbinyl H), 5.4–5.6 (m, vinyl H), 7.3–8.1 (m, aromatic H); MS, *m/e* 310 (M), 295 (M – CH_3), 205 (M – PhCO), 188 (M – 1 – $PhCO_2$). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39. Found: C, 81.16; H, 8.48.

5β-Isopropenyl-3β-methyl-2β,3α-divinyl-1α-cyclohexyl Benzoate (22). A solution of 238 mg (0.76 mmol) of the benzoate **21** in 5 mL of toluene was heated at reflux under argon for 3 h. The solution was concentrated and the residue was recrystallized from pentane to give 238 mg (100%) of a white solid: mp 85–86 °C; IR (KBr) ν 3070, 2980, 2940, 2870, 1705, 1630, 1440, 1305, 1240, 1100, 815, 805, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, CH_3), 1.4–1.8 (m, CH_2s), 1.71 (s, isopropenyl CH_3), 2.18 (t, J = 10 Hz, H2), 2.38 (dt, J = 10, 4 Hz, H5), 4.62, 4.74 (s, isopropenyl C=CH_2), 5.82–5.96 (m, vinyl C=CH_2s, 4 H), 5.30 (t, J = 10 Hz, carbinyl H), 5.54–5.82 (m, vinyl H, 2H), 7.3–8.0 (m, aromatic H); MS, *m/e* 310 (M), 189 (M – 1 – $PhCO_2$). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39. Found: C, 81.16; H, 8.49.

Methyl (2*Z*,6*E*)-8-Acetoxy-2,6-dimethyl-2,6-octadienoate (24). To a solution of 10.0 g (0.029 mol) of bis(2,2,2-trifluoroethyl) 1-(methoxycarbonyl)ethyl phosphonate[12] and 11.8 g (0.045 mol) of 18-crown-6 in 170 mL of THF was added 30 mL (0.030 mol) of 1 M KHMDS[3] in THF at –78 °C followed by the addition of 4.4 g (0.026 mol) of aldehyde **23**.[18] The solution was stirred 1 h at –78 °C and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether and ethyl acetate twice and the combined extracts were washed with water and brine and dried over anhydrous $MgSO_4$. Removal of solvent left an oil, which was purified by silica gel chromatography (10% ethyl acetate–hexanes), yielding 4.36 g (71%) of ester **24** as a colorless oil (greater than 99% pure by GC): IR (film) ν 2950, 2920, 1725, 1670, 1645, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, C6 vinyl CH_3), 1.87 (s, C2 vinyl CH_3), 2.03 (s, CH_3CO), 2.11 (t, J = 8 Hz, H5), 2.58 (q, J = 8 Hz, H5), 3.70 (s, CO_2Me), 4.56 (d, J = 7 Hz, CH_2OAc), 5.34 (t, J = 7 Hz, H7), 5.88 (t, J = 7 Hz, H2).

Methyl (2*Z*,6*E*)-8-Hydroxy-2,6-dimethyl-2,6-octadienoate (26). A slurry of 4.36 g (0.018 mol) of acetate **24** and a catalytic amount of K_2CO_3 in 30 mL of dry methanol at –20 °C was stirred overnight. The mixture was diluted with water and extracted three times with ether. The extracts were washed with brine and dried over anhydrous $MgSO_4$. Removal of solvent left an oil, which was purified by distillation, affording 3.45 g (97%) of alcohol **26** as a colorless oil: IR (film) ν 3400, 2960, 2940, 1720, 1670, 1645, 1455, 1435, 1200, 1140, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, C6 vinyl CH_3), 1.87 (s, C2 vinyl CH_3), 2.15 (t, J = 8 Hz, H5), 2.6 (q, J = 8 Hz, H4), 3.75 (s, CH_3O), 4.15 (d, J = 7 Hz, CH_2OH), 5.4 (t, J = 7 Hz, H7), 5.9 (t, J = 7 Hz, H3); MS (70 eV), *m/e* 198 (M), 180 (M – H_2O), base peak 121. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.73; H, 9.17.

Methyl (2*Z*,6*E*)-8-Chloro-2,6-dimethyl-2,6-octadienoate (27). The procedure of Collington and Meyers[7] described for **5** was followed by using 5.10 g (0.026 mol) of alcohol **26**, 1.55 g (0.044 mol) of anhydrous LiCl, 4.2 mL (0.044 mol) of 2,6-lutidine, and 2.8 mL (0.044 mol) of methanesulfonyl chloride in 25 mL of DMF. The mixture was stirred for 1.5 h at 0 °C whereupon 6.50 g of crude chloride **27** was isolated as a colorless oil used without purification. A sample purified by column chromatography on silica gel (5% EtOAc–hexanes) gave the following spectra: IR (film) ν 3010, 2980, 2950, 2930, 2860, 1720, 1665, 1650, 1455, 1435, 1385, 1365, 1245, 1200, 1130, 1070, 670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, C6 vinyl CH_3), 1.86 (s, C2 vinyl CH_3), 2.12 (t, J = 7.6 Hz), 2.58 (q, J = 7.5 Hz, H4), 3.71 (s, CH_3O), 4.07 (d, J = 8 Hz, CH_2Cl), 5.44 (t, J = 8 Hz, H7), 5.88 (t, J = 6 Hz, H3); MS, *m/e* 180 (M – HCl), 121 (M – HCl – CO_2Me).

(2*Z*,6*E*)-8-Chloro-2,6-dimethyl-2,6-octadien-1-ol (28). To a solution of 4.01 g (0.019 mol) of ester **27** in 50 mL of ether at –78 °C was added slowly 48.5 mL (0.048 mol) of 1 M DIBAH in toluene.[3] The solution was stirred at –78 °C for 15 min and was quenched with 20 mL of aqueous Rochelle's salt (sodium potassium tartrate). The mixture was warmed to room temperature and Celite was added. After filtration, the layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. Removal of solvent gave 3.34 g (92%) of a light oil: IR (film) ν 3340, 2970, 2920, 2880, 2860, 1665, 1450, 1250, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, vinyl CH_3), 1.77 (s, vinyl CH_3), 2.05 (t, J = 7 Hz, H5), 2.16 (q, J = 7 Hz, H4), 4.07 (J = 8 Hz, CH_2Cl), 4.10 (s, CH_2OH), 5.23 (t, J = 7 Hz, vinyl H), 5.42 (t, J = 8 Hz, vinyl H); MS, *m/e* 152 (M – HCl), 137 (M – HCl – Me), 134 (M – HCl – H_2O), 119 (M – HCl – H_2O – CH_3).

(2*Z*,6*E*)-2,6-Dimethyl-11-(triisopropylsilyl)-2,6-undecadien-10-yn-1-ol (29). To a slurry of 1.5 g (0.008 mol) of CuI in 18 mL of THF at –78 °C was added 23 mL of 1.15 M [3-(triisopropylsilyl)-2-propynyl]magnesium bromide dropwise. The resulting slurry was stirred at –78 °C for 30 min and the mixture was trasferred to a cold bath at –23 °C. After 40 min, 3.31 g (0.016 mol) of chloride **28**, which was pretreated at 0 °C with 1.0 equiv of a solution of 2.0 M ethylmagnesium bromide in THF, was added. The workup described for the preparation of **6** gave an oil, which was purified by column chromatography on silica gel (5% EtOAc–hexanes), providing 5.2 g (90%) of alcohol **29**: IR (film) ν 3330, 2950, 2870, 2180, 1465, 1385, 1045, 1000, 885, 680, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, isopropyls), 1.59 (s, C6 vinyl CH_3), 1.76 (s, C2 vinyl CH_3), 1.98 (t, J = 7 Hz, H5), 2.1–2.3 (m, CH_2), 4.09 (s, CH_2OH), 5.1–5.3 (m, H3, H7); MS, *m/e* 305 (M – Me_2CH), 287 (M – Me_2CH – H_2O), 245 (M – 1 – Me_2CH – H_2O).

(2*Z*,6*E*)-2,6-Dimethyl-2,6-undecadien-10-yn-1-ol (30). The alcohol **29** (5.2 g, 0.015 mol) was treated with 23.0 mL of 1 M *n*-Bu_4NF in THF. The solution was stirred overnight, then poured into water, and extracted three times with ether. The combined extracts were washed with water and brine and dried over anhydrous $MgSO_4$. Removal of solvent left an oil, which was purified by column chromatography on silica gel (12% EtOAc–hexanes), providing 2.85 g (99%) of acetylene **30**: IR (film) ν 3300, 2970, 2930, 2860, 2120, 1670, 1645, 1450, 1380, 1250, 1100, 1010 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, OH), 1.60 (s, C6 vinyl CH_3), 1.77 (s, C2 vinyl CH_3), 1.93 (t, J = 2.5 Hz acetylenic H), 1.97–2.24 (m, allylic, propargylic CH_2s), 4.09 (d, J = 4 Hz, CH_2OH), 5.15 (m, H7), 5.27 (t, J = 7 Hz, H3); MS, m/e 191 (M – 1), 177 (M – CH_3), 159 (M – H_2O – CH_3). Anal. Calcd for $C_{13}H_{20}O$: C, 81.25; H, 10.42. Found: C, 81.20; H, 10.51.

(2*Z*,6*E*)-1-Chloro-2,6-dimethyl-2,6-undecadien-10-yne (31). Following the procedure described for the preparation of allylic chloride **5**, 400 mg (9.0 mmol) of LiCl, 1.10 g (4.70 mmol) of the allylic alcohol **30**, 1.07 mL (9.12 mmol) of 2,6-lutidine in 6 mL of DMF, and 0.71 mL (9.12 mmol) of methanesulfonyl chloride afforded, after purification by column chromatography on silica gel (2% EtOAc–hexanes), 1.01 g (91%) of chloride **31** as a colorless oil: IR (film) ν 2970, 2940, 2920, 2860, 2120, 1670, 1445, 1435, 1380, 1255, 700, 630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, C6 vinyl CH_3), 1.79 (s, C2 vinyl CH_3), 1.93 (t, J = 2.5 Hz, acetylenic H), 2.0–2.2 (m, allylic, propargylic, CH_2s), 4.04 (s, CH_2Cl), 5.17 (m, H7), 5.35 (t, J = 7 Hz, H3); MS, m/e 175 (M – 1 – HCl), 161 (M – CH_2Cl), 159 (M – HCl – CH_3).

(6*E*,10*Z*)-7,11-Dimethyl-12-chloro-6,10-dodecadien-2-yn-1-ol (32). The procedure described for alcohol **9** was employed with 2.1 mL (5.14 mmol) of 2.5 M *n*-BuLi, 1.082 g (5.14 mmol) of acetylene **31**, and 0.38 g (8.22 mmol) of paraformaldehyde in 8 mL of THF. Column chromatography on silica gel (15% EtOAc–hexanes) afforded 1.166 g (94%) of a light yellow oil: IR (film) ν 3450, 2980, 2920, 2870, 2290, 2230, 1650, 1450, 1380, 1255, 1135, 1030, 850, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (t, J = 6 Hz, OH), 1.59 (s, C7 vinyl CH_3), 1.08 (s, C11 vinyl CH_3), 1.95–2.25 (m, allylic, propargylic CH_2s), 4.04 (s, CH_2Cl), 4.23 (d, J = 6 Hz, CH_2OH), 5.15 (m, H6), 5.34 (t, J = 6 Hz, H10); MS, m/e 204 (M – HCl), 189 (M – HCl – Me), 171 (M – HCl – Me – H_2O).

(3*Z*,7*E*)-3,7-Dimethyl-1-oxa-3,7-cyclotridecadien-11-yne (33). The cyclization procedure described for ether **10** was followed by using 1.639 g (0.068 mol) of alcohol **32** and 0.02 g of 1,10-phenanthroline in 350 mL of THF and 4.5 mL of hexamethylphosphoramide to which 3.4 mL of 2.0 M ethylmagnesium bromide in THF was added at 0 °C. The resulting mixture was heated for 5 h at reflux. Following workup and chromatography on silica gel (1% EtOAc–hexanes), 0.582 g (42%) of cyclic ether **33** was isolated as a colorless oil: IR (film) ν 2950, 2920, 2850, 2280, 2220, 1670, 1445, 1380, 1360, 1140, 1090, 1070, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, vinyl CH_3), 1.72 (s, vinyl CH_3), 2.0–2.2 (m, allylic, CH_2s), 4.04 (s, allylic carbinyl CH_2), 4.16 (s, propargylic carbinyl CH_2), 5.11 (t, J = 7 Hz, vinyl H), 5.26 (t, J = 7 Hz, vinyl H); MS, m/e 204 (M), 189 (M – CH_3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.26; H, 9.89.

Continued elution afforded 0.358 g (25%) of the dimer **34**: mp 80–81 °C (pentane); IR (KBr) ν 2980, 2940, 2850, 2290, 2220, 1460, 1440, 1250, 1180, 1060, 900, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, vinyl CH_3), 1.71 (s, vinyl CH_3), 1.9–2.3 (m, allylic CH_2s), 4.04 (s, allylic carbinyl CH_2), 4.10 (s, propargylic carbinyl CH_2), 5.10 (t, J = 7 Hz, vinyl H), 5.42 (t, J = 7 Hz, vinyl H); MS, m/e 408 (M), 393 (M – CH_3). Anal. Calcd for $C_{28}H_{40}O_2$: C, 82.35; H, 9.80. Found: C, 82.23; H, 9.90.

Acknowledgment. Support for this research was provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society, for which we are grateful. We thank Professor Gordon L. Lange for a sample of aristolactone and copies of spectra. Funding for the AM-300 NMR spectrometer used in this work was provided by NSF instrument grant CHE-8411172.

Stereocontrolled Synthesis of Highly Oxygenated Acyclic Systems via the Enolate Claisen Rearrangement of O-Protected Allylic Glycolates

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Received March 6, 1987

Enolate Claisen rearrangement of *E*- and *Z*-allylic glycolates yields the *syn*- and *anti*-2-alkoxy-3-alkyl 4-enoates, respectively, in good yields (60–90%) and with high internal diastereoselectivity. Incorporation of the glycolate Claisen procedure into an iterative sequence consisting of Claisen rearrangement and homologation by addition of vinyl nucleophiles results in the efficient, stereocontrolled generation of remotely functionalized, highly oxygenated acyclic systems. This strategy is demonstrated in stereoselective syntheses of pine sawfly pheromone **42** and tocopherol side-chain intermediate **30**.

Introduction

Advances in the technology associated with the isolation and characterization of complex organic molecules have resulted in the identification of an impressive number of new acyclic and macrocyclic natural products in recent years. Coincident with the discovery of novel, biologically significant acyclic compounds has been an intense focus on synthetic strategies which address the unique challenge of these systems.[1] In particular, attention has been directed to the development of new methods for the stereorational homologation of an existing acyclic intermediate. This type of linear elaboration is particularly well-suited to the synthesis of compounds of polyketide or polyisoprene origin, since the repeating structural units of these systems could, in principle, arise from the iterative application of a single, short homologation sequence.[2,3] The potential advantages of a linear route to functionalized

(1) For recent reviews, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron Lett.* **1985**, *41*, 3569. (b) Bartlett, P. A. *Tetrahedron Lett.* **1980**, *36*, 2.

(2) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.-T.; Faulkner, D. J. *Ibid.* **1970**, *92*, 4463. (c) Faulkner, D. J.; Peterson, M. R. *Ibid.* **1973**, *95*, 553. (d) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505, 3512. (e) Chan, K.-K.; Cohen, N.; DeNoble, J. P.; Specian, A. C.; Saucy, G. *Ibid.* **1976**, *41*, 3497. (f) Chan, K.-K.; Specian, A. C.; Saucy, G. *Ibid.* **1978**, *43*, 3435. (g) Midland, M. M.; Tsai, D. J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3915.

(3) (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (b) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *Ibid.* **1985**, *50*, 420. (c) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (d) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (e) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147.

0022-3263/87/1952-3889$01.50/0