Synthesis of 12-, 14-, and 16-Membered Propargylic Alcohols through Lewis Acid-Promoted Ene Cyclization

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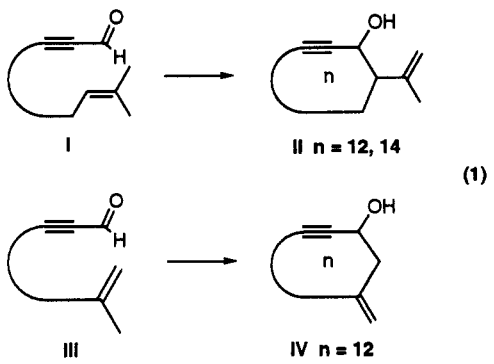
The scope of the Lewis acid-promoted ene cyclization has been expanded to include 12-, 14-, and 16-membered rings. Thus, the ynals **1.8**, **2.5**, and **3.5** undergo efficient type-I cyclization upon addition to 1.0 equiv of $EtAlCl_2$ in CH_2Cl_2 at −78 °C. The epoxy ynal **4.3** undergoes pinacol rearrangement under these conditions. However, treatment with a 1:1 mixture of Et_2AlCl and $EtAlCl_2$ effects conversion to the cyclic products **4.4**/**4.5** (92:8) in satisfactory yield. Facile type-II cyclizations were readily achieved with ynals **5.7**, **6.4**, **7.6**, and **8.3** with $EtAlCl_2$ as the Lewis acid. In the latter case, a 16-membered propargylic alcohol was produced in 84% yield.

We recently showed that certain terminal isopropylidene- and isopropenyl-substituted acetylenic aldehydes undergo efficient type-I and type-II ene cyclizations in the presence of alkylaluminum chlorides to afford cyclic propargylic alcohols of 12 and 14 members (eq 1).[1,2]



Prior to these studies such cyclizations had been employed for the synthesis of five-, six-,[3] and a few conformationally constrained seven-membered rings.[4] From our preliminary findings and a number of additional applications, it now appears that the approach is a fairly general one for rings of 12 or more members.

Type-I Cyclizations

In consideration of the numerous diterpenoid natural products featuring isopropenyl substituted 12- and 14-membered rings[5,6] it was of interest to examine type-I ene cyclizations leading to rings of this size.[7] A prototype system, ynal **1.8**, was readily prepared by homologation of enal **1.4** with 5-methyl-4-hexenylmagnesium bromide followed by alcohol protection and two-step alkyne formylation. Exposure to $EtAlCl_2$[8] in CH_2Cl_2 at −78 °C led to a mixture of 12-membered alcohol diastereomers (**1.9**) in 66% yield. Oxidation of this mixture with the Dess–Martin reagent[9] gave rise to a 1.5:1 mixture of diastereomeric ketones **1.11**. When reduced with DIBAH this ketone mixture yielded mainly the original cyclization products **1.9** and a small amount of two new alcohols. The latter were surmised to be trans isomers **1.12** based on the coupling constants of 10.1 Hz (major) and 8.9 Hz (minor) for the carbinyl protons in the ^1H NMR spectrum of a partially purified sample of the *p*-nitrobenzoate derivatives **1.13**. In contrast the *p*-nitrobenzoates **1.10** of the cyclization mixture showed coupling of *ca.* 4 Hz.[10] The spectrum of the initial cyclization mixture was devoid of signals associated with the trans alcohols **1.12**. Thus, ene cyclization of ynal **1.8** proceeds with high cis diastereoselectivity but only modest remote diastereocontrol.

We next investigated cyclizations leading to 14-membered propargylic alcohols related to cembrane natural products.[5] The first system examined, ynal **2.5**, was easily prepared from farnesol (**2.1**) along lines previously described.[11] Upon treatment with $EtAlCl_2$ in CH_2Cl_2 at −78 °C, ynal **2.5** afforded a 1:1 mixture of diastereomeric alcohols **2.6** and **2.7** in 79% yield along with oxetane **2.12**

(1) For a definition of terms and a recent review see Snider, B. B. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, pp 527–561.

(2) Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1992**, *57*, 2766.

(3) Cf. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203. Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538.

(4) Cf. Marshall, J. A.; Andersen, N. H.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 186. Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.

(5) *e.g.* Cembranes, Marshall, J. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers: Amsterdam, 1992; Vol. 10, pp 3–42. Weinheimer, A. J.; Chang, C. W.; Matson, J. A. *Prog. Chem. Org. Nat. Prod.* **1979**, *36*, 281.

(6) *e.g.* Pseudopteranes, Paquette, L. A. *Chemtracts: Org. Chem.* **1992**, *5*, 141.

(7) On the basis of our recent studies, it is assumed that these ene cyclizations proceed by a concerted pathway. However, it is possible that the energetic requirements of macrocyclization may favor a stepwise pathway. Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1992**, *57*, 5851.

(8) For a discussion of the merits of such Lewis acids for ene reactions, see Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426–432.

(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(10) Coupling constants derived from molecular mechanics calculations were 10.3, 10.6, 10.6 Hz and 9.7, 9.8, 9.8 Hz for the three lowest energy *trans, anti* and *trans, syn* isomers vs 5.6, 5.6, 0.6 Hz and 0.7, 0.6, 5.7 Hz for the three lowest energy *cis, anti* and *cis, syn* isomers. The program MacroModel V 3.1x was employed for these calculations. The TIPS grouping was replaced by *t*-Bu and the *p*-$NO_2C_6H_4$ by Ph to simplify the calculations. Each structure was subjected to a 1000-step Monte Carlo conformational search in the automated set-up mode. For each of the four diastereomers, multiple conformers (8–20) were found within 4 kJ of the "global" minimum. Hence, the actual coupling constants are most likely average values. MacroModel V 3.1x was obtained from Professor W. Clark Still to whom we are grateful. Cf. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.

(11) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616.

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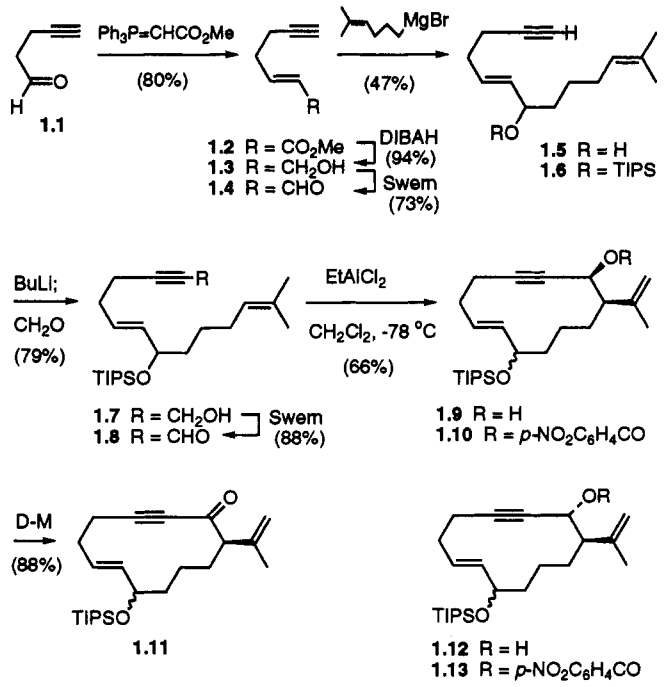


in 10% yield.[12] Best results were obtained by slow addition of a solution of the aldehyde to a well-stirred, dilute solution of the Lewis acid. Both dilution and stoichiometry were important variables as can been seen in Table I. The weaker Lewis acid Me_2AlCl was less effective. Although diastereoselectivity could be improved to 5:1 when excess $BF_3{\cdot}OEt_2$ was employed for the cyclization, the overall yield was in the 40–50% range for such reactions. In all cases examined, a full equivalent of Lewis acid was required for complete conversion of starting material to cyclic product. The stronger Lewis acids $TiCl_4$ and $SnCl_4$ caused extensive decomposition, possibly the result of HCl formation. The weaker Lewis acids, $ZnCl_2$ and $(i\text{-}PrO)_2TiCl_2$, failed to catalyze cyclization, even at room temperature.

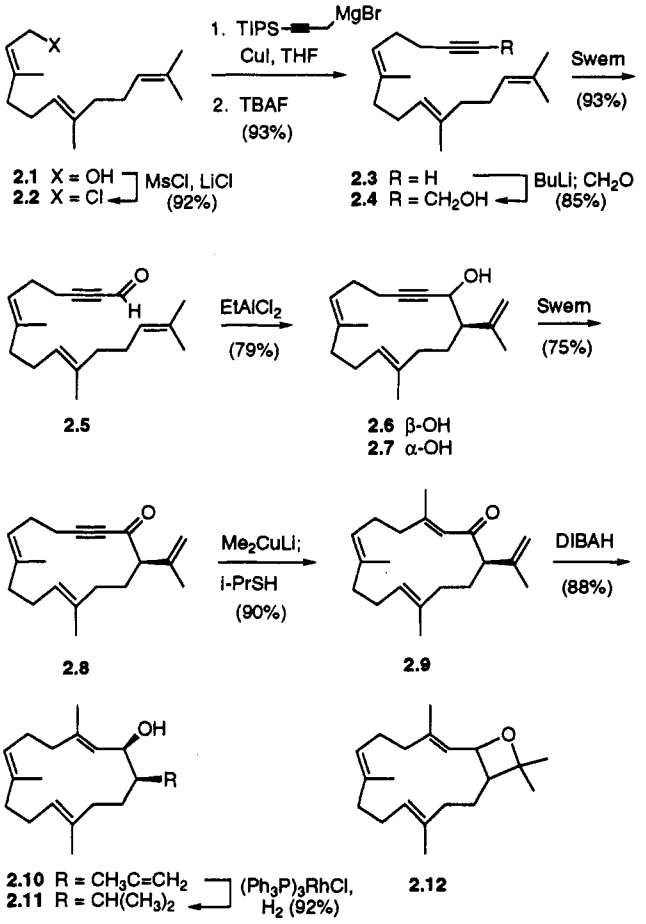
We have previously prepared propargylic alcohols **2.6** and **2.7** by [2,3] Wittig ring contraction of a 17-membered propargylic ether.[13] The former was converted to the cembrane mukulol (**2.11**) through directed hydroalanation, iodination, methyl cuprate coupling, and selective isopropenyl hydrogenation.[13] In the present case we adopted a different strategy to convert the mixture of **2.6** and **2.7** to mukulol. This was achieved through oxidation and treatment of the ketone **2.8** with the Gilman methyl cuprate to afford a 1:1 mixture of enones which was equilibrated *in situ* by addition of i-PrSH to the reaction mixture leading to a 96:4 mixture favoring the (*E*)-enone **2.9**. Reduction of **2.9** with DIBAH afforded a 90:10 mixture of epimeric alcohols favoring the syn isomer **2.10**. Selective hydrogenation of the isopropenyl double bond was achieved with Wilkinson's catalyst affording racemic mukulol (**2.11**) identical by spectral comparison with an authentic sample.

The issue of remote diastereocontrol in 14-membered type-I cyclizations was addressed with a second cembranoid-related system. Ynal **3.5** was prepared from *trans, trans*-farnesol by a sequence analogous to the one previously described.[14] This ynal gave rise to a mixture (*cis/trans, syn/anti*) of diastereomeric cyclization products **3.6** when subjected to the standard conditions ($EtAlCl_2$ in CH_2Cl_2 at −78 °C, slow addition). Swern oxidation afforded a 75:25 mixure of syn and anti ketones **3.7** and **3.8**. Ketone **3.7** was converted to the trans alcohol **3.14** previously prepared in our total synthesis of the cembrane diols α- and β-CBT.[14] Thus reduction of the ketone mixture with L-Selectride led to a like mixture of alcohols **3.9** and **3.10** assigned as cis isomers by comparison of the ^1H NMR spectrum with those of related compounds. The chemical shift (4.42, 4.46 ppm) and small coupling constant of the carbinyl H are typical for cis isomers.[13,14] Mitsunobu inversion of alcohol **3.9** with $PhCO_2H$[15] followed by desilylation, resilylation with TBSCl, and saponification afforded alcohol **3.14** (carbinyl H; δ = 4.05 ppm, J = 10.5 Hz) identical with an authentic sample prepared in the

Table I. Cyclization of Ynal 2.5

Lewis acid	equiv	M	conditions[a]	time, h	yield, %	2.6/2.7
$EtAlCl_2$	1.5	0.01	A	0.2	35	1:1
	1.0	0.01	A	0.2	64–75[b]	1:1
	1.0	0.001	A	0.5	67	1:1
	1.0	0.005	B	0.5	75–80[b]	1:1
Me_2AlCl	1.0	0.005	B	2	*c*	1:1
	1.5	0.005	B	0.5	35–55[b]	1:1
$BF_3{\cdot}OEt_2$	2.0	0.005	B	12	40–50[b]	5:1

[a] A = Lewis acid added to aldehyde in CH_2Cl_2 at −78 °C. B = aldehyde added to Lewis acid in CH_2Cl_2 at −78 °C. [b] Range of several runs. [c] Incomplete reaction.

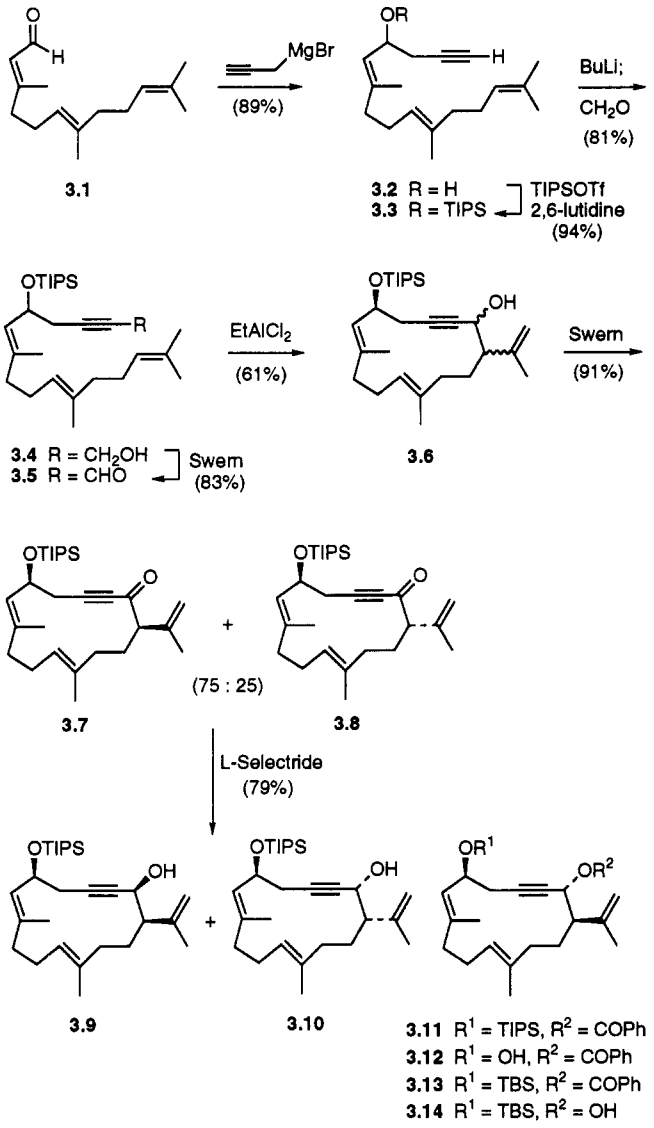


(12) For an additional example of oxetane formation under these conditions, see Demole, E.; Enggist, P.; Borer, M. C. *Helv. Chim. Acta.* **1971**, *54*, 1845.

(13) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860.

(14) Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, *55*, 227.

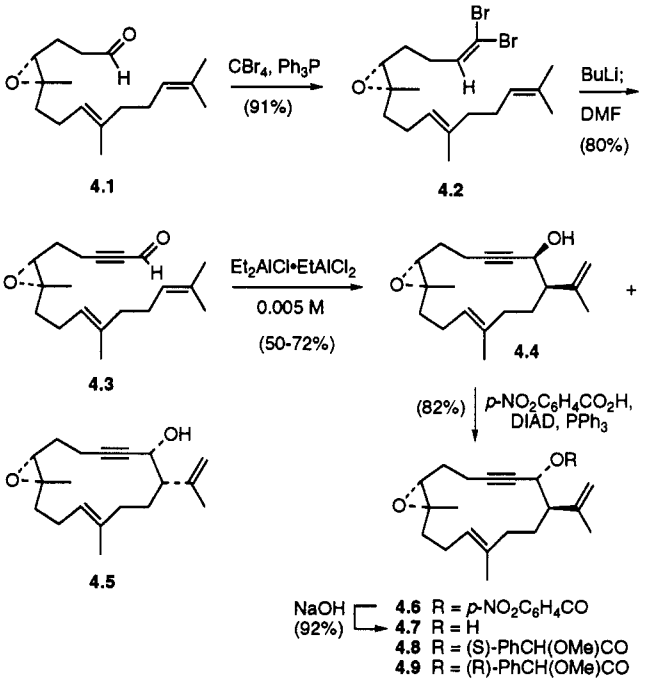
(15) Mitsunobu, O. *Synthesis* **1981**, 1. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.



aforementioned synthesis of α- and β-CBT.[14] Thus, we conclude that the cyclization of aldehyde **3.5** proceeds with modest remote stereocontrol and slight, if any, 1,2-diastereoselectivity. However, the syn isomers (**3.9, 3.10**) can be easily produced from the mixture through sequential oxidation–reduction. These, in turn, can be inverted by the Mitsunobu sequence.

Epoxy ynal **4.3** represents a second system for investigating remote stereocontrol in the 14-membered type-I ene cyclization. Previously, Still showed that such an epoxide grouping was an effective control element in the Hiyama type cyclization ($CrCl_2$) of an enal allylic bromide analogue of **4.3**.[16] Subsequently we observed remarkably high levels of remote diastereocontrol in Lewis acid-initiated cyclizations of α-alkoxy allylic stannane analogues of **4.3**.[17]

Our synthesis commenced with the known farnesol-derived (+)-(*R,R*)-epoxy aldehyde **4.1**[18] and proceeded by Corey–Fuchs homologation[19] and dehydrobromination–formylation. Attempted cyclization of epoxy ynal **4.3** with $EtAlCl_2$ in CH_2Cl_2 under the usual conditions led to pinacol rearrangement and decomposition with only small amounts (<25%) of desired cyclic product. The use of $BF_3{\cdot}OEt_2$ gave rise to uncyclized fluorohydrin as the sole isolable product. However, when a 1:1 mixture of $EtAlCl_2$ and Et_2AlCl was used, cyclization proceeded in high yield. The product, a 92:8 mixture of diastereomers **4.4** and **4.5**, was converted to the crystalline and readily purifiable *p*-nitrobenzoate **4.6** through Mitsunobu inversion.[15]



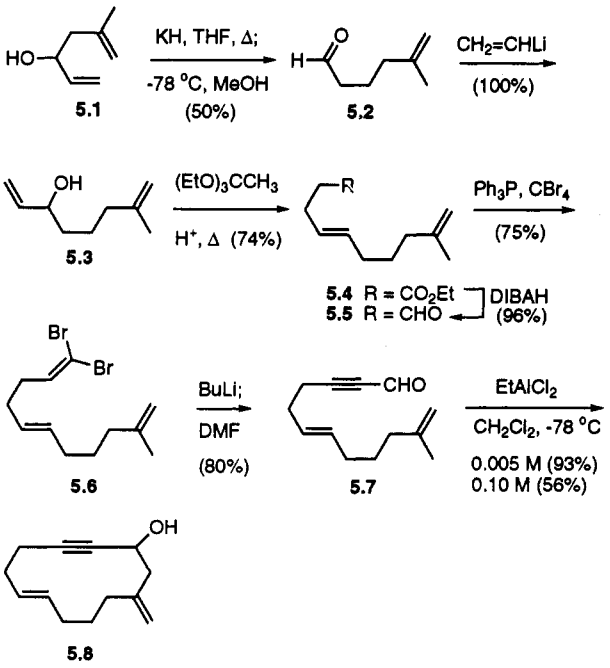
Saponification of **4.6** afforded the trans alcohol **4.7** (carbinyl H; δ = 4.15 ppm, J = 10.2 Hz), also a solid, in 92% yield. Assignment of (*R,R*) absolute stereochemistry to the epoxide is based on the Sharpless asymmetric epoxidation.[18] Assignment of carbinyl absolute stereochemistry as (*R*) derives from ^1H NMR analysis of the (*S*)- and (*R*)-*O*-methylmandelates **4.8** and **4.9** as previously described.[14] In particular the isopropenyl protons of the (*S*)-mandelate **4.8** are appreciably shielded relative to those of the (*R*) diastereomer **4.9** (vinyl H's at 4.43, 4.03 vs 4.71 ppm and vinyl Me at 1.27 vs 1.56 ppm).

Type-II Cyclizations

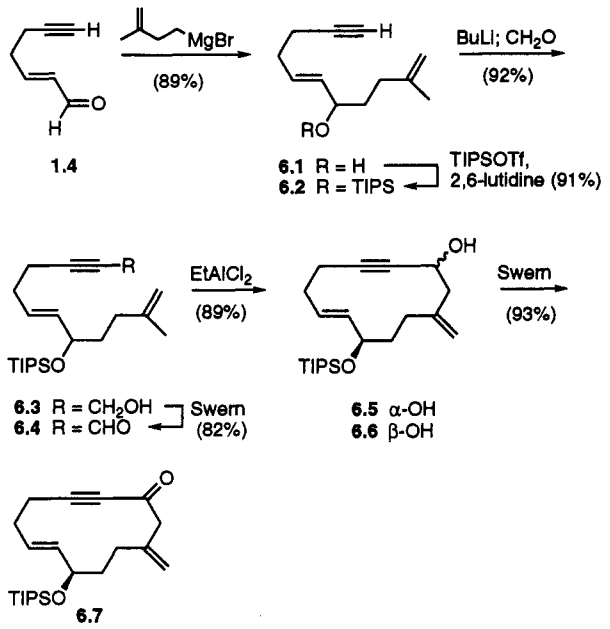
To further extend the approach we examined a number of type-II cyclizations. Our first system, ynal **5.7**, was readily prepared from dienol **5.1** through anionic oxy-Cope rearrangement[20a] (**5.1** → **5.2**), orthoester Claisen rearrangement[21] (**5.3** → **5.4**), Corey–Fuchs homologation[19] (**5.5** → **5.6**) and dehydrobromination–formylation. Cyclization proceeded readily with $EtAlCl_2$ in CH_2Cl_2 at −78 °C. It was found that aldehyde concentrations of 0.005 M were quite satisfactory leading to the propargylic alcohol **5.8** in 93% yield. However, an increase in aldehyde concentration to 0.1 M led to significant lowering of yield.

To explore the effect of a remote stereocenter on the type-II cyclization we prepared the silyloxy-substituted ynal **6.4** by homologation of the acetylenic enal **1.4**. Upon

(16) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785.
(17) Marshall, J. A.; Markwalder, J. A. *Tetrahedron Lett.* **1988**, *29*, 4811.
(18) Kigoshi, H.; Ojika, M.; Shizuri, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1982**, *23*, 5413; reported $[\alpha]^{21}_D$ +11.3° (*c* 4.41, $CHCl_3$) for material of 96% ee. Our sample showed $[\alpha]^{21}_D$ +11.1° (*c* 4.40, $CHCl_3$).
(19) Corey. E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.
(20) (a) Evans, D. A.; Golob, A. M.; *J. Am. Chem. Soc.* **1975**. (b) Viola, A; Iorio, J. E.; Chen, K. K.; Glover, G. M.; Nayak, V.; Kocienski, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 3462.
(21) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.



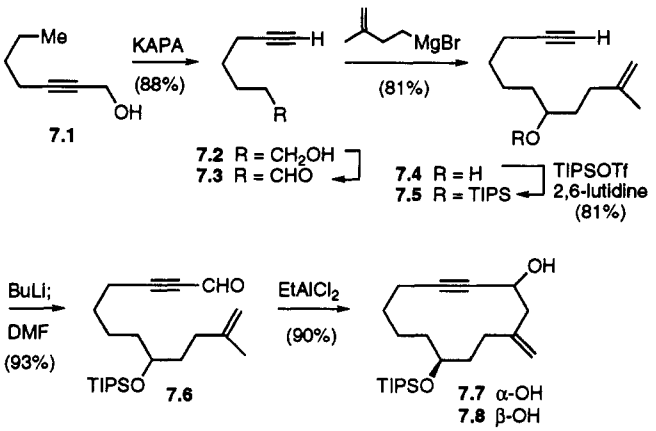
treatment with $EtAlCl_2$, as described for ynal **5.7**, aldehyde **6.4** afforded a 1:1 mixture of the diastereomeric alcohols



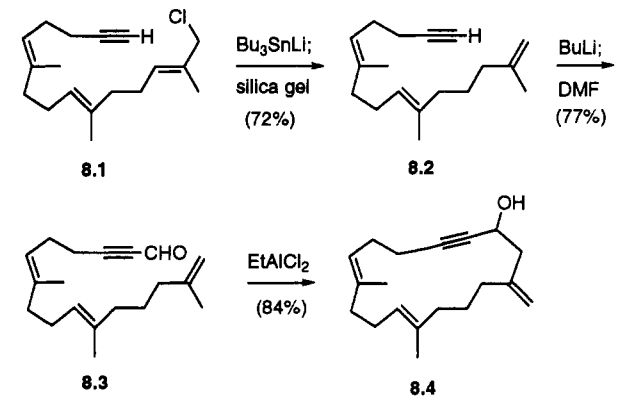
6.5 and **6.6** in 89% yield. The relationship of these alcohols was confirmed through Swern oxidation to a single ketone **6.7**. Thus, the silyoxy grouping of ynal **6.4** exerts no conformational control on the cyclization reaction.

It was of interest to determine what role, if any, the (*E*)-double bond plays in the cyclization of aldehydes **5.7** and **6.4**. *A priori*, the entropic and enthalpic requirements of these substrates would expectedly be lower than those of their dihydro analogues. Accordingly, we prepared ynal **7.6** from aldehyde **7.3**, the dihydro counterpart of enal **1.4**. When treated with $EtAlCl_2$ at −78 °C, as for **5.7** and **6.4**, ynal **7.6** was converted to a 1:1 mixture of alcohols **7.7** and **7.8** in 91% yield. Evidently the ene process itself provides a strong cyclization driving force independent of entropy- and enthalpy-lowering functionality in the tether that joins the aldehyde and ene moieties.

As a final test of the methodology, we examined the ynal **8.3**, readily prepared from the known farnesol-derived



chloride **8.1**[13]. Treatment with $EtAlCl_2$ under the standard conditions smoothly converted ynal **8.3** to the 16-membered propargylic alcohol **8.4** in 84% yield.



It can thus be seen that the catalyzed ene methodology offers a simple and efficient approach to rings in the 12–16 membered range. Presumably larger rings could also be accessed in this manner as well. However, attempts to cyclize the geranyl or neryl analogues of ynal **2.5** to the 10-membered alcohols led to decomposition products.[23]

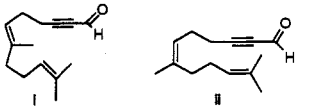
The type-II reactions are particularly facile. Except for the epoxy ynal **4.3**, the type-I systems examined do not show high remote diastereoselectivity. High vicinal syn stereoselectivity can be achieved through reduction of the derived isopropenyl-substituted ketones with DIBAH or L-Selectride. Subsequent Mitsunobu inversion affords the trans diastereomers. In the absence of remote nonracemic stereocenters racemic products are produced in these cyclizations. Possibly, through use of appropriate chiral nonracemic Lewis acid catalysts, enantioenriched products could be realized from achiral aldehyde substrates.[24] Work along these lines is planned.

Experimental Section[25]

(5*E*,9*E*)-6,10,14-Trimethyl-5,9,13-pentadecatrien-1-yn-4-ol (3.2). A slurry of 5.50 g (225 mmol) of oven-dried magnesium

(22) Omura, K.; Swern, D. *Tetrahedron Lett.* **1978**, *34*, 1651.

(23) Ynals *i* and *ii* were prepared from geraniol and nerol, respectively, by the sequence used for **2.1** → **2.5**. Both gave only decomposition products when treated with $EtAlCl_2$ at −78 °C to room temperature.



(24) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(25) Experimental procedures and copies of NMR spectra for **1.1**–**1.13**, **2.1**–**2.12**, and **6.1**–**6.7** can be found in the supplementary material of ref 2. For a summary of experimental protocols, see Marshall, J. A.; Wang, X-j *J. Org. Chem.* **1991**, *56*, 960.

powder, a catalytic amount of mercuric chloride, and 100 mL of anhydrous Et_2O was stirred as 0.5 mL of 80% propargyl bromide in toluene was added by syringe. After 10 min, the reaction initiated, whereupon the slurry was cooled to −20 °C and a solution of 6.2 mL (70 mmol) of 80% propargyl bromide in toluene and 5 g (22.5 mmol) of farnesal (**3.1**)[26] in 40 mL of Et_2O was added by syringe pump over 6 h. After an additional 6 h of stirring at −20 °C, the reaction mixture was carefully quenched with saturated aqueous NH_4Cl and immediately suction filtered through a plug of Celite with ether. The resulting mixture was extracted with ether and the combined organic extracts were washed with brine and dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure left an oil that was purified by flash chromatography (10% then 25% Et_2O/hexanes) affording 5 g (89%) of alcohol **3.2**: IR (film) ν 3315, 3302, 2114, 1665 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 5.24 (d, J = 7.2 Hz, C=C*H*CHOH), 5.05 (m, vinyl H's), 4.50 (m, C=CHC*H*OH), 2.39 (m, CCCH_2), 2.20–1.94 (m, allylic and OH), 1.85 (d, J = 3.9 Hz, CC*H*), 1.69, 1.58 × 2, 1.66 (s, vinyl Me's). Anal. Calcd for $C_{18}H_{28}O$: C, 83.22; H, 11.02. Found: C, 83.05; H, 11.05.

(5*E*,9*E*)-4-[(Triisopropylsilyl)oxy]-6,10,14-trimethyl-5,9,13-pentadecatrien-1-yne (3.3). To a solution of 2.00 g (7.68 mmol) of alcohol **3.2** in 50 mL of anhydrous CH_2Cl_2 at room temperature was added successively 1.34 mL (11.50 mmol) of 2,6-lutidine and 2.17 mL (8.06 mmol) of triisopropylsilyl trifluoromethanesulfonate. The reaction mixture was stirred an additional 30 min, then partitioned between 50 mL of 1 N HCl and 100 mL of Et_2O. The aqueous phase was extracted with ether, the combined organic extracts were dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (hexanes then 5% Et_2O/hexanes) afforded 3.00 g (94%) of silyl ether **3.3**: IR (film) ν 3313, 2125, 1665 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 5.19 (d, J = 8.6 Hz, C=C*H*CHOR), 5.05 (m, vinyl H's), 4.60 (ddd, J = 8.6, 7.2, 5.5 Hz, C=CHC*H*OR), 2.45 (ddd, J = 16.4, 5.5, 2.6 Hz, CCCH_2^a), 2.30 (ddd, J = 16.4, 7.2, 2.7 Hz, CCCH_2^b), 2.10–1.94 (m, allylic), 1.88 (t, J = 2.7 Hz, CCH), 1.66, 1.64, 1.58, 1.53 (s, vinyl Me's), 1.03 (bs, i-Pr_3Si).

(6*E*,10*E*)-5-[(Triisopropylsilyl)oxy]-7,11,15-trimethyl-6,10,14-hexadecatrien-2-yn-1-ol (3.4). To a stirred solution of 2.30 g (5.52 mmol) of acetylene **3.3** in 100 mL of THF at −78 °C was added 4.4 mL (11.0 mmol) of 2.5 M *n*-BuLi in hexanes. After 1 h, 1.60 g (110 mmol) of paraformaldehyde was added and the mixture was allowed to warm to room temperature and stirred an additional 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (10% then 25% ether in hexanes) afforded 2.00 g (81%) of alcohol **3.4**: IR (film) ν 3346, 1665 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 5.18 (d, J = 7.3 Hz, C=C*H*CHOR), 5.07 (m, vinyl H's), 4.61 (dd, J = 7.0, 14.4 Hz, C=CHC*H*OR), 4.19 (bs, CH_2OH), 2.44 (ddt, J = 14.3, 5.8, 2.0 Hz, CCCH_2^a), 2.30 (ddt, J = 14.2, 7.0, 2.2 Hz, CCCH_2^b), 2.06–1.95 (m, allylic), 1.66, 1.64, 1.58 × 2 (s, vinyl Me's), 1.50 (bs, OH), 1.03 (bs, i-Pr_3Si). Anal. Calcd for $C_{28}H_{50}O_2Si$: C, 75.27; H, 11.28. Found: C, 75.05; H, 11.27.

(6*E*,10*E*)-5-[(Triisopropylsilyl)oxy]-7,11,15-trimethyl-6,10,14-hexadecatrien-2-ynal (3.5). The method of Swern was used.[22] To a solution of 0.35 mL (3.96 mmol) of oxalyl chloride in 15 mL of CH_2Cl_2 at −78 °C was slowly added 0.56 mL (7.92 mmol) of DMSO. After 5 min, alcohol **3.4** (1.18 g, 2.64 mmol) was added as a solution in 5 mL of CH_2Cl_2. The resulting mixture was stirred for 30 min and triethylamine (3 mL, 20 mmol) was added. The suspension was then warmed to 0 °C for 15 min, diluted with 50 mL of ether, and washed with 15 mL of 10% HCl . The aqueous phase was extracted with ether, and the combined organic extracts were washed with water and then brine and dried over Na_2SO_4. Filtration and removal of solvents under reduced pressure followed by flash chromatography (hexanes then 5% Et_2O/hexanes) provided 0.98 g (83%) of acetylenic aldehyde **3.5**: IR (film) ν 1665 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.13 (s, C*H*O), 5.20 (d, J = 8.5 Hz, C=C*H*CHOR), 5.08 (m, vinyl H's), 4.70 (dd, J = 8.5, 6.4 Hz, C=CHC*H*OR), 2.60 (dd, J = 14.8, 5.8 Hz, CCCH_2^a), 2.50 (dd J = 15.0, 6.6 Hz, CCCH_2^b), 2.06–1.92 (m, allylic), 1.66, 1.64, 1.58 × 2 (s, vinyl Me's), 1.03 (bs, i-Pr_3Si). Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.58; H, 10.86.

(7*E*,11*E*)-1-Isopropenyl-6-[(triisopropylsilyl)oxy]-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-ol (3.6). To a solution of $EtAlCl_2$ (2.10 mL, 2.10 mmol, 1 M in hexanes) in 350 mL of anhydrous CH_2Cl_2 at −78 °C was added a solution of aldehyde **3.5** (0.90 g, 2.02 mmol) in 40 mL of CH_2Cl_2 over 2 h (syringe pump). The resulting yellow solution was stirred for an additional 50 min before 50 mL of saturated aqueous $NaHCO_3$ was added, and the reaction mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with ether, and the combined extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatography (10 and then 25% Et_2O/hexanes) provided 0.55 g (61%) of **3.6** as an inseparable mixture of diastereomers: IR (film) ν 3466, 2201, 1665 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 5.16 (m, vinyl H), 4.94, 4.80 (bs, =CH_2), 4.60 (m, C*H*OR), 4.10 (C*H*OH), 2.60–1.50 (m, allylic), 1.65, 1.63, 1.61, 1.58 (s, vinyl Me's), 1.03 (s, i-Pr_3Si). Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.53; H, 10.79.

(7*E*,11*E*)-1-Isopropenyl-6-[(triisopropylsilyl)oxy]-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-one (3.7/3.8). The method of Swern was used[22] as described for aldehyde **3.5** with 0.18 g (0.40 mmol) of epimeric alcohols **3.6**. Flash chromatography (10% Et_2O/hexanes) provided 0.16 g (91%) of the acetylenic ketones as an inseparable 75:25 mixture of diastereomers **3.7** and **3.8**: IR (film) ν 2191, 1670 cm^{-1}. Anal. Calcd for $C_{28}H_{46}O_2Si$: C, 75.95; H, 10.47. Found: C, 75.79; H, 10.45.

3.7: ^1H-NMR (300 MHz, $CDCl_3$) δ 5.18 (d, J = 9.2 Hz, C=C*H*CHOR), 5.05 (m, vinyl H), 4.87 (bs, =CH_2), 4.64 (ddd, J = 14.0, 9.5, 4.6 Hz, C=CHC*H*OR), 3.29 (dd, J = 11.1, 3.1 Hz, COC*H*), 2.71 (dd, J = 17.4, 4.6 Hz, CCCH_2^a), 2.53 (dd, J = 17.5, 9.8 Hz, CCCH_2^b), 2.40–1.70 (m, allylic), 1.68, 1.64, 1.55 (s, vinyl Me's), 1.03 (bs, i-Pr_3Si).

3.8: Partial ^1H-NMR δ 5.30 (d, J = 8.2 Hz, C=C*H*OR), 4.86 (bs, =CH_2), 3.45 (dd, J = 11.0, 3.0 Hz, C=CHC*H*OR), 1.70, 1.60 (s, vinyl Me's).

***rel*-(1*R*,2*S*,6*S*,7*E*,11*E*)-1-Isopropenyl-6-[(triisopropylsilyl)oxy]-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-ol (3.9/3.10).** To a solution of ketones **3.7** and **3.8** (0.42 g, 0.95 mmol) in 20 mL of THF at −78 °C was added 4.7 mL of 1.0 M L-Selectride in THF over several min. The reaction mixture was stirred 1 h at −78 °C, then warmed to 0 °C, and treated dropwise successively with 50 mL of dilute NaOH and 5 mL of 30% H_2O_2 (slow addition—exothermic!). The resulting mixture was allowed to warm to room temperature, stirred for 2 h, and then saturated with solid K_2CO_3. The phases were separated, the aqueous phase was extracted with ether, and the combined extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatography (10% then 25% Et_2O/hexanes) provided 0.33 g (79%) of an inseparable 85:15 mixture of diastereomers **3.9** and **3.10**: IR (film) ν 3402 cm^{-1}. Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.69; H, 10.89.

3.9: ^1H-NMR (300 MHz, $CDCl_3$) δ 5.18 (d, J = 9.9 Hz, C=C*H*CHOR), 5.17 (bt, vinyl H), 4.94, 4.80 (s, =CH_2), 4.56 (ddd, J = 12.9, 9.8, 3.9 Hz, C=CHC*H*OR), 4.42 (bs, C*H*OH), 2.59 (ddd, J = 13.9, 2.0, 1.9 Hz, CCCH_2^a), 2.43 (ddd, J = 13.0, 10.0, 3.0 Hz, CCCH_2^b), 2.29–1.59 (m, allylic/homoallylic), 1.74, 1.59, 1.58 (s, vinyl Me's), 1.03 (bs, i-Pr_3Si).

3.10: Partial ^1H-NMR δ 5.35 (d, J = 8 Hz, C=C*H*CHOR), 4.46 (bs, C*H*OH), 1.77 (s, vinyl Me).

***rel*-(1*R*,2*R*,6*S*,7*E*,11*E*)-1-Isopropenyl-2-(benzoyloxy)-6-[(triisopropylsilyl)oxy]-8,12-dimethyl-7,11-cyclotetradecadien-3-yne (3.11).** To a solution of alcohols **3.9** and **3.10** (59 mg, 0.133 mmol) in 0.5 mL of cold anhydrous benzene was added 20 mg (0.16 mmol) of benzoic acid and 42 mg (0.16 mmol) of triphenylphosphine followed by dropwise addition of 33 uL (0.16 mmol) of diisopropyl azodicarboxylate (97%, Aldrich).[15] The reaction mixture was allowed to warm to room temperature over 5 h and purified directly by flash chromatography (hexanes and then 25% Et_2O/hexanes) affording 59 mg (81%) of benzoate **3.11**: IR (film) ν 3073, 2234, 1725 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7 Hz, ArH), 7.52 (d, J = 7.4 Hz, ArH), 7.40 (t, J = 7.7 Hz, ArH), 5.37 (d, J = 11.0 Hz, C*H*OBz), 5.21 (bt, $J \leq 1$ Hz, vinyl H), 5.19 (d, J = 8.9 Hz, C=C*H*CHOTIPS), 4.81,

(26) Prepared by Swern oxidation [22] of commercially available *trans, trans*-farnesol.

4.74 (s, =CH_2), 4.57 (m, C=CHC*H*OTIPS), 2.64–2.30 (m, $CCCH_2$ and methine), 2.30–1.80 (allylic), 1.30–1.50 (m, homoallylic), 1.66, 1.61, 1.54 (s, vinyl Me's). Anal. Calcd for $C_{35}H_{52}O_3Si$: C, 76.59; H, 9.55. Found: C, 76.68; H, 9.67.

***rel*-(1*R*,2*R*,6*S*,7*E*,11*E*)-1-Isopropenyl-2-(benzoyloxy)-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-6-ol (3.12).** To a solution of silyl ether **3.11** (0.64 g, 1.17 mmol) in 5 mL of THF at room temperature was added several drops of acetic acid followed by 2.50 mL of 1 M TBAF in THF. The reaction mixture was stirred for 1 h and then poured into 10 mL of saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic extracts were dried over Na_2SO_4 and filtered and the solvents were removed under reduced pressure. Purification by flash chromatography (25% Et_2O in hexanes then ether) afforded 0.38 g (84%) of alcohol **3.12** as a viscous oil: IR (film) ν 3400, 3073, 2234, 1725 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3 Hz, ArH), 7.52 (t, J = 8.0 Hz, ArH), 7.39 (d, J = 8.0 Hz, ArH), 5.38 (d, J = 10.8 Hz, C*H*OBz), 5.26 (d, J = 8.8 Hz, C=C*H*CHOH), 5.20 (bt, $J \leq 1$ Hz, vinyl H), 4.83, 4.77 (s, =CH_2), 4.52 (m, C*H*OH), 2.61 (bt, J = 11 Hz, methine), 2.57 (bd, J = 17 Hz, $CCCH_2^a$), 2.40 (dd, J = 16.3, 10.3 Hz, $CCCH_2^b$), 2.22–2.00 (m, allylic), 1.50 (m, homoallylic), 1.73, 1.61, 1.56 (s, vinyl Me's). Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.17; H, 8.66.

***rel*-(1*R*,2*R*,6*S*,7*E*,11*E*)-1-Isopropenyl-2-(benzoyloxy)-6-[(*tert*-butyldimethylsilyl)oxy]-8,12-dimethyl-7,11-cyclotetradecadien-3-yne (3.13).** To a solution of 0.110 g (0.280 mmol) of alcohol **3.12** in 2.5 mL of anhydrous DMF at room temperature was added successively 0.044 g (0.294 mmol) of imidazole and 0.021 g (0.308 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred for 14 h and then partitioned between 25 mL of water and 25 mL of ether. The aqueous phase was extracted with ether and the combined extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatography (hexanes then 5% Et_2O/hexanes) provided 0.12 g (86%) of silyl ether **3.13** as a viscous oil: IR (film) ν 3076, 1717 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8 Hz, ArH), 7.52 (d, J = 7 Hz, ArH), 7.41 (t, J = 8 Hz, ArH), 5.36 (d, J = 11.0 Hz, C*H*OBz), 5.23 (bt, vinyl H), 5.15 (d, J = 9.6 Hz, C=C*H*CHOTBS), 4.82, 4.75 (s, =CH_2), 4.49 (ddd, J = 13, 9.6, 4.0 Hz, C=CHC*H*OTBS), 2.67 (bt, J = 11 Hz, methine), 2.52 (dd, J = 16, 4 Hz, $CCCH_2^a$), 2.35 (dd, J = 16.5, 13.0 Hz, $CCCH_2^b$), 2.23–2.00 (m, allylic), 1.40 (m, homoallylic), 1.67, 1.61, 1.54 (s, vinyl Me's), 0.82 (s, t-BuSi), –0.04, –0.02 (s, Me_2Si); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.5, 143.1, 136.5, 133.3, 132.9, 130.4, 129.8, 129.1, 128.3, 121.5, 115.4, 82.9, 78.5, 68.0, 66.1, 50.0, 38.6, 32.7, 28.9, 25.9, 25.8, 23.8, 18.9, 18.1, 18.0, 16.3, –4.3, –4.7; HRMS (EI), calcd for $C_{32}H_{46}O_3Si$ 506.3316, found 506.3223.

***rel*-(1*R*,2*R*,6*S*,7*E*,11*E*)-1-Isopropenyl-6-[(*tert*-butyldimethylsilyl)oxy]-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-ol (3.14).** A mixture of 0.100 g (0.197 mmol) of benzoate **3.13** and a small amount of K_2CO_3 in 2.5 mL of MeOH was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the crude alcohol was purified by flash chromatography (5% then 25% ether/hexanes) affording 72 mg (94%) of alcohol **3.14** as a white solid. Recrystallization from MeOH/H_2O gave 50 mg as fine white needles: mp 99–100 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.17 (bt, $J \leq 1$ Hz, vinyl H), 5.16 (d, J = 9.3 Hz, =C*H*CHOTBS), 4.98, 4.78 (s, =CH_2), 4.53 (ddd, J = 10.6, 9.2, 4.1 Hz, =CHC*H*OTBS), 4.05 (bd, J = 10.5 Hz, C*H*OH), 2.56 (dd, J = 16.3, 4.0 Hz, $CCCH_2^a$), 2.40 (ddd, J = 16.3, 10.5, 4.0, 1.4 Hz, $CCCH_2^b$), 2.34–1.85 (m, allylic), 1.75–1.57 (m, homoallylic), 1.65, 1.61, 1.58 (s, vinyl Me's), 1.41–1.33 (m, methine), 0.84 (s, *t*-BuSi), –0.04, –0.01 (s, Me_2Si). Anal. Calcd for $C_{25}H_{42}O_2$: C, 74.56; H, 10.51. Found: C, 74.36; H, 10.61. The ^{1}H NMR spectrum was identical to that of an authentic sample of this material.[14]

(5*R*,6*R*,9*E*)-1,1-Dibromo-5,6-epoxy-6,10,14-trimethyl-1,9,13-pentadecatriene (4.2). To a solution of PPh_3 (5.56 g, 21.18 mmol) in 50 mL of CH_2Cl_2 at room temperature was added CBr_4 (3.51 g, 10.59 mmol) followed by TEA (5.9 mL, 42.40 mmol). The reaction mixture was cooled to –78 °C, and aldehyde **4.1**[18] (1.40 g, 5.30 mmol) was added as a solution in 10 mL of CH_2Cl_2. The reaction was allowed to warm to room temperature over 12 h and the burgundy colored solution was poured into 200 mL of stirring pentanes. The precipitated solids were removed by suction filtration and the filtrate was concentrated under reduced pressure providing the crude dibromide. Purification by flash chromatography (5% then 10% Et_2O/hexanes) afforded 2.04 g (91%) of **4.2** as a colorless oil: $[\alpha]^{21}_D$ +7.5° (*c* 4.05, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.42 (t, J = 7.3 Hz, $CHCBr_2$), 5.07 (m, vinyl H's), 2.71 (t, J = 6.3 Hz, epoxide OCH), 2.24 (t, J = 8.3 Hz, CH_2CHCBr_2), 2.09–1.96 (m, allylic), 1.70–1.58 (m, CH_2), 1.60, 1.58, 1.59 (s, vinyl Me's), 1.25 (s, epoxide Me); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.4, 135.6, 131.3, 124.2, 123.4, 89.8, 62.4, 60.8, 39.7, 38.7, 30.1, 27.1, 26.7, 25.7, 23.7, 17.7, 16.6, 16.0; HRMS (EI), calcd for $C_{18}H_{28}Br_2O$ 418.0507, found 418.0486.

(6*R*,7*R*,10*E*)-7,11,15-Trimethyl-6,7-epoxy-10,14-hexadecadien-2-ynal (4.3). To a solution of 1.80 g (4.28 mmol) of dibromide **4.2** in 10 mL of THF at –78 °C was added 3.60 mL (8.90 mmol) of 2.5 M *n*-BuLi in hexanes. The reaction was stirred for 0.5 h at –78 °C, warmed to 0 °C for 15 min, cooled back down to –78 °C, and treated dropwise with 1.70 mL (21.4 mmol) of anhydrous DMF. The cooling bath was removed, and the reaction mixture was stirred for 30 min at room temperature and then partitioned between 50 mL of saturated aqueous NH_4Cl and 50 mL of ether. The aqueous phase was extracted with ether and the combined organic extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatography (hexanes, then 10% Et_2O/hexanes) afforded 0.90 g (80%) of acetylenic aldehyde **4.3**: $[\alpha]^{21}_D$ +23.5° (*c* 4.40, $CHCl_3$); IR (film) ν 2276, 2205, 1666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.16 (s, CHO), 5.07 (m, vinyl H's), 2.81 (dd, J = 7.1, 5.5 Hz, epoxide OCH), 2.56 (t, J = 7.3 Hz, $CCCH_2$), 2.09–1.38 (m, CH_2's), 1.66, 1.58 × 2 (s, vinyl Me's), 1.27 (s, epoxide Me); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.9, 135.7, 131.4, 124.2, 123.3, 97.3, 81.8, 61.8, 61.2, 39.7, 38.6, 27.1, 26.6, 25.7, 23.7, 17.7, 16.7, 16.5, 16.0; HRMS (EI), calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2086.

(1*R*,2*S*,7*R*,8*R*,11*E*)-1-Isopropenyl-7,8-epoxy-8,12-dimethyl-11-cyclotetradecen-3-yn-2-ol (4.4/4.5). To a solution of $EtAlCl_2$·Et_2AlCl (2.52 mL, 2.29 mmol, 0.91 M in toluene) in 450 mL of anhydrous CH_2Cl_2 at –78 °C was added a solution of aldehyde **4.3** (0.50 g, 1.84 mmol) in 20 mL of CH_2Cl_2 over 2 h (syringe pump). The resulting yellow solution was stirred for an additional 30 min before 50 mL of saturated aqueous $NaHCO_3$ was added, and the reaction mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with ether (2 × 50 mL), and the combined extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatography (20% then 50% Et_2O/hexanes) provided 0.36 g (72%) of an inseparable 92:8 mixture of diastereomers **4.4** and **4.5**: $[\alpha]^{21}_D$ +5.8° (*c* 6.70, $CHCl_3$); IR (film) ν 3505, 3073 cm^{-1}; HRMS (EI), calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2095.

4.4: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.22 (bt, J = 7.9 Hz, vinyl H), 4.91, 4.85 (bs, =CH_2), 4.51 (bs, C*H*OH), 3.01 (dd, J = 6.7, 3.5 Hz, epoxide OCH), 2.39 (m, $CCCH_2$), 2.34–1.55 (m, CH_2), 1.75, 1.55 (s, vinyl Me's), 1.21 (s, epoxide Me), 1.08 (dt, J = 12.9, 3.5 Hz, methine); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.0, 136.7, 123.0, 113.5, 85.7, 80.8, 63.7, 62.5, 60.0, 51.9, 39.3, 37.4, 28.9, 28.5, 23.5, 22.0, 16.6, 16.5, 16.0.

4.5: Partial ^{1}H-NMR δ 4.45 (bs, C*H*OH), 3.10 (dd, J = 7.0, 3.7 Hz, epoxide OCH), 1.23 (s, epoxide Me); ^{13}C-NMR δ 145.1, 135.9, 123.3, 113.4, 64.0, 61.7, 59.9, 50.8.

(1*R*,2*R*,7*R*,8*R*,11*E*)-Isopropenyl-8,12-dimethyl-7,8-epoxy-2-[(*p*-nitrobenzoyl)oxy]-11-cyclotetradecen-3-yne (4.6). To a solution of alcohol **4.5** (0.200 g, 0.693 mmol) in 3 mL of cold anhydrous benzene was added 0.116 g (0.693 mmol) of *p*-nitrobenzoic acid and 0.182 g (0.693 mmol) of triphenylphosphine followed by dropwise addition of 0.14 mL (0.693 mmol) of diisopropyl azodicarboxylate (97%, Aldrich).[15] The reaction mixture was allowed to warm to room temperature over 1 h and purified directly by flash chromatography (hexanes then 25% Et_2O/hexanes) affording 0.24 g (82%) of benzoate **4.6** as a yellow solid. Recrystallization from hexanes afforded yellow needles: mp 135–136 °C; $[\alpha]^{21}_D$ +75.7° (*c* 3.25, $CHCl_3$); IR (film) ν 3077, 2236, 1728, 1528, 1266 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, Ar H), 8.16 (d, J = 9.1 Hz, ArH), 5.51 (dt, J = 10.0, 1.9 Hz, C*H*OCOAr), 5.30 (bt, J = 6.6 Hz, vinyl H), 4.82 (bs, =CH_2), 3.00 (dd, J = 6.7, 3.8 Hz, epoxide OCH), 2.61 (dt, J = 9.7, 4.0 Hz, $CCCH_2$), 2.45 (m, $CCCH_2CH_2$), 2.28–1.59 (m, CH_2), 1.64, 1.62 (s, vinyl Me's), 1.27 (s, epoxide Me), 1.15 (dt, J = 11.0, 3.4 Hz, methine). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14. Found: C, 71.40; H, 7.22.

(1*R*,2*R*,7*R*,8*R*,11*E*)-1-Isopropenyl-7,8-epoxy-8,12-dimethyl-11-cyclotetradecen-3-yn-2-ol (4.7). A mixture of 60 mg (0.137 mmol) of benzoate **4.6** and a small piece of solid NaOH in 5 mL of 2:1 (THF/H_2O) was stirred for 12 h at room temperature. The reaction mixture was partitioned between 10 mL of water and 25 mL of ether, and the aqueous layer was extracted with ether. The combined ether extracts were dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (50% ether/hexanes) afforded 36 mg (92%) of alcohol **4.7** as a solid: $[\alpha]^{21}_D$ +80.6° (*c* 1.80, $CHCl_3$); IR (film) ν 3540, 3076 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.24 (bt, J = 6.5 Hz, vinyl H), 4.92, 4.84 (s, $=CH_2$), 4.15 (dt, J = 10.2, 1.9 Hz, C*H*OH), 2.97 (dd, J = 6.6, 3.9 Hz, epoxide OCH), 2.43 (ddd, J = 6.8, 4.9, 1.9 Hz, $CCCH_2CH_2$), 2.25 (dt, J = 9.2, 3.5 Hz, $CCCH_2CH_2$), 2.19–1.56 (m, CH_2), 1.65, 1.56 (s, vinyl Me's), 1.24 (s, epoxide Me), 1.07 (dt, J = 13.0, 3.9 Hz, methine); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.1, 136.4, 122.9, 115.3, 85.3, 81.3, 64.1, 62.7, 60.2, 55.9, 39.3, 37.3, 29.8, 28.8, 23.6, 18.0, 16.6, 16.4 × 2.

(*S*)-(+)-Mandelate (4.8). To a mixture of alcohol **4.7** (11 mg, 0.038 mmol), DCC (12 mg, 0.57 mmol), and 8 mg (0.46 mmol) of (*S*)-(+)-mandelic acid was added 1 mL of anhydrous CH_2Cl_2. The resulting suspension was stirred 15 min and the solvents were removed under a stream of nitrogen. The crude reaction mixture was purified by flash chromatography (5, 20, and then 50% ether/hexanes) affording 14.6 mg (87%) of mandelate **4.8**: Partial ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.71 (s, C*H*OMe), 4.43, 4.03 (s, $=CH_2$), 1.53, 1.27 (s, vinyl Me's).

(*R*)-(−)-Mandelate (4.9). The foregoing procedure was followed. From 10.9 mg of alcohol **4.7**, 11.7 mg of DCC, and 8 mg of (*R*)-(−)-mandelic acid was obtained 11 mg (66%) of mandelate **4.9**: Partial ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.71 (s, $=CH_2$ and C*H*OMe), 1.56, 1.52 (s, vinyl Me's).

5-Methyl-5-hexenal (5.2).[20b] The method of Evans was employed.[20a] Potassium hydride (13.4 g, 0.117 mmol, 35% in mineral oil, Aldrich) was weighed into a flame-dried flask fitted with a reflux condenser. The mineral oil was next removed by washing the KH with dry hexanes under a stream of N_2, and 300 mL of anhydrous THF was added. Alcohol **5.1**[20b] (12.5 g, 0.111 mmol) was then added dropwise as a solution in 50 mL of THF over 15 min. After evolution of hydrogen ceased, the reaction was brought to a gentle reflux and maintained at that temperature for 36 h. The reaction mixture was cooled to −78 °C, carefully quenched dropwise with 50 mL of MeOH, and allowed to warm to room temperature. After the solids had dissolved, the mixture was poured into 300 mL of saturated aqueous NH_4Cl and extracted with ether. The ether extracts were dried over Na_2SO_4 and filtered, and the ether was removed by distillation. The crude product was purified by distillation affording 6.2 g (50%) of aldehyde **5.2** as a fragrant oil: bp 70–74 °C/10 torr:[20b] IR (film) ν 3073, 1725, 1643 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J = 1.7 Hz, CHO), 4.72, 4.66 (s, $=CH_2$), 2.42 (dt, J = 7.3, 1.7 Hz, CH_2CHO), 2.03 (t, J = 7.5 Hz, allylic), 1.81–1.76 (m, CH_2), 1.75 (s, vinyl Me).

7-Methyl-1,7-octadien-3-ol (5.3). A solution of aldehyde **5.2** (3.90 g, 34.8 mmol) in 50 mL of THF was added dropwise over 0.5 h to a solution of vinyllithium (19 mL, 2.2 M in THF) in 100 mL of THF at −78 °C. The reaction mixture was warmed to room temperature, poured into 200 mL of saturated ammonium chloride, and extracted with ether. The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (25% Et_2O/hexanes) afforded 4.9 g (100%) of allylic alcohol **5.3**: IR (film) ν 3378, 3073, 1648 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.85 (ddd, J = 16.7, 10.4, 6.2 Hz, $H_2C{=}CHCHOH$), 5.20 (ddd, J = 17.2, 2.8, 1.4 Hz, $C{=}CH_2^a$), 5.08 (ddd, J = 10.4, 2.7, 1.2 Hz, $C{=}CH_2^b$), 4.68, 4.65 (bs, $=CH_2$), 4.10 (m, C*H*OH), 2.02 (m, allylic), 1.69 (s, vinyl Me), 1.52 (m, CH_2). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.22; H, 11.40.

(4*E*)-Ethyl 9-Methyl-4,9-decadienoate (5.4). A mixture of alcohol **5.3**, a few drops of propionic acid, and 50 mL of triethyl orthoacetate, in a flask fitted with a short-path distillation apparatus, was heated to *ca.* 100 °C under a stream of N_2. Ethanol distilled first (90–100 °C) and the temperature of the heating bath was gradually raised until the remaining solvents distilled (*ca.* 120–150 °C). The residual oil was chromatographed directly, affording 3.5 g (74%) of ester **5.4** as a single isomer: IR (film) ν 3073, 1735, 1643 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.50–5.35 (m, HC=CH), 4.66, 4.63 (bs, $=CH_2$), 4.10 (q, J = 7.1 Hz, CH_2CH_3), 2.37–2.26 (m, $RO_2CH_2CH_2CH{=}$), 1.91–1.92 (m, allylic), 1.68 (s, vinyl Me), 1.50–1.40 (m, homoallylic), 1.23 (t, J = 7.1 Hz, CH_2CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.5, 146.0, 131.7, 128.7, 110.2, 60.5, 37.5, 34.7, 32.4, 28.3, 27.7, 22.7, 14.6.

(4*E*)-9-Methyl-4,9-decadienal (5.5). To a solution of ester **5.4** (1.80 g, 8.57 mmol) in 50 mL of Et_2O at −78 °C was added dropwise 9.0 mL of 1 M DIBAH in hexanes. The reaction mixture was stirred for several minutes, poured into 100 mL of dilute aqueous HCl, and shaken vigorously until the emulsion was broken. The phases were separated, the aqueous phase was extracted with ether, and the combined organic extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatograghy (10% ether/hexanes) provided 1.35 g (96%) of aldehyde **5.5** which was used directly without further purification: IR (film) ν 3073, 1725, 1648 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.7 Hz, CHO), 5.50–5.33 (m, HC=CH), 4.67, 4.63 (s, $=CH_2$), 2.48 (m, CH_2CHO), 2.33 (m, $=CCH_2CH_2CHO$), 1.97 (m, allylic), 1.68 (s, vinyl Me), 1.47 (m, homoallylic).

(5*E*)-10-Methyl-1,1-dibromo-1,5,10-undecatriene (5.6). The procedure described for dibromide **4.2** was followed with 8.80 g (33.7 mmol) of PPh_3 in 50 mL of CH_2Cl_2 at room temperature and 5.6 g (16.8 mmol) of CBr_4 followed by TEA (9.4 mL, 67.4 mmol) and aldehyde **5.5** (1.35 g, 8.12 mmol) in 5 mL of CH_2Cl_2. Purification by flash chromatography (hexanes and then 5% Et_2O/hexanes) afforded 1.9 g (75%) of dibromide **5.6** as a colorless oil: IR (film) ν 3076, 1651 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.36 (t, J = 7.0 Hz, $CH{=}CBr_2$), 5.49–5.33 (m, HC=CH), 4.68, 4.65 (s, $=CH_2$), 2.11 (m, $=CHCH_2CH_2C{=}$), 1.99 (m, allylic), 1.70 (s, vinyl Me), 1.48 (m, homoallylic); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.9, 138.2, 131.8, 128.5, 109.9, 88.8, 37.3, 33.0, 32.2, 30.8, 27.4, 22.5; HRMS (EI), calcd for $C_{12}H_{18}Br_2$ 319.9775, found 319.9778.

(6*E*)-11-Methy-6,11-dodecadien-2-ynal (5.7). The procedure described for ynal **4.3** was employed with 1.90 g (5.90 mmol) of dibromide **5.6**. Flash chromatography (hexanes and then 10% Et_2O/hexanes) afforded 0.90 g (80%) of acetylenic aldehyde **5.7**: IR (film) ν 3073, 2278, 2201, 1665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.16 (t, J = 0.8 Hz, CHO), 5.56–5.36 (m, HC=CH), 4.68, 4.64 (s, $=CH_2$), 2.44 (t, J = 7.1 Hz, $CCCH_2CH_2C{=}$), 2.26 (dt, J = 13.2, 6.8 Hz, $CCCH_2CH_2C{=}$), 1.98 (m, allylic), 1.68 (s, vinyl Me), 1.48 (m, homoallylic). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.95; H, 9.48.

(6*E*)-11-Methylene-6-cyclododecen-2-yn-1-ol (5.8). To a solution of $EtAlCl_2$ (0.52 mL, 0.52 mmol, 1 M in hexanes) in 85 mL of anhydrous CH_2Cl_2 at −78 °C was added a solution of aldehyde **5.7** (0.100 g, 0.523 mmol) in 5 mL of CH_2Cl_2 over 1 h (syringe pump). The resulting yellow solution was stirred for an additional 2 h before 10 mL of saturated aqueous $NaHCO_3$ was added, and the reaction mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with ether, and the combined extracts were dried over Na_2SO_4. Filtration and removal of the solvents under reduced pressure followed by flash chromatography (50% Et_2O in hexanes) afforded 0.093 g (93%) of alcohol **5.8**. When the reaction was carried out by adding 1 M $EtAlCl_2$ dropwise directly to the aldehyde in 5 mL of CH_2Cl_2, the yield of **5.8** was 56 mg (56%): IR (film) ν 3378, 3073, 3030, 2223, 1643 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.34 (dt, J = 15.0, 7.3 Hz, $CH{=}CH$), 5.20 (dt, J = 15.1, 6.9 Hz, $CH{=}CH$), 4.92, 4.79 (s, $=CH_2$), 4.39 (m, C*H*OH), 2.49–1.95 (allylic, propargylic), 1.48 (s, OH), 1.47 (m, homoallylic).

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Supplementary Material Available: Selected ^{1}H and ^{13}C NMR spectra for series **3.x**, **4.x**, **5.x**, **7.x**, and **8.x** compounds. Experimental procedures for series **7.x** and **8.x** compounds (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.