Total Syntheses of (±)-Isosteviol and (±)-Beyer-15-ene-3β,19-diol by Manganese(III)-Based Oxidative Quadruple Free-Radical Cyclization

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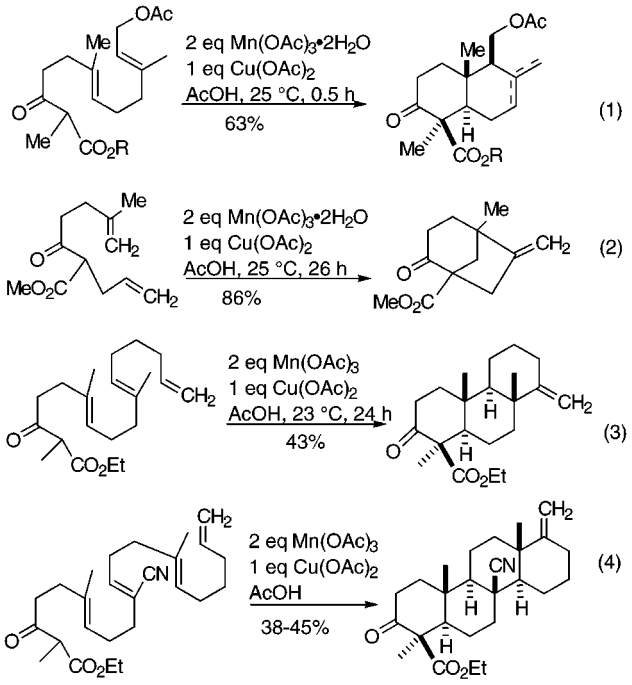
Tetraene **1** was prepared in nine steps from the known propargylic alcohol **7** in 17% overall yield or as a 2:1 *E*/*Z* mixture in only five steps in 7% overall yield. Oxidative cyclization of **1** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in MeOH at 25 °C provided 35% of tetracycle **2**. Further elaboration provided (±)-isosteviol (**3**) in six steps in 51% yield and (±)-beyer-15-ene-3β,19-diol in four steps in 17% yield.

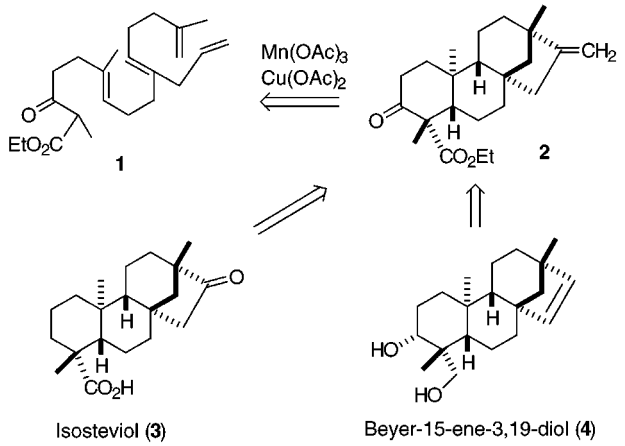
Introduction

We have shown that oxidation of unsaturated β-keto esters by $Mn(OAc)_3$ generates a radical that will cyclize to form five- to eight-membered rings.[1] The cyclic radical that is formed can be oxidized by $Cu(OAc)_2$ to generate an alkene. Tandem cyclizations can be carried out leading to *trans*-decalins (eq 1), bicyclo[3.2.1]octanes (eq



2), and other bicyclic systems; triple cyclizations also proceed efficiently.[2] Zoretic has extended these reactions to quadruple cyclizations and prepared fused tri- and tetracyclic precursors of (±)-isospongiadiol (eq 3),[3b] D-homosteroids (eq 4),[3c] and other natural products.[3]

We were interested in the possibility of using oxidative free-radical cyclizations to prepare tetracyclic diterpenes[4] containing both bridged and fused rings. Oxidative cyclization of **1** should give tetracycle **2**, which contains



the complete skeleton of, and suitable functionality for the syntheses of, isosteviol (**3**), the hydrolysis product of stevioside,[5] and *ent*-beyer-15-ene-3β,19-diol (**4**), which was isolated from the leaves of *Helichrysum dendroideum* N. H. Wakefield.[6]

Results and Discussion

Preparation of 10 and 11. Propargylic alcohol **7** was prepared by a modification of the Negishi procedure.[7] Methallylmagnesium chloride, prepared from magnesium turnings activated by mechanical stirring under N_2 for

(1) For reviews of $Mn(OAc)_3$ as an oxidant see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Melikyan, G. G. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 49, Chapter 3.

(2) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *Tetrahedron Lett.* **1987**, 841. (b) Snider, B. B.; Dombroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487. (c) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759.

(3) (a) Zoretic, P. A.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1162. (b) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z. *J. Org. Chem.* **1996**, *61*, 1806. (c) Zoretic, P. A.; Chen, Z.; Zhang, Y.; Ribeiro, A. A. *Tetrahedron Lett.* **1996**, 7909. (d) Zoretic, P. A.; Zhang, Y.; Ribeiro, A. A. *Tetrahedron Lett.* **1996**, 1751. (e) Zoretic, P. A.; Wang, M. *Synth. Commun.* **1996**, *26*, 2783 and references therein. (f) Zoretic, P. A.; Fang, H.; Riberio, A. A. *J. Org. Chem.* **1998**, *63*, 4779.

(4) For a review of diterpene synthesis see: Goldsmith, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 8, pp 1−243.

(5) (a) Mosettig, E.; Beglinger, U.; Dolder, F.; Lichti, H.; Quitt, P.; Waters, J. A. *J. Am. Chem. Soc.* **1963**, *85*, 2305. (b) Mosettig, E.; Nes, W. *J. Org. Chem.* **1955**, *20*, 884.

(6) Lloyd, H. A.; Fales, H. M. *Tetrahedron Lett.* **1967**, 4891.

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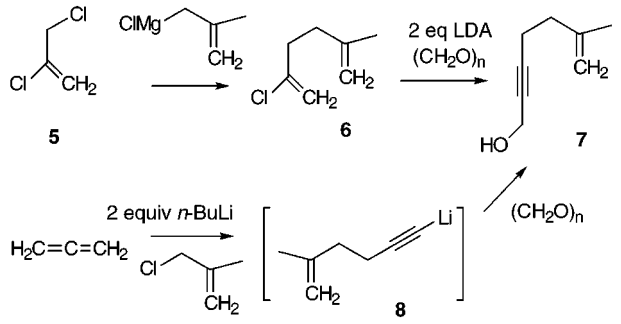
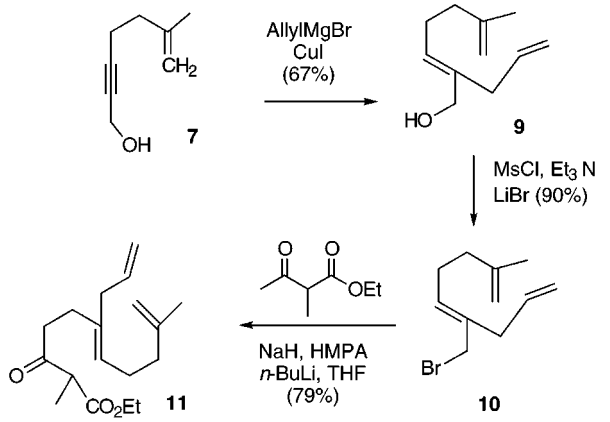


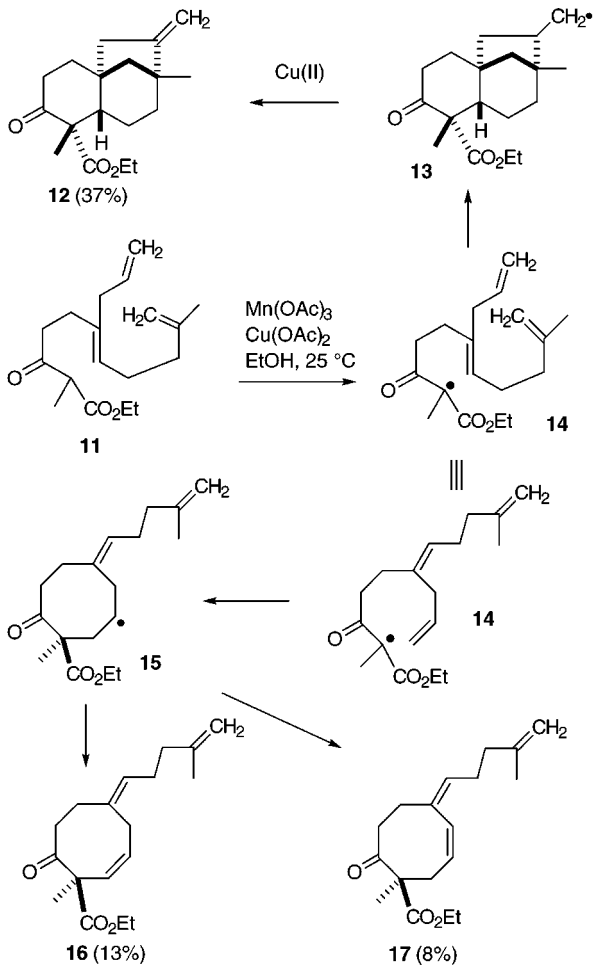
24 h,[8b] was treated with 2,3-dichloropropene (**5**) to give a mixture of 2-chloro-5-methyl-1,5-hexadiene (**6**) and 2,5-dimethyl-1,5-hexadiene, from coupling of the Grignard reagent with unreacted methallyl chloride, that was carried on to the next step without purification. Reaction of crude **6** with 2 equiv of LDA and 1.5 equiv of paraformaldehyde afforded propargylic alcohol **7** in 20−40% yield from **5**. Alternatively **7** was prepared in a single step from allene using the Hooz procedure.[9] Reaction of allene with 2 equiv of *n*-BuLi at −78 °C gave the propargyl dianion that was treated with methallyl chloride to give lithium acetylide **8**, which was treated with paraformaldehyde to provide the desired propargylic alcohol **7** in ≈30% unoptimized yield.

Addition of allylmagnesium bromide to **7** in the presence of a catalytic amount of CuI by the procedure of



Duboudin and Jousseaume[10] provided 67% of allylic alcohol **9** regio- and stereospecifically. The one-pot reaction of allylic alcohol **9** with MsCl, Et_3N, and LiBr afforded 90% of bromide **10**.[11] Before elaborating **10** to tetraene **1**, we chose to investigate the model triple cyclization of triene **11**. Alkylation of the dianion of ethyl 2-methylacetoacetate with bromide **10** provided *β*-keto ester **11** in 79% yield.

Oxidative Cyclization of 11. Treatment of **11** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in



EtOH at 25 °C gave 37% of the expected tricycle **12** accompanied by 8-*endo* cyclization products **16** (13%) and **17** (8%). The structure of **16** was assigned on the basis of characteristic peaks for the 4-methyl-4-pentenylidene side chain and an isolated 1,2-disubstituted cyclooctene double bond at δ 5.76 (d, 1, $J = 11.0$) and δ 5.66 (ddd, 1, $J = 11.0, 9.0, 8.4$) in the ^{1}H NMR spectrum. The data for **17** are similar to those of **16**, except that the chemical shift of the 1,2-disubstituted double bond protons at δ 6.11 (d, 1, $J = 10.5$) and δ 5.65 (ddd, 1, $J = 10.5, 9.8, 7.0$) indicated the presence of a conjugated diene.[12] This was confirmed by the UV spectrum of **17**, which showed the characteristic absorption at 222 nm ($\epsilon = 5500$) for a conjugated diene.

Oxidation of **11** gave acyclic keto radical **14**, which underwent two 6-*endo* cyclizations followed by a 5-*exo* cyclization to give tricyclic primary radical **13**, which was oxidized by $Cu(OAc)_2$ to provide **12**. 8-*Endo* cyclization of keto radical **14** to give cyclooctyl radical **15** is well-precedented.[13] Oxidation of radical **15** by $Cu(OAc)_2$ gave a mixture of **16** and **17**. The formation of **12** in synthetically useful yield indicated that the synthesis of bridged and fused rings can be combined, while the formation of cyclooctenes **16** and **17** indicated that cyclooctene formation might be a side reaction in the cyclization of **1**.

Synthesis of Tetraene 1. Having established that the triple cyclization of **11** was successful, we turned our

(7) (a) Negishi, E.; Zhang, Y.; Bagheri, V. *Tetrahedron Lett.* **1987**, *28*, 5793 and references therein. (b) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (c) Zhang, Y. Ph.D. Thesis, Purdue University, 1989.

(8) (a) Takacs, J. M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 5, p 3191. (b) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.

(9) Hooz, J.; Calzada, J. G.; McMaster, D. *Tetrahedron Lett.* **1985**, 271.

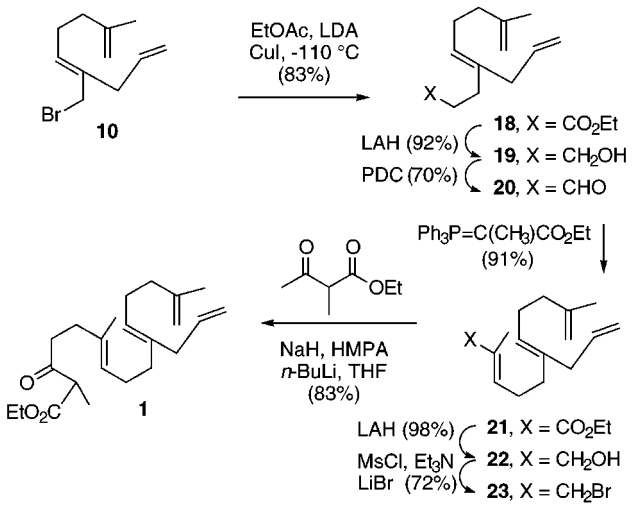
(10) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.

(11) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.

(12) These chemical shifts are very similar to those of 3-methylenecyclooctene: Stierman, T. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 3971.

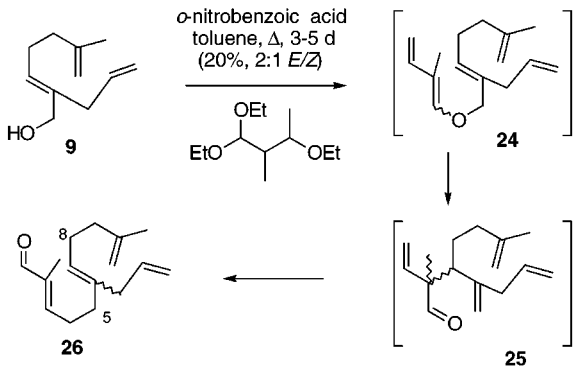
(13) Snider, B. B.; Merritt, J. E. *Tetrahedron* **1991**, *47*, 8663.

attention to the elaboration of bromide **10** to tetraene **1**.



Alkylation of the copper/lithium enolate of ethyl acetate with **10** by the procedure of Kuwajima and Doi[14] afforded 83% of unsaturated ester **18**. Reduction of **18** with LAH afforded 92% of alcohol **19**, which was oxidized with PDC to give 70% of aldehyde **20**. Reaction of aldehyde **20** with (carbethoxyethylidene)triphenylphosphorane provided 91% of *E*-isomer **21** stereospecifically,[15] which was reduced with LAH to give 98% of **22**. This sequence provided tetraenol **22** in 6 steps from trienol **9** in 44% overall yield.

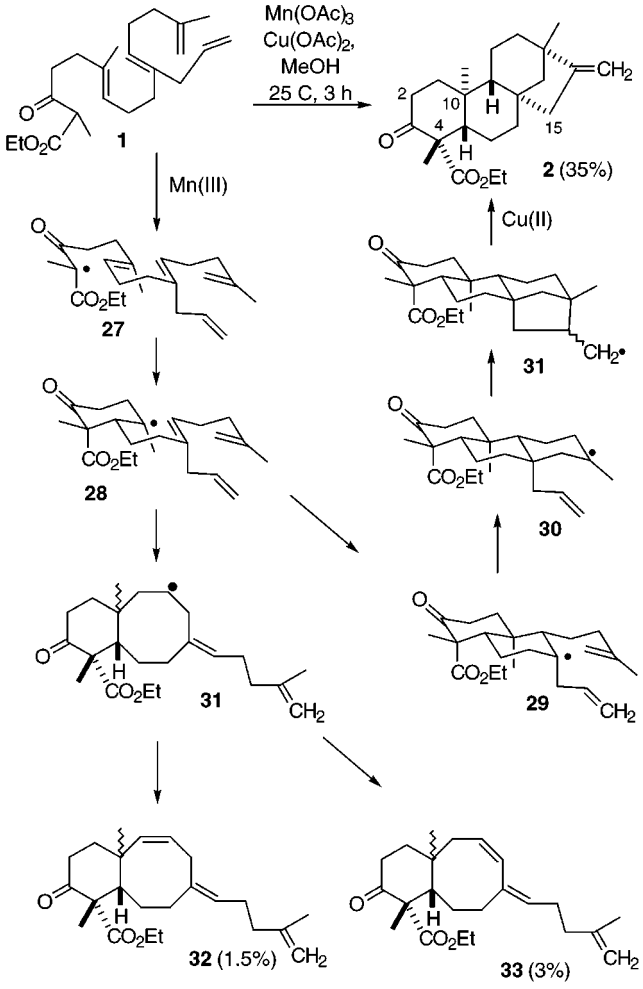
Alternatively, the Thomas tandem Claisen−Cope protocol[16] afforded tetraenol **22** in only 2 steps from trienol **9**, but in just 15% overall yield, as a 2:1 mixture of *E*/*Z* isomers at the central double bond. Heating a mixture of 1,1,3-triethoxy-2-methylbutane[16b] and allylic trienol **9** with a catalytic amount of *o*-nitrobenzoic acid in toluene at reflux for 3−5 d formed the dienyl allyl ether **24**, which



underwent a Claisen rearrangement to give **25** as a diastereomeric mixture. A Cope rearrangement of tetraene **25** gave the more stable conjugated aldehyde **26**, presumably as a mixture of four stereoisomers. Under the reaction conditions, the *Z*-enal isomerizes to the more stable *E*-enal,[16] so that **26** is formed as a 2:1 mixture of isomers at the central double bond in 20% yield. The aldehyde protons of **26** absorb at δ 9.38 and 9.39 indicating that the enal is *E*, since *Z*-enals absorb at δ 10.1. The allylic carbons absorb at δ 35.5 (C_5) and δ 34.8 (allyl CH_2) in the *E*-isomer and at δ 28.5 (C_5) and δ 41.4 (allyl CH_2) in the *Z*-isomer. The allyl CH_2 carbon is shifted upfield by 7 ppm by the γ-interaction with C_8 in the *E*-isomer, while C_5 is shifted upfield by 7 ppm in the *Z*-isomer. Reduction of **26** with LAH afforded 91% of **22** as a 2:1 *E*/*Z* mixture of tetraenols that was carried on to **1**.

Tetraenol **22** was converted to 72% of bromide **23** by treatment with MsCl, Et_3N, and LiBr. Alkylation of the dianion of ethyl 2-methylacetoacetate with **23** afforded 83% of tetraene **1**, which is available in nine steps from propargyl alcohol **7** in 17% overall yield or as a 2:1 *E*/*Z* mixture in only five steps from **7** in 7% overall yield.

Oxidative Quadruple Cyclization of 1. β-Keto ester **1** was treated with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and



1 equiv of $Cu(OAc)_2$ in MeOH at 25 °C to provide a complex mixture of the desired tetracycle **2** and partially cyclized compounds. Purification by chromatography on silver nitrate impregnated silica gel gave 35% of pure **2** as a white crystalline solid, followed by the tetracycle epimeric at C_4 (0.4%), bicyclo[6.4.0]dodecanes **32** (1.5%) and **33** (3%), and partially cyclized products that could not be characterized. A similar oxidative cyclization of the 2:1 mixture of *E*/*Z* isomers of **1** gave 20% of the desired ester **2**, followed by 1% of **32**, 2% of **33**, and uncharacterized partially cyclized products.

(14) (a) Kuwajima, I.; Doi, Y. *Tetrahedron Lett.* **1972**, 1163. (b) Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915.

(15) Horner−Emmons reaction of aldehyde **20** with triethyl 2-phosphonopropionate yielded 84% of α,β-unsaturated ester **21** as a 1.3:1 mixture of *E*- and *Z*-isomers.

(16) (a) Thomas, A. F. Swiss Patent 510,602, 1971. (b) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281. (c) Thomas, A. F. *Chem. Commun.* **1967**, 947. (d) Cookson, R. C.; Rogers, N. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2741.

The structure of tetracycle **2** was established by 2D NMR experiments and confirmed by X-ray crystallographic structure determination.[17] The NOESY spectrum showed cross-peaks between the C_{10} methyl group at δ 1.06 and H_{2ax} at δ 2.94 and H_{15} at δ 2.81 establishing that the C_{10} methyl group and the 2-carbon bridge are cis to each other and axial on the B-ring. The absence of a cross-peak between the C_{10} and C_4 methyl groups indicated that the ester is axial. X-ray crystallographic structure determination confirmed the stereochemical assignment of **2**.

The structure of the epimeric tetracycle was tentatively assigned on the basis of 1D NOESY experiments, which showed an NOE between the C_{10} methyl group at δ 1.07 and the C_4-methyl group at δ 1.34 and between H_{15} at δ 2.80 and the C_{10} methyl group. The structures of **32** and **33** were assigned by analogy to **16** and **17**. The cyclooctene protons of **33** absorb at δ 6.42 and 5.47, while those of **32** absorb at δ 5.76 and 5.66.

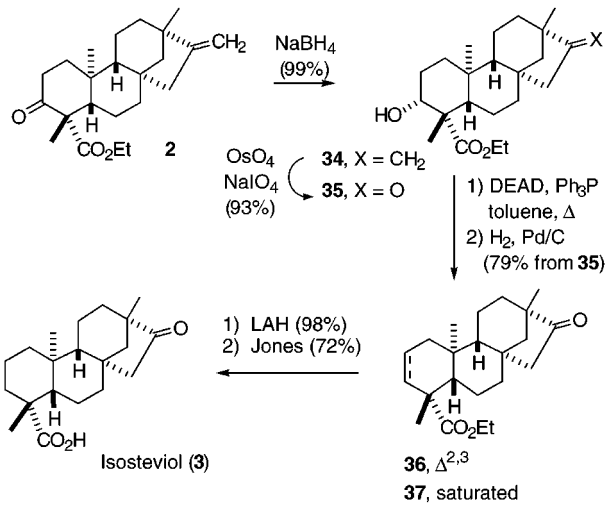
Reaction of β-keto ester **1** with $Mn(OAc)_3 \cdot 2H_2O$ gave keto radical **27** that underwent a 6-*endo* cyclization to produce tertiary radical **28**. A second 6-*endo* cyclization established the *trans*-AB ring fusion, providing radical **29**. A third 6-*endo* cyclization provided **30** with *trans*-BC ring fusion. Finally, **30** cyclized 5-*exo* since the double bond is unsubstituted giving tetracyclic primary radical **31** as a mixture of stereoisomers, both of which were oxidized by $Cu(OAc)_2$ to afford **2**. The final 5-*exo* cyclization unambiguously established that oxidation is occurring after the fourth radical cyclization rather than during the sequence since cyclization of the cation analogous to **30** would have given a cyclohexyl cation.

Synthesis of Isosteviol (3). To elaborate **2** to isosteviol (**3**) we had to remove the carbonyl group, oxidatively cleave the exocyclic double bond to a ketone, and hydrolyze the ethyl ester. The Clemmensen and Wolff–Kishner procedures were not compatible with the ester and alkene functionality of **2**. The ketone of **2** was therefore reduced with $NaBH_4$ to give 99% of alcohol **34**. Barton–McCombie radical deoxygenation procedures proceeded poorly, so we decided to remove the hydroxyl group by dehydration followed by hydrogenation.

The exocyclic double bond of **34** was oxidatively cleaved with OsO_4 and $NaIO_4$ to provide 93% of hydroxy keto ester **35**. Elimination was accomplished under Mitsunobu conditions in the absence of a nucleophile as described by Aranda and Lallemand.[18] Reaction of **35** with DEAD and Ph_3P in refluxing THF provided **36** in good yield, which was most easily purified after hydrogenation that afforded pure **37** in 79% yield from **35**.

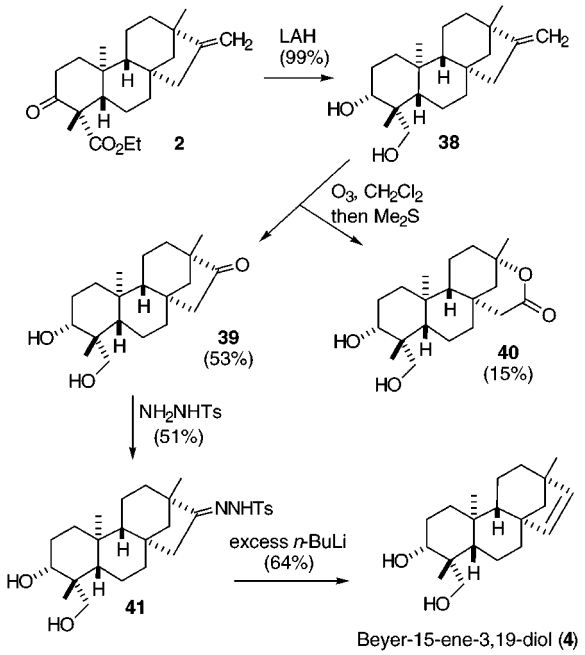
Ester **37** was resistant to basic hydrolysis, so isosteviol was prepared by reduction to the diol with LAH (98%) followed by Jones' oxidation (72%) to give isosteviol (**3**). The ^1H and ^{13}C NMR spectral data of synthetic **3** are identical to those of isosteviol obtained by acid hydrolysis of stevioside.[5] Isosteviol was prepared from tetracycle **2** in 6 steps in 51% overall yield.

Synthesis of Beyer-15-ene-3β,19-diol (4). To elaborate **2** to diol **4** we had to reduce the ketone and ester groups to a 1,3-diol, oxidatively cleave the exocyclic double bond, and form the cyclopentene double bond.



Previous beyer-15-ene syntheses have established that introduction of the double bond by elimination proceeds in poor yield under forcing conditions.[19] We therefore decided to introduce the double bond from the tosylhydrazone by the Shapiro reaction.[20]

Keto ester **2** was reduced with LAH to give 99% of diol **38** stereospecifically. Ozonolysis of unprotected diol **38**



followed by reductive workup with Me_2S provided a mixture of the desired ketone **39** (53%) and the anomalous ozonolysis product,[21a] lactone **40** (15%). Formation of lactones by anomalous ozonolysis of 16-kaurene derivatives is well-known.[21b,c] The structure of **40** was established on the basis of the downfield shift of the C_{13} methyl group from δ 0.98 in **39** to δ 1.35 in **40** and the characteristic δ-lactone IR absorption at 1732 cm^{-1} (cyclopentanone **39** absorbs at 1741 cm^{-1}). Oxidative

(17) X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

(18) Aranda, G.; Lallemand, J.-Y.; Azerad, R.; Maurs, M.; Cortes, M.; Ramirez, H.; Vernal, G. *Synth. Commun.* **1994**, *24*, 2525.

(19) Ireland, R. E.; Mander, L. N. *Tetrahedron Lett.* **1965**, 2627; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1970**, 3287.

(20) Shapiro, R. H. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1976; Vol. 23, Chapter 3.

(21) (a) Bailey, P. S. In *Ozonation in Organic Chemistry*; Trahanovsky, W., Ed.; Academic: New York, 1978; Vol. 1, pp 147–183. (b) Bailey, P. S. *Chem. Ber.* **1955**, *88*, 795. (c) Hanson, J. R. *J. Chem. Soc.* **1963**, 5061.

cleavage of diol **38** with OsO_4 and $NaIO_4$ was investigated since lactone **40** would not be formed with these reagents. Unfortunately, the primary alcohol was partially oxidized to the aldehyde under these conditions, and **39** was obtained in lower yield than by ozonolysis.

Reaction of keto diol **39** with $TsNHNH_2$ gave 51% of tosylhydrazone **41**, which was treated with 20 equiv of *n*-BuLi to provide 64% of beyer-15-ene-3β,19-diol (**4**). The structure of **4** was established by the identity of the ^1H NMR spectral data to those of the natural product[6] and the similarity of the ^{13}C NMR spectral data to those of closely related beyer-15-enes.[22−24] Diol **4** was prepared from **2** in 4 steps in 17% overall yield.

In conclusion, we have established that quadruple oxidative free-radical cyclization of **1** provides a practical route to **2**, which has the tetracyclic skeleton of the beyerane diterpenes and showed that **2** can be elaborated to complete the first syntheses of (±)-isosteviol (**3**) and beyer-15-ene-3β,19-diol (**4**). This work further demonstrates the synthetic utility of stereospecific Mn(III)-based oxidative free-radical polycyclizations for the preparation of synthetically useful fused and bridged polycyclic systems.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$ at 300 and 400 MHz unless otherwise indicated. Chemical shifts are reported in δ, coupling constants are reported in Hz, and IR data are reported in cm^{-1}.

6-Methyl-6-hepten-2-yn-1-ol (7) was prepared by a modification of Negishi's procedure.[7] Mg turnings (21 g, 860 mmol) were stirred under N_2 for 2 d in a three-neck 1 L round-bottom flask supplied with a mechanical stirrer and addition funnel.[8b] Freshly distilled ether (250 mL) was added, and the mixture was cooled to 0 °C. Methallyl chloride (28 mL, 284 mmol) was slowly added to the reaction over 30 h. The resulting reaction, containing some gray precipitate, was warmed to room temperature during the addition. Stirring was continued for 2 h at room temperature, and then the precipitate was allowed to settle. The clear solution was transferred via cannula under N_2 into another three-neck 1 L flask equipped with a condenser. The precipitate was washed with ether, and the clear solution was combined with the first portion of the methallylmagnesium chloride solution.

A solution of 2,3-dichloro-1-propene (**5**) (15 mL, 163 mmol) in THF (250 mL) was slowly added to the solution of methallylmagnesium chloride. During the addition the reaction mixture began to reflux. After addition was complete, the reaction was stirred at mild reflux overnight. The reaction was cooled to 0 °C and quenched with 1 M HCl. The resulting mixture was separated, and the aqueous phase was extracted with ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was partially evaporated giving a 4:1 mixture of 2-chloro-5-methyl-1,5-hexadiene (**6**) and 2,5-dimethyl-1,5-hexadiene. The ^1H NMR spectral data for **6** are identical to those reported by Negishi.[7]

The above solution containing **6** was added to a solution of LDA, prepared from diisopropylamine (36.5 mL, 279 mmol) and *n*-BuLi (2.5 M in hexane, 102 mL, 255 mmol) in THF (400 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C, warmed to room temperature, and stirred for another 1.5 h. A solution of paraformaldehyde (4.2 g, 140 mmol) in THF (5 mL) was added via cannula. The resulting mixture was stirred for 30 min, quenched with 1 M HCl, and extracted with ether. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). The solvent was partially removed giving 12.1 g of a 1:1 mixture of **7** and THF, which was carried on to the next step because of the volatility of **7**. The ^1H NMR spectral data of **7** are identical to those reported by Negishi.[7]

6-Methyl-2-(2-propenyl)-2*E*,6-heptadien-1-ol (9). Allylmagnesium bromide (1.0 M in ether, 122 mL, 122 mmol) was added dropwise to the above mixture of propargyl alcohol **4** and THF and CuI (929 mg, 4.9 mmol) in 100 mL of ether at −10 °C. The reaction was warmed to room temperature and stirred for 8 h. The resulting black solution was cooled to 0 °C, quenched with saturated NH_4Cl, and extracted with ether. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent provided crude **9** which was purified by flash chromatography on silica gel (6:1 hexane/EtOAc) to afford 3.45 g of pure alcohol **9** followed by 3.0 g of 65% pure **9**. The calculated yield of **9** is 20% from **5**: ^1H NMR 5.79 (ddt, 1, J = 17.0, 10.0, 6.4), 5.51 (br t, 1, J = 6.9), 5.06 (br d, 1, J = 17.0), 5.01 (br d, 1, J = 10.0), 4.72 (br s, 1), 4.69 (br s, 1), 4.02 (br s, 2), 2.87 (br d, 2, J = 6.4), 2.30−1.95 (m, 4), 1.75 (s, 3); ^{13}C NMR 145.3, 136.6, 135.8, 127.4, 115.4, 110.1, 66.9, 37.5, 32.5, 25.6, 22.4; IR (neat) 3332, 3075, 1649, 993, 912, 887.

1-Bromo-6-methyl-2-(2-propenyl)-2*E*,6-heptadiene (10). Et_3N (5.05 mL, 36.2 mmol) was added dropwise to a mixture of alcohol **10** (3.0 g, 18.1 mmol) and MsCl (1.82 mL, 23.5 mmol) in 130 mL of THF at −45 °C. The reaction was stirred for 45 min, warmed to 0 °C, and treated with a solution of LiBr (6.3 g, 72.4 mmol) in 20 mL of THF, which was added via cannula. The resulting mixture was stirred for 1 h at 0 °C, diluted with ice-cold water, and extracted with hexane. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure giving 3.96 g of crude **10**. Purification by flash chromatography on silica gel (4:1 hexane/EtOAc) afforded 3.75 g (90%) of pure bromide **10**: ^1H NMR 5.74 (ddt, 1, J = 16.6, 10.0, 6.6), 5.69 (br t, 1, J = 7.0), 5.09 (br d, 1, J = 16.6), 5.05 (br d, 1, J = 10.0), 4.73 (br s, 1), 4.68 (br s, 1), 3.99 (br s, 2), 2.97 (d, 2, J = 6.6), 2.30−2.00 (m, 4), 1.72 (s, 3); ^{13}C NMR 144.8, 134.9, 133.9, 132.4, 116.3, 110.4, 39.2, 37.0, 32.6, 26.2, 22.4; IR (neat) 3076, 1649, 994, 916, 889. Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48. Found: C, 57.65; H, 7.42.

Ethyl 2,10-Dimethyl-3-oxo-6-(2-propenyl)-6*E*,10-undecadienoate (11). A solution of ethyl 2-methylacetoacetate (1.54 mL, 11.0 mmol) in 3 mL of THF was added dropwise at −78 °C to a solution of LDA, which was prepared from freshly distilled diisopropylamine (3.2 mL, 24.2 mmol) and *n*-BuLi (2.5 M in hexane, 8.8 mL, 22.0 mmol) in 12 mL of THF at −5 °C and then cooled to −78 °C. The resulting mixture was stirred for 1 h at −78 °C and then warmed to −50 °C. DMPU (2.82 g, 22.0 mmol) was added to the reaction followed by a solution of bromide **10** (500 mg, 2.2 mmol) in 5 mL of THF. The mixture was slowly warmed to room temperature, stirred for an additional 30 min, and quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent afforded crude **11**, which was purified by flash chromatography on silica gel (12.5:1 hexane/EtOAc) giving 507 mg (79%) of β-keto ester **11**: ^1H NMR 5.73 (ddt, 1, J = 16.5, 10.0, 6.4), 5.21 (br t, 1, J = 6.7), 5.04 (br d, 1, J = 16.5), 5.00 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.67 (br s, 1), 4.19 (q, 2, J = 7.1), 3.51 (q, 1, J = 7.2), 2.78 (br d, 2, J = 6.4), 2.66 (dt, 1, J = 17.3, 7.9), 2.60 (dt, 1, J = 17.3, 7.9), 2.28 (br t, 2, J = 7.9), 2.13 (br dt, 2, J = 6.7, 6.8), 2.02 (br t, 2, J = 6.8), 1.71 (s, 3), 1.33 (d, 3, J = 7.2), 1.27 (t, 3, J = 7.1); ^{13}C NMR 205.3, 170.5, 145.4, 135.8, 135.3, 126.1, 115.4, 110.0, 61.2, 52.8, 40.1, 37.7, 35.0, 30.6, 25.9, 22.4, 14.0, 12.7; IR (neat) 3076, 1743, 1715, 1649, 889.

Oxidative Cyclization of 11. A solution of β-keto ester **11** (419 mg, 1.43 mmol) in 5 mL of EtOH was added to a degassed solution of $Mn(OAc)_3 \cdot 2H_2O$ (786 mg, 2.93 mmol) and $Cu(OAc)_2$ (260 mg, 1.43 mmol) in 9 mL of EtOH. The reaction was stirred at room temperature overnight. The resulting blue solution, containing some white precipitate, was diluted with

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water and extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$, water, and brine and dried ($MgSO_4$). Removal of the solvent afforded 415 mg of crude product. Flash chromatography on silica gel (50:1 hexane/EtOAc) afforded 291 mg of a mixture of **12**, **16**, and **17**. Further purification of this mixture by flash chromatography on silica gel (2:1 benzene/CH_2Cl_2) afforded 21 mg of pure **17**, followed by 7.8 mg of a 3:1:2 mixture of **12**, **16**, and **17**, and 131 mg of pure **12**.

Oxidative cyclization of **11** (100 mg, 0.34 mmol) under the same conditions gave 90 mg of crude product, which was purified by flash chromatography on silica gel (12.5:1 hexane/EtOAc) affording 2.9 mg of 80% pure **16**, followed by 3.4 mg of pure **16**, 1.5 mg of a 1:2.3 mixture of **12** and **16**, 6.6 mg of a 4.5:2:1 mixture of **12**, **16**, and **17**, 13.3 mg of a 5:1.5:1 mixture of **12**, **16**, and **17**, 11.6 mg of a 7:1:1.2 mixture of **12**, **16**, and **17**, 6.6 mg of a 19:1:4.2 mixture of **12**, **16**, and **17**, and 13.6 mg of a 4.2:1 mixture of **12** and **17**. The calculated yields are 36 mg (37%) of **12**, 12.7 mg (13%) of **16**, and 7.4 mg (8%) of **17**.

Data for ethyl (1α,4a*β*,7*β*,9a*β*)-decahydro-1,7-dimethyl-6-methylene-3-oxo-4a,7-methano-4aH-benzocycloheptane-1-carboxylate (**12**): ^{1}H NMR 4.79 (br s, 1), 4.69 (br dd, 1, J = 2.2, 2.2), 4.25−4.06 (m, 2), 2.93 (ddd, 1, J = 14.4, 6.9, 6.9), 2.94−2.80 (m, 1), 2.45 (ddd, 1, J = 14.4, 3.8, 3.8), 2.09 (dt, 1, J = 17.1, 2.4), 1.88−1.13 (m, 8), 1.54 (dd, 1, J = 11.0, 2.2), 1.33 (s, 3), 1.27 (t, 3, J = 7.1), 1.09 (s, 3); ^{13}C NMR 209.5, 172.4, 158.0, 102.5, 61.0, 58.0, 55.5, 53.5, 44.1, 41.0, 40.6, 39.9, 38.7, 37.0, 23.6, 23.4, 21.3, 13.9; IR (neat) 3070, 1714, 1653, 874. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.44; H, 8.85.

Data for ethyl 1-methyl-5-(4-methyl-4-pentenylidene)-8-oxo-2-cyclooctene-1-carboxylate (**16**): ^{1}H NMR 5.76 (d, 1, J = 11.0), 5.66 (ddd, 1, J = 11.0, 9.0, 8.4), 5.21 (br t, 1, J = 7.1), 4.73 (br s, 1), 4.69 (br s, 1), 4.27−4.09 (m, 2), 2.76 (dd, 1, J = 13.7, 8.4), 2.71−2.39 (m, 4), 2.38 (dd, 1, J = 13.7, 9.0), 2.23−2.00 (m, 4), 1.73 (s, 3), 1.47 (s, 3), 1.24 (t, 3, J = 7.2); ^{13}C NMR 211.2, 171.5, 145.3, 134.6, 129.0, 128.5, 125.6, 110.1, 61.7, 61.5, 39.3, 38.1, 37.8, 28.3, 26.0, 22.5, 21.7, 14.0; UV (EtOH) λ_{max} (ϵ) 199 nm (14 100).

Data for ethyl 1-methyl-5-(4-methyl-4-pentenylidene)-8-oxo-3-cyclooctene-1-carboxylate (**17**): ^{1}H NMR 6.11 (d, 1, J = 10.5), 5.65 (ddd, 1, J = 10.5, 9.8, 7.0), 5.39 (br t, 1, J = 6.4), 4.71 (br s, 1), 4.66 (br s, 1), 4.26−4.08 (m, 2), 3.07 (dd, 1, J = 13.7, 9.8), 2.72 (ddd, 1, J = 13.7, 13.5, 4.9), 2.54−2.30 (m, 3), 2.25 (dd, 1, J = 13.7, 7.0), 2.14−1.97 (m, 4), 1.7 (s, 3), 1.32 (s, 3), 1.24 (t, 3, J = 7.1); ^{13}C NMR 208.1, 172.9, 145.2, 135.6, 132.4, 129.6, 126.0, 110.1, 62.1, 61.3, 40.8, 37.1, 35.2, 32.0, 26.7, 22.4, 18.6, 14.0; IR (neat) 3074, 1714, 1650; UV (EtOH) λ_{max} (ϵ) 222 (5500), 199 (13 000).

Ethyl 8-Methyl-4-(2-propenyl)-4*E*,8-nonadienoate (18). A solution of LDA prepared from diisopropylamine (2.5 mL, 19.1 mmol) and *n*-BuLi (2.5 M in hexane, 7 mL, 17.4 mmol) in 10 mL of THF at −5 °C was slowly added to a stirred suspension of EtOAc (1.7 mL, 17.4 mmol) and CuI (6.7 g, 34.8 mmol) in 27 mL of THF at −110 °C. After the addition was complete, the mixture was warmed to −30 °C and a solution of bromide **10** (2.0 g, 8.7 mmol) in 7 mL of THF was added dropwise. The reaction was stirred at −30 °C for 1 h and then poured into 250 mL of water. Saturated NH_4Cl was added to the resulting mixture, and it was extracted with hexane. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure affording 189 mg (83%) of 90% pure **18** that was used for the next step. An analytical sample was prepared by flash chromatography on silica gel (49:1 hexane/EtOAc): ^{1}H NMR 5.73 (ddt, 1, J = 16.5, 10.0, 6.4), 5.24 (br t, 1, J = 6.8), 5.04 (br d, 1, J = 16.5), 5.00 (br d, 1, J = 10.0), 4.70 (br s, 1), 4.66 (br s, 1), 4.11 (q, 2, J = 7.1), 2.79 (d, 2, J = 6.4), 2.44−2.26 (m, 4), 2.20−1.98 (m, 4), 1.71 (s, 3), 1.25 (t, 3, J = 7.1); ^{13}C NMR 173.3, 145.3, 135.8, 135.2, 126.0, 115.3, 110.0, 60.1, 37.7, 34.8, 33.1, 31.9, 25.9, 22.4, 14.2; IR (neat) 3077, 1737, 913, 888. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.82; H, 10.26.

8-Methyl-4-(2-propenyl)-4*E*,8-nonadien-1-ol (19). LAH (339 mg, 8.9 mmol) was added to a solution of crude **18** (2.1 g, 8.9 mmol) in 75 mL of ether at 0 °C. The resulting mixture was warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C, and 0.4 mL of water was added, followed by 0.4 mL of 15% aqueous NaOH and 1.2 mL of water. Filtration of the resulting suspension afforded 1.58 g (92%) of **19**: ^{1}H NMR 5.74 (ddt, 1, J = 16.5, 10.0, 6.4), 5.25 (br t, 1, J = 6.7), 5.04 (br d, 1, J = 16.5), 4.99 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.68 (br s, 1), 3.62 (t, 2, J = 6.4), 2.79 (d, 2, J = 6.4), 2.22−1.92 (m, 6), 1.74−1.54 (m, 2), 1.72 (s, 3); ^{13}C NMR 145.5, 136.4, 136.1, 125.8, 115.2, 109.9, 62.7, 37.8, 34.7, 33.1, 30.8, 25.9, 22.4; IR (neat) 3332, 3075, 1649, 1638, 993, 911, 887. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.26; H, 11.33.

8-Methyl-4-(2-propenyl)-4*E*,8-nonadien-1-al (20). PDC (19.0 g, 50.5 mmol) was added to a solution of alcohol **19** (90% pure) (2.45 g, 12.6 mmol) in 250 mL of CH_2Cl_2, and the resulting mixture was stirred overnight. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure affording 1.97 g (80%) of crude **20**. Purification by flash chromatography on silica gel (50:1 hexane/EtOAc) gave 1.51 g (70%) of pure **20**: ^{1}H NMR 9.74 (t, 1, J = 1.8), 5.73 (ddt, 1, J = 16.5, 10.0, 6.4), 5.23 (br t, 1, J = 6.8), 5.04 (br d, 1, J = 16.5), 5.01 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.67 (br s, 1), 2.80 (d, 2, J = 6.4), 2.52 (br t, 2, J = 7.9), 2.33 (br t, 2, J = 7.9), 2.20−1.90 (m, 4), 1.71 (s, 3); ^{13}C NMR 202.3, 145.2, 135.6, 134.8, 126.3, 115.5, 110.0, 42.0, 37.7, 34.9, 29.1, 25.8, 22.3; IR (neat) 3076, 2718, 1726, 1648, 1637, 994, 912, 888. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.39; H, 10.49.

Ethyl 2,10-Dimethyl-6-(2-propenyl)-2*E*,6*E*,10-undecatrienoate (21). A mixture of aldehyde **20** (2.9 g, 15.1 mmol) and (carbethoxyethylidene)triphenylphosphorane (10.97 g, 30.3 mmol) in toluene (200 mL) was heated at 110 °C for 2 h. Toluene was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (12.5:1 hexane/EtOAc) giving 3.8 g (91%) of pure **21**: ^{1}H NMR 6.73 (dt, 1, J = 1.4, 7.3), 5.73 (ddt, 1, J = 16.6, 10.0, 6.4), 5.24 (br t, 1, J = 7.0), 5.04 (br d, 1, J = 16.6), 5.00 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.67 (br s, 1), 4.18 (q, 2, J = 7.1), 2.80 (d, 2, J = 6.4), 2.26 (dt, 2, J = 7.3, 7.3), 2.20−1.97 (m, 6), 1.82 (s, 3), 1.71 (s, 3), 1.28 (t, 3, J = 7.1); ^{13}C NMR 168.0, 145.3, 141.7, 136.0, 135.8, 127.7, 126.1, 115.2, 110.0, 60.2, 37.8, 35.4, 34.8, 27.3, 25.9, 22.3, 14.2, 12.3; IR (neat) 3076, 1711, 1649, 911, 888.

2,10-Dimethyl-6-(2-propenyl)-2*E*,6*E*,10-undecatrien-1-al (26*E*) and 2,10-dimethyl-6-(2-propenyl)-2*E*,6*Z*,10-undecatrien-1-al (26*Z*). A solution of 1,1,3-triethoxy-2-methylbutane[16b] (6.33 g, 31.0 mmol), alcohol **9** (5.0 g, 30.1 mmol), and *o*-nitrobenzoic acid (105 mg, 0.63 mmol) in toluene (31 mL) was refluxed for 18 h. Ethanol was then distilled from the mixture, and another portion of *o*-nitrobenzoic acid (110 mg, 0.66 mmol) was added. The reaction mixture was refluxed for 11 h, ethanol was removed as before, and more *o*-nitrobenzoic acid was added (100 mg, 0.60 mmol). This process was repeated 4 more times, and almost no more ethanol distilled over, indicating the completion of reaction. The dark brown mixture was diluted with ether (100 mL) and washed with saturated $NaHCO_3$ solution and water. The aqueous layer was further extracted twice with ether, and the combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed giving 9.3 g of crude product. Flash chromatography on silica gel (50:1 hexane/EtOAc) afforded 1.3 g (18%) of a 2:1 mixture of **26*E*** and **26*Z***.

Data for **26*E***: ^{1}H NMR 9.38 (s, 1), 6.47 (ddd, 1, J = 7.0, 7.0, 1.2), 5.77 (ddt, 1, J = 16.6, 10.0, 6.3), 5.25 (br t, 1, J = 6.6), 5.05 (br d, 1, J = 16.6), 5.00 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.67 (br s, 1), 2.81 (br d, 2, J = 6.3), 2.51−2.35 (m, 2), 2.28−1.95 (m, 6), 1.74 (s, 3), 1.72 (s, 3).

Partial data for **26*Z***: ^{1}H NMR 9.39 (s, 1), 6.50 (ddt, 1, J = 16.6, 10.0, 6.8), 2.76 (br d, 2, J = 6.8, 1.0).

2,10-Dimethyl-6-(2-propenyl)-2*E*,6*E*,10-undecatrien-1-ol (22). LAH (2.0 g, 52.6 mmol) was added to a solution of ester **21** (3.8 g, 13.8 mmol) in 150 mL of ether at 0 °C. The

reaction was stirred for 8 h and quenched with water (2 mL), followed by 15% aqueous NaOH (2 mL) and another portion of water (6 mL). Filtration and further evaporation of the solvent gave 3.15 g (98%) of **22**: ^{1}H NMR 5.73 (ddt, 1, J = 16.6, 10.0, 6.4), 5.38 (dt, 1, J = 1.0, 6.8), 5.22 (br t, 1, J = 6.7), 5.03 (br d, 1, J = 16.6), 4.98 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.68 (br s, 1), 3.95 (br s, 2), 2.79 (br d, 2, J = 6.4), 2.23−1.95 (m, 8), 1.71 (s, 3), 1.65 (s, 3), 1.46 (br s, 1, OH); ^{13}C NMR 145.4, 136.4, 136.1, 134.6, 125.7, 125.5, 115.0, 109.8, 68.6, 37.8, 36.4, 34.8, 26.1, 25.9, 22.3, 13.5; IR (neat) 3323, 3076, 1648, 1637, 995, 911, 887. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.68; H, 10.62.

1-Bromo-2,10-dimethyl-6-(2-propenyl)-2*E*,6*E*,10-undecatriene (23). Et_3N (0.92 mL, 6.6 mmol) was added dropwise to a mixture of alcohol **22** (780 mg, 3.3 mmol) and MsCl (0.4 mL, 5.0 mmol) in 25 mL of THF at −45 °C. The reaction was stirred for 1 h and then warmed to 0 °C at which time a solution of LiBr (1.15 g, 13.2 mmol) in 5 mL of THF was added via cannula. The resulting mixture was stirred for 2 h at 0 °C and then diluted with ice-cold water and extracted with hexane. The combined organic extracts were washed with saturated $NaHCO_3$, water, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure giving 1.00 g of crude product. Purification by flash chromatography on silica gel (100:1 hexane/EtOAc followed by 50:1 hexane/EtOAc) afforded 705 mg (72%) of pure bromide **23**: ^{1}H NMR 5.73 (ddt, 1, J = 16.6, 10.0, 6.4), 5.57 (br t, 1, J = 6.3), 5.21 (br t, 1, J = 6.8), 5.03 (br d, 1, J = 16.6), 4.98 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.68 (br s, 1), 3.96 (br s, 2), 2.78 (br d, 2, J = 6.4), 2.21−1.98 (m, 8), 1.74 (s, 3), 1.72 (s, 3); ^{13}C NMR 145.5, 136.1, 136.0, 131.9, 131.1, 126.0, 115.1, 109.9, 41.7, 37.9, 36.0, 34.8, 26.8, 26.0, 22.4, 14.6; IR (neat) 3075, 1649, 1636, 993, 912, 888.

Ethyl 2,6,14-Trimethyl-3-oxo-10-(2-propenyl)-6*E*,10*E*,14-pentadecatrienoate (1). Ethyl 2-methylacetoacetate (5.26 g, 36.5 mmol) was added dropwise to a solution of NaH (1.53 g, 38.3 mmol) and HMPA (3.81 mL, 21.9 mmol) in THF (240 mL) at 0 °C. The reaction was stirred for 1 h and then treated with *n*-BuLi (15.3 mL, 38.3 mmol of 2.5 M in hexane). The resulting mixture was stirred for 1 h, and a solution of bromide **23** (2.71 g, 9.1 mmol) in THF (10 mL) was transferred to the reaction via cannula. The reaction mixture was stirred for 2 h, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (50:1 hexane/EtOAc) gave 2.74 g (83%) of pure **1**: ^{1}H NMR 5.73 (ddt, 1, J = 16.6, 10.0, 6.4), 5.20 (br t, 1, J = 6.8), 5.11 (dt, 1, J = 1.4, 6.8), 5.03 (br d, 1, J = 16.6), 4.98 (br d, 1, J = 10.0), 4.71 (br s, 1), 4.68 (br s, 1), 4.19 (q, 2, J = 7.1), 3.52 (q, 1, J = 7.1), 2.78 (br d, 2, J = 6.4), 2.67 (dt, 1, J = 17.1, 7.8), 2.58 (dt, 1, J = 17.1, 7.4), 2.25 (br t, 2, J = 7.8), 2.20−1.98 (m, 8), 1.72 (s, 3), 1.59 (s, 3), 1.33 (d, 3, J = 7.1), 1.27 (t, 3, J = 7.1); ^{13}C NMR 205.5, 170.5, 145.6, 136.6, 136.3, 133.3, 125.5, 125.0, 115.0, 109.9, 61.2, 52.9, 40.1, 37.9, 36.8, 34.9, 33.2, 26.6, 26.0, 22.4, 16.0, 14.1, 12.7; IR (neat) 3075, 1745, 1716, 1650, 1448, 910, 887.

Ethyl (4α,8*β*,13*β*)-13-Methyl-3-oxo-16-kauren-18-oate (2). A solution of *β*-keto ester **1** (2.74 g, 7.6 mmol) in MeOH (10 mL) was added to a degassed solution of $Mn(OAc)_3{\cdot}2H_2O$ (4.08 g, 15.2 mmol) and $Cu(OAc)_2$ (1.38 g, 7.6 mmol) in MeOH (160 mL), and the resulting mixture was stirred for 2.5 h at room temperature. The reaction was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine and dried ($MgSO_4$). Evaporation of the solvent afforded 2.59 g of crude product. Flash chromatography on silica gel (impregnated with 20% $AgNO_3$) (24:1 hexane/EtOAc) gave 940 mg (35%) of pure **2**, followed 10 mg (0.4%) of the epimer of **2** at C_4, 50 mg of 80% pure **32** (1.5%), 64 mg (2%) of **33**, 57 mg (1%) of 50% pure **33**, and 397 mg of unidentified products with 2-propenyl and 4-methyl-4-pentenyl side chains, and polymeric material.

Data for **2**: mp 87.0−88.0 °C; ^{1}H NMR 4.73 (br s, 1), 4.63 (br s, 1), 4.23−4.04 (m, 2), 2.94 (ddd, 1, J = 14.8, 14.8, 6.6), 2.81 (dd, 1, J = 17.0, 2.4), 2.36 (ddd, 1, J = 14.8, 4.8, 2.4), 2.05 (ddd, 1, J = 13.2, 6.6, 2.4), 1.97 (dt, 1, J = 17.0, 2.4), 1.90−1.74 (m, 2), 1.62−1.05 (m, 11), 1.35 (s, 3), 1.26 (t, 3, J = 7.1), 1.06 (s, 3), 1.04 (s, 3); ^{13}C NMR 209.0, 173.7, 159.7, 101.4, 61.0, 58.5, 57.6, 57.0, 54.8, 43.9, 42.1, 41.2, 41.0, 40.6, 40.2, 37.7, 36.6, 23.7, 22.3, 21.1, 20.9, 13.9, 13.2; IR (neat) 1714, 1652. Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.66; H, 9.22.

Data for the epimer of **2** at C_4: ^{1}H NMR 4.74 (br s, 1), 4.64 (br s, 1), 4.26−4.10 (m, 2), 2.80 (br d, 1, J = 15.6), 2.57 (ddd, 1, J = 16.8, 12.2, 7.0), 2.44 (ddd, 1, J = 16.8, 6.4, 3.1), 2.30−0.92 (m, 15), 1.34 (s, 3), 1.25 (t, 3, J = 7.0), 1.07 (s, 3), 1.05 (s, 3); ^{13}C NMR 211.0, 173.3, 159.6, 101.6, 61.2, 61.0, 57.1, 55.1, 51.5, 43.9, 42.2, 41.2 (2 C), 39.8, 37.7, 36.3, 34.5, 23.8, 22.6, 20.7, 17.0, 14.7, 14.1.

Partial data for **32** were determined from the mixture: ^{1}H NMR 5.76 (d, 1, J = 11.0), 5.66 (ddd, 1, J = 11.0, 9.3, 9.3).

Data for **33**: ^{1}H NMR 6.42 (d, 1, J = 11.0), 5.47 (ddd, 1, J = 11.0, 8.8, 8.8), 5.24 (br t, 1, J = 7.4), 4.71 (br s, 1), 4.67 (br s, 1), 4.25−4.05 (m, 2), 2.95 (ddd, 1, J = 14.5, 14.5, 6.4), 2.85−0.85 (m, 13), 2.37 (ddd, 1, J = 14.5, 4.7, 2.4), 1.71 (s, 3), 1.32 (s, 3), 1.25 (t, 3, J = 7.1), 1.07 (s, 3).

Ethyl (4α,8*β*,13*β*)-3-Hydroxy-13-methyl-16-kauren-18-oate (34). Sodium borohydride (22.0 mg, 5.8 mmol) was added to a solution of **2** (51.5 mg, 0.14 mmol) in EtOH (1 mL) at 0 °C, and the resulting mixture was stirred for 1 h. The reaction was warmed to room temperature, quenched with 1 M HCl, and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). Removal of the solvent afforded 50.5 mg (99%) of **34**: mp 99.0−99.5 °C; ^{1}H NMR 4.71 (br s, 1), 4.61 (br s, 1), 4.21−4.05 (m, 2), 3.45 (d, 1, J = 12.0, OH), 3.06 (ddd, 1, J = 12.0, 12.0, 4.5), 2.75 (br d, 1, J = 16.7), 2.09−0.93 (m, 16), 1.92 (br d, 1, J = 16.7), 1.40 (s, 3), 1.30 (t, 3, J = 7.1), 1.03 (s, 3), 0.79 (s, 3); ^{13}C NMR 178.0, 160.0, 101.2, 78.4, 60.2, 57.1, 56.8, 55.4, 48.9, 43.9, 42.1, 41.3, 41.0, 41.0, 38.7, 37.7, 28.1, 23.8, 23.8, 21.8, 20.8, 14.1, 13.4; IR (neat) 3537, 3068, 1699, 1653, 872. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.43; H, 9.82.

Ethyl (4α,8*β*,13*β*)-3-Hydroxy-13-methyl-16-oxo-17-norkauran-18-oate (35). OsO_4 (25 μL, 1.9×10^{-6} mmol of 2.5% solution in *tert*-butyl alcohol) was added to a mixture of **34** (50.3 mg, 0.14 mmol), $NaHCO_3$ (163 mg, 1.94 mmol), and $NaIO_4$ (249 mg, 1.16 mmol) in *tert*-butyl alcohol (3.6 mL) and water (0.72 mL) at room temperature. The reaction was stirred for 4 h, and another portion of OsO_4 (25 μL) was added. The resulting mixture was stirred overnight and then quenched with 10% $Na_2S_2O_4$. After being stirred for 30 min, the mixture was extracted with ether. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent afforded 47 mg (93%) of **35**: ^{1}H NMR 4.14 (q, 2, J = 7.1), 3.44 (d, 1, J = 12.1, OH), 3.08 (ddd, 1, J = 12.1, 12.1, 4.2), 2.60 (dd, 1, J = 18.5, 3.8), 2.00 (dddd, 1, J = 13.5, 12.1, 11.2, 3.4), 1.93−1.00 (m, 15), 1.81 (d, 1, J = 18.5), 1.42 (s, 3), 1.28 (t, 3, J = 7.1), 0.98 (s, 3), 0.74 (s, 3); ^{13}C NMR 222.1, 177.7, 78.2, 60.4, 56.6, 54.6, 54.1, 48.9, 48.8, 48.3, 41.4, 39.3, 38.6, 37.7, 37.3, 28.0, 23.8, 21.7, 20.5, 19.8, 14.0, 13.6; IR (CCl_4) 3546, 1740, 1704.

Ethyl (4α,8*β*,13*β*)-13-Methyl-16-oxo-17-norkaur-3-en-18-oate (36). A mixture of **35** (18.4 mg, 0.051 mmol), PPh_3 (53.3 mg, 0.2 mmol), and DEAD (32 μL, 0.2 mmol) in 1.0 mL of THF was heated at reflux overnight. Evaporation of the solvent and partial purification of the reaction mixture by flash chromatography on silica gel (10:1 hexane/EtOAc) afforded 23.4 mg of 50% pure **36** that was carried on to the next step without purification: ^{1}H NMR 5.61 (br s, 2), 4.09 (q, 2, J = 7.1), 2.59 (dd, 1, J = 18.7, 3.8), 2.04 (br d, 1, J = 17.0), 1.97 (br d, 1, J = 12.0), 1.81 (d, 1, J = 18.7), 1.71−1.20 (m, 12), 1.30 (s, 3), 1.23 (t, 3, J = 7.1), 0.99 (s, 3), 0.81 (s, 3).

Ethyl (4α,8*β*,13*β*)-13-Methyl-16-oxo-17-norkauran-18-oate (37). The 50% pure **36** (23.4 mg, approximately 0.03 mmol) and 5 mg of 5% Pd on carbon in EtOH (3 mL) was stirred under 1 atm of H_2 overnight. Filtration and removal of the solvent gave 17.2 mg of crude **37**. Flash chromatography on silica gel (50:1 hexane/EtOAc) afforded 14 mg (79% for two steps) of pure **37**: ^{1}H NMR 4.10 (q, 2, J = 7.1), 2.64 (dd, 1, J = 18.7, 3.7), 2.18 (br d, 1, J = 13.5), 1.90 (dddd, 1, J = 14.5, 3.8, 3.8, 3.8), 1.86−1.10 (m, 14), 1.80 (d, 1, J = 18.7), 1.26 (t,

3, J = 7.1), 1.19 (s, 3), 1.00 (ddd, 1, J = 13.5, 13.5, 4.2), 0.98 (s, 3), 0.90 (ddd, 1, J = 13.2, 13.2, 4.1), 0.72 (s, 3); ^{13}C NMR 222.5, 177.3, 63.4, 60.0, 57.0, 54.7, 54.3, 48.7, 48.4, 43.7, 41.5, 39.8, 38.0, 37.9, 37.3, 28.9, 21.7, 20.3, 19.8, 18.9, 14.1, 13.4; IR (CCl_4) 1740, 1722.

(4α,8β,13β)-13-Methyl-16-oxo-17-norkauran-18-oic Acid (Isosteviol, 3). LAH (10 mg, 0.26 mmol) was added to a solution of **37** (14 mg, 0.040 mmol) in ether (2 mL) at 0 °C. The reaction was stirred overnight at room temperature, cooled to 0 °C, and quenched with water (10 μL), followed by 15% aqueous NaOH (10 μL), and another portion of water (30 μL). The white precipitate was filtered off, and the solvent was evaporated to provide 12 mg (98%) of (4α,8β,13β)-13-methyl-17-norkaurane-16,18-diol: ^{1}H NMR 3.85 (dd, 1, J = 10.7, 4.4), 3.76 (d, 1, J = 11.0), 3.41 (d, 1, J = 11.0), 1.83 (ddd, 1, J = 14.5, 4.6, 3.1), 1.80−0.80 (m, 16), 1.67 (dd, 1, J = 14.1, 10.7), 1.49 (dt, 1, J = 12.8, 3.3), 1.29 (dd, 1, J = 11.5, 2.9), 0.96 (s, 3), 0.90 (s, 3), 0.89 (s, 3); ^{13}C NMR 80.6, 65.6, 56.9, 56.6, 55.4, 42.9, 42.0, 42.0, 39.6, 38.5, 37.6, 35.5, 33.6, 29.7, 27.1, 24.9, 20.2, 18.0, 15.4, 12.0; IR (CCl_4) 3725, 3625.

The above diol (10 mg, 0.033 mmol) was dissolved in acetone (1 mL), and freshly prepared Jones reagent (0.3 mL) was added at 5 °C. The reaction was stirred for 5 h at room temperature and quenched with 2-propanol. The mixture was diluted with water and extracted with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent gave 11 mg of crude isosteviol. Purification by flash chromatography on silica gel (3:1 hexane/EtOAc) provided 9 mg (72%) of pure **3**: mp 246.0−246.5 °C; ^{1}H NMR 2.64 (dd, 1, J = 18.6, 3.7), 2.16 (br d, 1, J = 13.4), 1.93−1.12 (m, 14), 1.82 (d, 1, J = 18.6), 1.55 (dd, 1, J = 11.5, 2.6), 1.25 (s, 3), 1.03 (ddd, 1, J = 13.5, 13.5, 4.2), 0.98 (s, 3), 0.91 (ddd, 1, J = 13.4, 13.4, 4.2), 0.78 (s, 3); ^{13}C NMR 222.7, 183.8, 57.0, 54.7, 54.3, 48.7, 48.4, 43.7, 41.4, 39.7, 39.5, 38.2, 37.6, 37.3, 28.9, 21.6, 20.3, 19.8, 18.8, 13.3; IR (CCl_4) 1739, 1695. The ^{1}H and ^{13}C NMR and IR spectral data for **3** are identical to those of isosteviol obtained by acidic hydrolysis of stevioside.[5]

(4α,8β,13β)-13-Methyl-16-methylene-17-norkaurane-3,18-diol (38). LAH (26 mg, 0.68 mmol) was added to a solution of **2** (32 mg, 0.089 mmol) in ether (2 mL) at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. The reaction was cooled to 0 °C and quenched by the sequential addition of water (26 μL), followed by 15% aqueous NaOH and another portion of water (78 μL). Filtration and evaporation of the solvent gave 28 mg (99%) of **38**: mp 177.0−178 °C; ^{1}H NMR 4.70 (br s, 1), 4.60 (br s, 1), 4.20 (d, 1, J = 10.8), 3.41 (dd, 1, J = 11.7, 4.6), 3.29 (d, 1, J = 10.8), 2.75 (br d, 1, J = 17.0), 1.87 (dt, 1, J = 17.0, 2.4), 1.83−0.86 (m, 16), 1.23 (s, 3), 1.02 (s, 3), 0.87 (s, 3); ^{13}C NMR 160.1, 101.2, 80.7, 64.4, 57.3, 56.2, 56.0, 43.8, 42.7, 42.3, 41.3, 41.03, 40.96, 37.6, 37.1, 27.5, 23.8, 22.6, 20.6, 20.0, 15.7; IR (CCl_4) 3632, 3549, 1654, 876.

(4α,8β,13β)-3,18-Dihydroxy-3-methyl-17-norkauran-16-one (39). A solution of **38** (32 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C, and O_3 was bubbled through for 10 min. When the reaction turned blue, oxygen was bubbled through for 10 min and dimethyl sulfide (1.5 mL) was added. The reaction was warmed to room temperature and the solvent was removed affording 42 mg of crude **39**. Flash chromatography on silica gel (10:4:1 hexane/EtOAc/MeOH) afforded 17 mg (53%) of **39**, followed by 5.0 mg (15%) of **40**.

Data for **39**: ^{1}H NMR 4.18 (d, 1, J = 11.0), 3.44 (dd, 1, J = 11.6, 3.4), 3.30 (d, 1, J = 11.0), 2.62 (dd, 1, J = 18.7, 3.7), 1.86−0.95 (m, 16), 1.76 (d, 1, J = 18.7), 1.25 (s, 3), 0.98 (s, 3), 0.83 (s, 3); ^{13}C NMR 222.2, 80.7, 64.3, 56.0, 55.2, 54.3, 48.7, 48.5, 42.8, 41.4, 39.2, 37.4, 37.2, 37.1, 27.5, 22.6, 20.3, 19.9, 19.8, 15.5; IR (CCl_4) 3622, 3539, 1741.

Data for **40**: ^{1}H NMR 4.18 (d, 1, J = 11.3), 3.43 (dd, 1, J = 11.0, 4.0), 3.33 (d, 1, J = 11.3), 3.02 (dd, 1, J = 18.3, 2.9), 2.03−0.81 (m, 16), 1.99 (d, 1, J = 18.3), 1.35 (s, 3), 1.24 (s, 3), 0.89 (s, 3); ^{13}C NMR 172.3, 80.5, 80.3, 64.2, 56.3, 56.2, 47.6, 43.7, 42.9, 38.7, 38.2, 37.8, 36.9, 34.8, 28.2, 27.5, 22.5, 18.6, 17.9, 16.3; IR (CCl_4) 3736, 3622, 1732.

Preparation of Tosylhydrazone 41. Tosylhydrazide (17 mg, 0.092 mmol) was added in one portion to a solution of **39** (24 mg, 0.077 mmol) in 3 × 10^{-3} M HCl in EtOH (2.5 mL), and the resulting mixture was heated at reflux for 3 h. Additional $TsNHNH_2$ (14 mg, 0.075 mmol) was added, and heating was continued for another 2 h. The reaction was cooled to room temperature, and the solvent was removed. Purification of the residue by flash chromatography on silica gel (2:1 EtOAc/hexane) gave 19 mg (51%) of **41**: ^{1}H NMR 7.80 (d, 2, J = 8.3), 7.66 (s, 1, NH), 7.28 (d, 2, J = 8.3), 4.20 (d, 1, J = 11.0), 3.44 (dd, 1, J = 11.3, 4.4), 3.25 (d, 1, J = 11.0), 2.55 (dd, 1, J = 17.4, 2.6), 2.41 (s, 3), 1.87−0.80 (m, 15), 1.59 (d, 1, J = 17.4), 1.32 (dd, 1, J = 11.3, 2.4), 1.23 (s, 3), 0.98 (s, 3), 0.78 (s, 3); ^{13}C NMR 170.2, 143.6, 135.6, 129.3 (2 C), 127.9 (2 C), 80.5, 64.3, 55.8, 55.7, 55.1, 44.8, 42.7, 40.8, 40.8, 38.9, 37.6, 37.4, 37.0, 27.3, 22.7, 21.9, 21.6, 20.2, 19.8, 15.6.

(4α,8β,13β)-13-Methyl-17-norkaur-15-ene-3,18-diol (Beyer-15-ene-3β,19-diol, 4). *n*-BuLi (200 μL, 0.50 mmol of 2.5 M solution in hexane) was added to a solution of **41** (13 mg, 0.026 mmol) in ether (4 mL), and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded 6.2 mg of crude product. Purification by flash chromatography on silica gel (1:1 hexane/EtOAc) gave 5.0 mg (64%) of pure **4**: ^{1}H NMR 5.63 (d, 1, J = 5.5), 5.46 (d, 1, J = 5.5), 4.20 (d, 1, J = 11.0), 3.42 (dd, 1, J = 10.7, 4.3), 3.32 (d, 1, J = 11.0), 1.82−0.80 (m, 15), 1.45 (dd, 1, J = 9.8, 2.8), 1.23 (s, 3), 0.99 (s, 3), 0.68 (s, 3); ^{13}C NMR 136.7, 134.7, 81.0, 64.5, 60.9, 55.9, 52.6, 48.7, 43.6, 42.8, 37.4, 37.1, 36.8, 33.1, 27.8, 24.9, 22.6, 20.4, 19.9, 15.7; IR (CCl_4) 3629, 3539. The ^{1}H NMR spectral data for **4** are identical to those reported for the natural product.[6] The ^{13}C NMR spectral data for **4** correspond appropriately to those reported for beyer-15-ene, beyer-15-ene-19-ol, and beyer-15-en-3β-ol.[22−24]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of selected compounds and tables of X-ray data for **2** (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm edition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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