Total Synthesis of (1*RS*,4*SR*,5*RS*)-4-(5-Hydroxy-4,8-dimethyl-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic Acid from Geraniol

Zoltan G. Hajos,* Michael P. Wachter,* Harvey M. Werblood, and Richard E. Adams

Research Laboratories, Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

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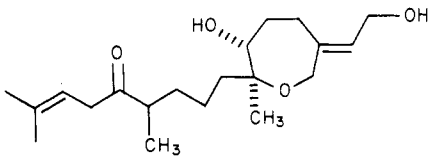
(*E*)-Geraniol (4) has been converted via 13 steps involving epoxidations, hydrolytic epoxide ring opening, and two ring closures to the key intermediate 3,8-dioxabicyclo[3.2.1]octane alcohol **10** having stereochemical integrity at all three centers of asymmetry. Extension of the three-carbon side chain of **10** and attachment of the acetic acid side chain at C-1 in nine steps completed the geraniol-based total synthesis of the zoapatanol related bicyclic acid **3**. The total synthesis of **3** from the ketal–ketone **5** has also been described.

In an earlier account the isolation and structure elucidation of zoapatanol (**1**) have been reported.[1] This novel



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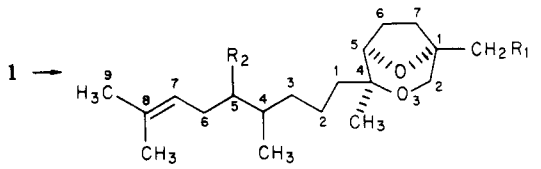
oxepane diterpenoid is an important active menses and labor-inducing principle of the Mexican plant *Montanoa tomentosa* (zoapatle, Family Compositae), from which it has been isolated.[1] It was established in the structure elucidation of zoapatanol (**1**) that the oxepane ring can readily be converted to the bicyclo[3.2.1]octane system by MnO_2 to give the saturated bicyclic aldehyde **2**.[1] It was



2, R_1 = CHO; R_2 = =O
3, R_1 = CO_2H; R_2 = OH

also found that the title compound[2] of this article, the bicyclic acid **3**, showed interesting zoapatanol-like biological activities. Compound **3** is clearly related to the keto aldehyde **2** and in turn to zoapatanol (**1**). The partial synthesis of the bicyclic acid **3** from naturally occurring zoapatanol (isolated from the leaves of *Montanoa tomentosa*) has already been disclosed.[3]

In the present paper we shall report the total synthesis of the racemic bicyclic acid **3** starting with geraniol (**4**).[4] The related, earlier total synthesis[5] of racemic **3** starting with the ketal–ketone **5**[6] shall also be described. Before discussing in detail the two synthetic schemes, a brief outline of the conversion operators determining the synthetic strategies shall be given.

1. The synthetic strategy of both schemes called for the construction of a 1,4-cis-disubstituted tetrahydrofuran intermediate (**27**, Scheme IV, and **30a**, Scheme V), the upper segment of the 3,8-dioxabicyclo[3.2.1]octane ring system of **3**.

2. Ring closure via the 1,4-cis substituents (OH and Br) should then give the additional six-membered, 1,4-dioxane ring, the lower part of the desired bicyclic system of **3**. This approach would result in the synthesis of two related bicyclic alcohols (**7**, Schemes I and IV, and **10**, Schemes I and V), the key intermediates of both routes.

3. To achieve the desired 4,5-trans relationship of the oxygen atoms of the bicyclic system, an (*E*)-olefinic intermediate had to be synthesized (**6**, Schemes I and II, and **9**, Schemes I and III). We envisioned converting these *E*-substituted intermediates in a stereocontrolled fashion to the 3,8-dioxabicyclo[3.2.1]octane ring system of the bicyclic acid **3**.

4. The construction of the racemic bicyclic ring system was designed in a stereocontrolled fashion to render a 4,5-trans relationship of the O bridges, and a cis relationship of the C-4 methyl group of the ring to O-8, the oxygen bridge connecting C-1 and C-5. The stereochemical uniformity of the C-1 position is a prerequisite of bicyclic ring formation. The details of the strategy will be discussed during the description of the individual schemes.

5. The synthesis of the disubstituted nonenyl side chain would proceed through two alcohol derivatives (**7**, Schemes I and IV, and **10**, Schemes I and V), resulting in a mixture of four diastereomers.

6. The synthesis of the acetic acid side chain at C-1 could arise via a Wittig-type reaction of the C-1 hemiacetal in both schemes (**39**, Scheme VIII). The synthetic strategies of the two schemes are summarized in Scheme I.

Results and Discussion

Synthesis of 5(*E*)-Unsaturated Intermediates. In the "ketal–ketone route A" the target compound was the 5*E*-unsaturated benzyloxy bromo methyl ketone **6**. Its synthesis has been achieved in 11 steps starting with the ketal–ketone **5**[6] (Scheme II). Wittig reaction of **5** with methylenetriphenylphosphorane (**11**) gave the methylene ketal **12** (38%). Treatment of **12** with borane–dimethyl sulfide, followed by oxidation with 30% H_2O_2 in aqueous alcoholic base gave the primary alcohol **13** (91%). Benzylation of the primary hydroxyl group followed by hydrolysis of the cyclic acetal gave the benzyloxy ketone **14** (70%). The Wadsworth–Emmons modification of the

(1) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R. H. K.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huetteman, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L.; Shefter, E. *J. Org. Chem.* **1982**, *47*, 1310 and references cited therein.
(2) Wachter, M. P.; Kanojia, R. M. U.S. Patent 4 086 358, April 25, 1978.
(3) Kanojia, R. M.; Wachter, M. P.; Chen, R. H. K. U.S. Patent 4 102 895, July 25, 1978.
(4) Hajos, Z. G. U.S. Patent 4 284 565, Aug 18, 1981.
(5) Hajos, Z. G.; Wachter, M. P. U.S. Patent 4 237 055, Dec 2, 1980.
(6) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3244.

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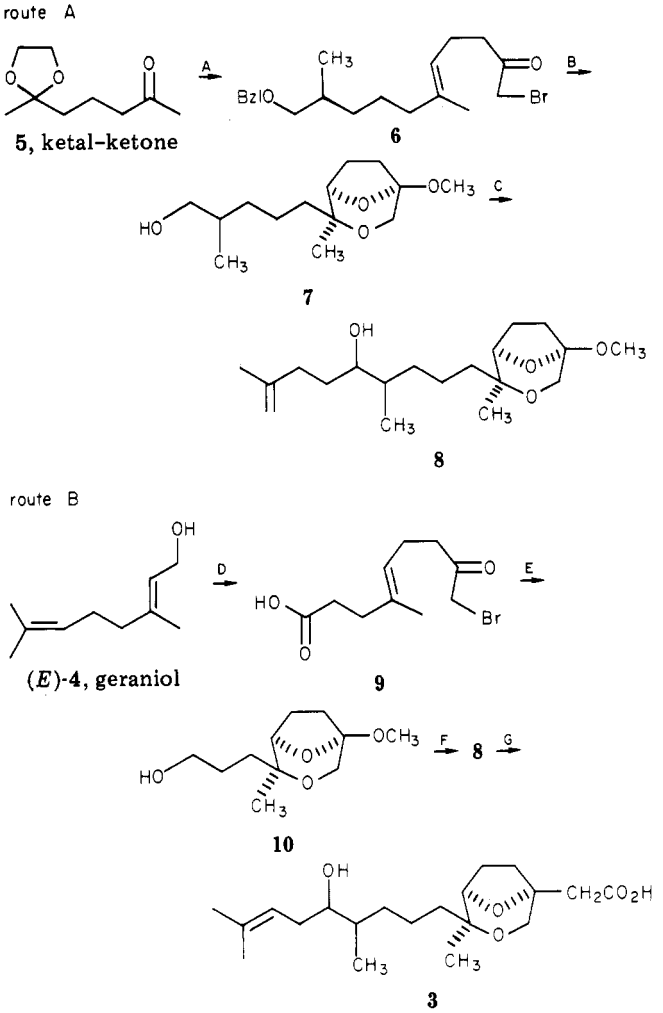
Scheme I. Strategic Outline of the Ketal-Ketone Route A and the Geraniol Route B[a]

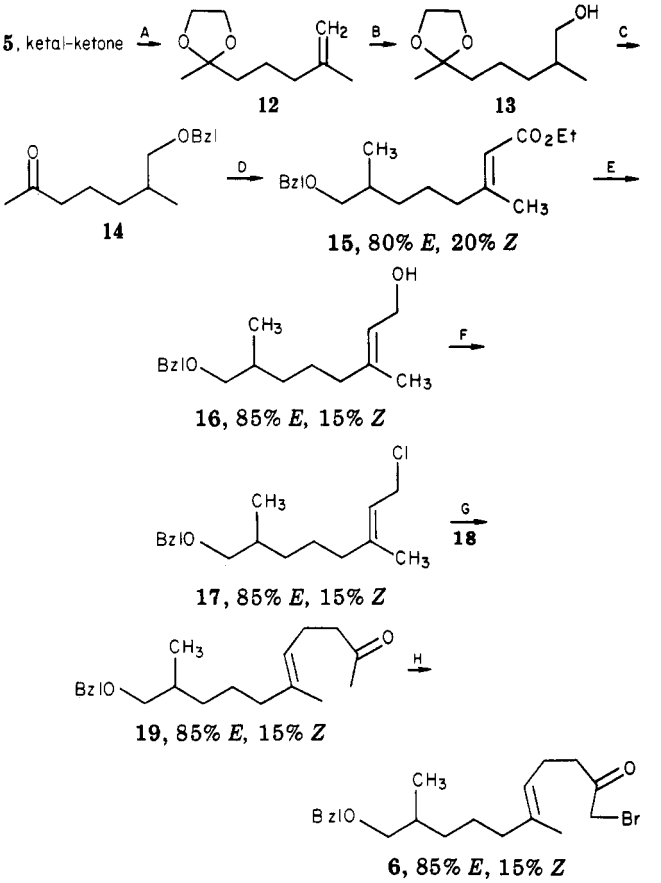


[a] A, 11 steps, Scheme II; B, 5 steps, Scheme IV; C, 2 steps, Scheme VI; D, 8 steps, Scheme III; E, 5 steps, Scheme V; F, 4 steps, Scheme VII; G, 5 steps, Scheme VIII.

Wittig reaction on **14** with triethyl phosphonoacetate/NaH/benzene gave the unsaturated ester **15** (82%) with an *E*:*Z* ratio of approximately 80:20 as determined by ^{1}H NMR. Reduction with LAH gave the allylic alcohol **16** (95%). Purification by silica gel column chromatography followed by preparative HPLC gave the desired unsaturated alcohol **16** (22%) containing approximately 85% *E* and 15% *Z* isomers. Treatment of the unsaturated alcohol **16** with CH_3SO_2Cl/LiCl/collidine in DMF[7] gave the allylic chloride **17**. This was converted to the methyl ketone **19** by treatment with the sodio salt of ethyl acetoacetate **18**, followed by hydrolysis and decarboxylation of the intermediate β-keto ester. The unsaturated methyl ketone **19** was purified by column chromatography, and contained approximately 85% *E* and 15% *Z* isomers (61% yield). It was converted to the terminal enol silyl ester, which upon treatment with NBS gave the desired unsaturated bromo ketone **6** (90%),[8] an approximately 85/15 mixture of *E*/*Z* isomers (Scheme II).

In order to improve the economy (number of steps) and the stereochemical integrity of the synthesis of the intermediate olefinic bromo ketone, (5*E*)-geranylacetone (**20**) was the chosen synthon in our second total synthesis of

Scheme II. Ketal-Ketone Route (Steps 1-11)[a]



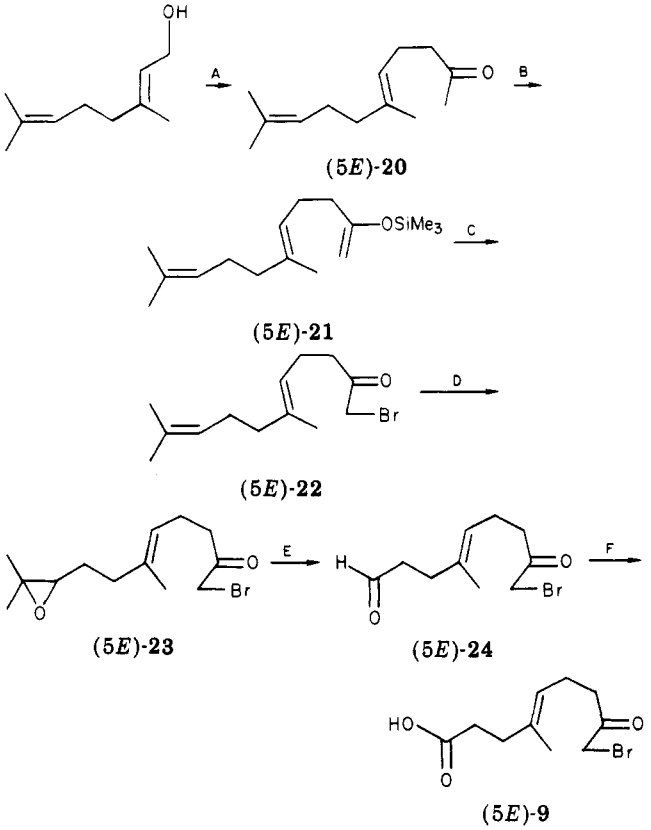
[a] A, $Ph_3P{=}CH_2$; B, $BH_3{\cdot}Me_2S$, H_2O_2/NaOH; C, NaH/BzlBr; D, $(EtO)_2P(O)CH_2CO_2Et$/NaH/benzene; chromatographic enrichment; E, LAH/Et_2O, HPLC; F, CH_3SO_2Cl, LiCl/DMF; G, $CH_3COCHNaCO_2Et$ (**18**), 2 N NaOH/H_2O, MeOH/Δ; H, LDA/THF/Me_3SiCl, NBS.

the bicyclic acid **3**. Geranylacetone (**20**) can readily be prepared[9] from the naturally occurring *E*-unsaturated terpene alcohol, geraniol.[10] (5*E*)-Geranylacetone (**20**) has sufficient C atoms to construct an intermediate 3,8-dioxabicyclo[3.2.1]octane synthon (**10**, Scheme I and V), and the C-5 double bond has the proper *E* geometry, which allows the production of the desired stereoisomer of **10** in a stereocontrolled process.

Scheme III shows the conversion of (*E*)-geraniol (**4**) to the 5*E*-unsaturated bromo keto acid **9** in an eight-step procedure. The conversion of (*E*)-geranylacetone via the enol silyl ether **21** to the 5*E*-unsaturated bromo ketone **22** has been executed in the same fashion as in the conversion of **19** to **6** (Scheme II). Compound **22** was obtained in excellent yield (98%), and the stereochemical integrity of the 5*E*-double bond remained intact in this two-step procedure (Scheme III). In order to proceed with the synthesis of the bicyclic key synthon **10** (Schemes I and V), it was necessary to convert the homoprenyl side chain by oxidative degradation to the propionic acid side chain of (5*E*)-**9**. This was achieved by regioselective epoxidation of the terminal double bond[11] to the epoxy compound **23** (70%). Epoxide **23** was then converted to the aldehyde **24** (38%) with periodic acid in aqueous THF. Reaction of the aldehyde **24** with Jones reagent gave the 5*E*-un-

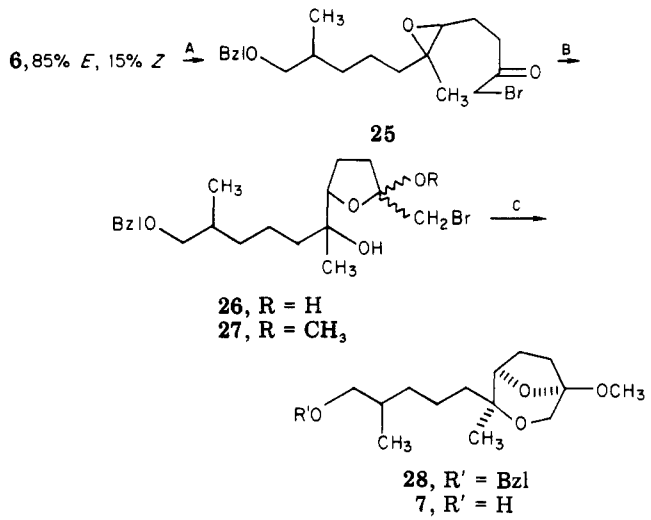
(7) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.
(8) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, 194.
(9) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068.
(10) Geraniol, 99+ %, Gold Label, Aldrich Chemical Co., has been used.
(11) Ito, S.; Inone, K.; Matsumoto, M. *J. Am. Chem. Soc.* **1982**, *104*, 6450.

Scheme III. Geraniol Route (Steps 1-8)[a]



[a] A, three steps;[9] B, LDA/Me_3SiCl; C, NBS; D, MCPBA; E, H_5IO_6; F, CrO_3/H_2SO_4.

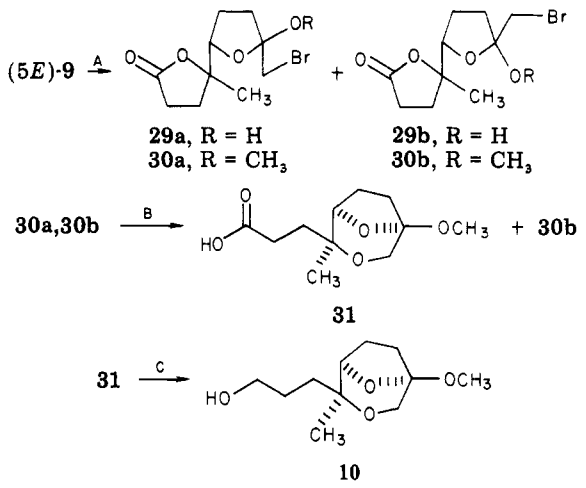
Scheme IV. Ketal-Ketone Route (Steps 12-16)[a]



[a] A, MCPBA; B, 0.02 N HCl/acetone, $HC(OMe)_3/H^+$; C, KOH/Me_2SO, chromatography, H_2/Pd.

saturated bromo keto acid (5*E*)-**9** (76%). The stereochemical integrity of the 5*E* double bond remained unchanged during the three-step conversion of **22** to (5*E*)-**9** (Scheme III). Next the synthetic strategy of both schemes called for the construction of the bicyclic key intermediate alcohols (**7**, Schemes I and IV, and **10**, Schemes I and V) via the 1,4-cis-disubstituted tetrahydrofuran intermediates (**27**, Scheme IV, and **29a**, Scheme V). Scheme IV shows how this has been achieved in the course of the ketal ketone route. The unsaturated bromo ketone derivative **6** was epoxidized with MCPBA in CH_2Cl_2 at 0 °C for 3 h to give the corresponding epoxide **25**, as a 85/15 mixture of

Scheme V. Geraniol Route (Steps 9-13)[a]



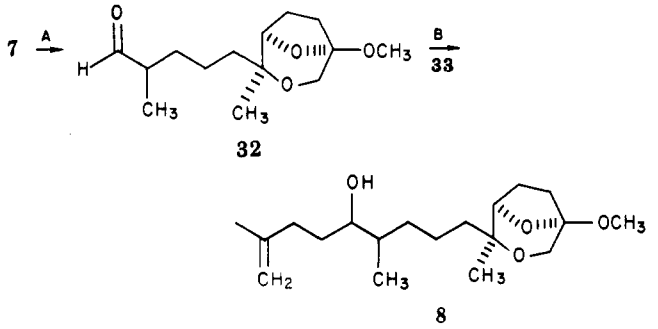
[a] A, MCPBA, H^+/acetone, $HC(OMe)_3/H^+$; B, KOH/Me_2SO, H^+; C, BH_3·THF.

5,6-trans and -cis isomers. This is a reflection of the 5*E* and 5*Z* ratio of **6**. Hydrolysis of the epoxide **25** under extremely mild reaction conditions resulted in concomitant ring closure to the tetrahydrofuran hemiacetal derivative **26** as a mixture of C-2 epimers. The hemiacetal **26** was then converted to the acetal **27** by treatment with trimethyl orthoformate and acid at low temperature. Cyclization with KOH in Me_2SO at 65 °C for 1.5 h gave the bicyclic benzyloxy derivative **28** in approximately 16% overall yield from **6** and an 85/15 isomer purity at the respective 4,5-positions. Due to the steric relationship of the functional groups of **27**, only the 1,4-cis-substituted isomer could be cyclized to the bicyclic derivative **28**. The noncyclized portion could be separated by column chromatography and converted to a mixture of C-2 epimeric hemiacetals **26** by mild acidic hydrolysis. Hydrogenolysis of the benzyl-protective group of **27** gave the bicyclic alchol **7**, the key intermediate of scheme A in the same 85/15 isomer purity at C-4 and C-5. This is a reflection of the 5-*E* and -*Z* isomer ratio of compound **6** (Scheme IV).

The stereocontrolled five-step conversion of the unsaturated bromo keto acid (5*E*)-**9** to the key intermediate bicyclic ketal alcohol **10** is shown in Scheme V of the geraniol route. The (5*E*)-unsaturated acid **9** formed a single (trans) epoxide by treatment with MCPBA.[12a,b] Hydrolytic trans diaxial opening of this epoxide (not shown) was followed by immediate five-ring hemiacetal and five-ring lactone formation to give a single hemiacetal lactone **29a** in the kinetically controlled process. There was no evidence of the C-2 epimeric compound **29b** by ^1H NMR spectroscopy. The same, very mild acidic reaction conditions (0.02 N acidic acetone) were applied as in the conversion of **25** to **26**. The hemiacetal **29a** was converted to the acetal **30a** and **30b** to protect it during the subsequent strongly basic step of ring closure. Acetalization has been executed with trimethyl orthoformate and acid to give an approximately 60/40 mixture of cis and trans bromo acetals, **30a** and **30b**, as shown by ^1H NMR and GC/MS. Of these, the 1,4-cis bromo ketal lactone **30a** has been cyclized to the desired bicyclic ketal acid **31** with KOH in Me_2SO, followed by acidification; the trans bromo ketal lactone **30b** could readily be isolated as the neutral component of the reaction mixture. It was possible to recycle

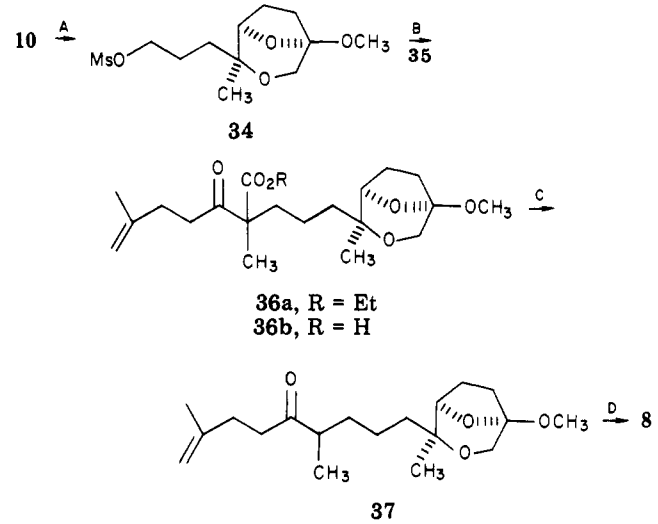
(12) (a) The system quite clearly lends itself for the introduction of chirality via asymmetric epoxidation (ref 12b). (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

Scheme VI. Ketal-Ketone Route (Steps 17 and 18)[a]



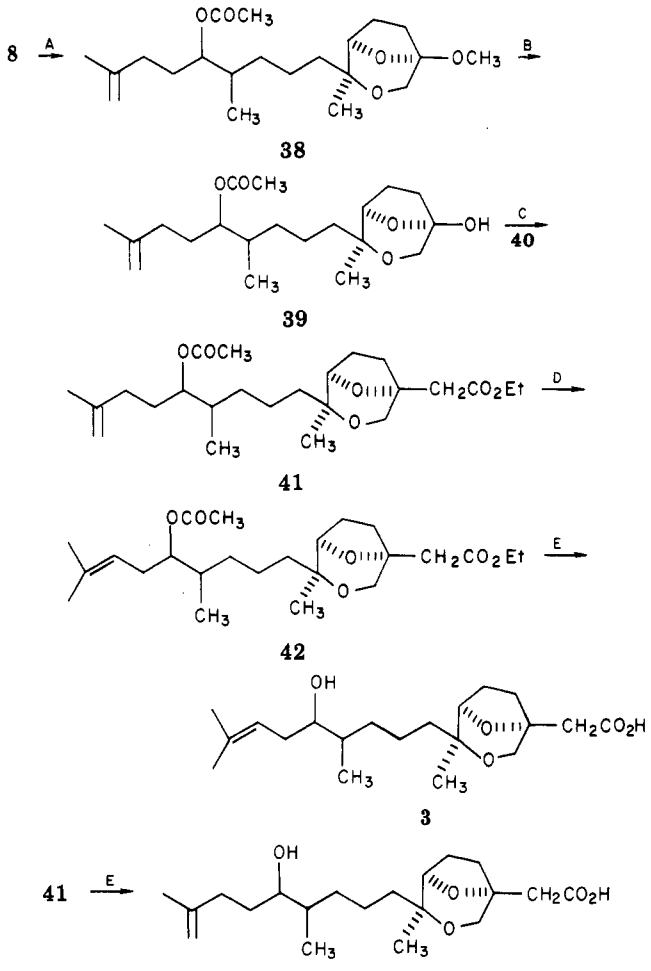
[a] A, CrO_3/pyridine; B, $H_2C{=}C(CH_3)CH_2CH_2MgBr$ (33).

Scheme VII. Geraniol Route (Steps 14-17)[a]



[a] A, $MsCl/Et_3N/CH_2Cl_2$; B, $H_2C{=}C(CH_3)CH_2CH_2COCH(CH_3)CO_2Et$ (35), NaI/LDA/hexane/THF → DMF; NaOH/H_2O/MeOH, H^+; C, toluene/Δ; D, $NaBH_4$.

Scheme VIII. Five-Step Conversion of Common Intermediate 8 to Bicyclic Acid 3 (Steps 18-22)[a]



[a] A, Ac_2O/pyridine; B, H^+; C, $Ph_3P{=}CHCO_2Et$ (40)/Δ; D, TsOH/benzene/Δ; E, NaOH/H_2O/MeOH, H^+.

30b by mild acid hydrolysis of the acetal group to give an approximately 60/40 mixture of the hemiacetal lactones **29a** and **29b**.

The bicyclic ketal acid **31** has been reduced to the key intermediate bicyclic alcohol **10** with borane in THF (Scheme V). The two-step synthesis of **8** from the intermediate bicyclic ketal alcohol **7** via the ketal ketone route is shown in Scheme VI. Treatment of the bicyclic alcohol **7** with CrO_3/pyridine in CH_2Cl_2 gave the aldehyde **32** in quantitative yield. Grignard reaction of **32** with 3-methyl-3-butenylmagnesium bromide **33** gave **8** in 30% yield after column chromatography. The compound was a mixture of C-4 and C-5 epimers, reflecting the original *E*/*Z* ratio of the olefinic starting material **6** (Scheme II). The major diastereoisomer of **8** (approximately 80%) corresponded by ^1H NMR and GC/MS to the *4RS,5SR* isomer of **8** obtained by the geraniol route. The five-step synthesis of the pure *4RS,5SR* isomer of **8** from the bicyclic alcohol **10** is shown in Scheme VII. The bicyclic alcohol **10**, the key synthon of the geraniol route B, was converted to its mesylate **34** by treatment with methanesulfonyl chloride in the presence of triethylamine in methylene chloride. The mesylate was then converted in situ to the corresponding iodide with NaI in THF. The unsaturated β-keto ester **35**[13] was then added, followed by the addition of lithium diisopropylamide (LDA) in hexane (0 °C to room temperature). The solvent (THF) was then exchanged to the more polar dimethylformamide to allow smooth alkylation to the β-keto ester intermediate **36a** (65%, chromatographed material).

Treatment of **36a** with aqueous NaOH in methanol at room temperature for 4 days gave the bicyclic ketone **37** (72%). Additional **37** (15%) could be obtained by isolation of the intermediate β-keto acid **36b** after aqueous basic treatment. Compound **36b** could be decarboxylated by refluxing in toluene for 2 h. Reduction of ketone **37** with sodium borohydride gave the pure *4RS,5SR* isomer of the bicyclic ketal alcohol **8** (93%). Isomer purity has been proven by ^1H NMR spectroscopy and GC/MS. The 4,5-positions of the side chain, on the other hand, constitute an approximately 1:1 mixture of diastereoisomers (Scheme VII). The five-step conversion of **8** to the desired final product, the bicyclic acid **3**, is shown in Scheme VIII. The bicyclic ketal alcohol **8** was converted to the corresponding acetate **38** (99%) to protect it during the subsequent operations. Selective hydrolysis of the acetal group of **38** with 0.25 N HCl–H_2O–acetone at 55 °C for 4 h gave the bicyclic hemiketal acetate **39** (91%).

The addition of the last two carbon atoms of the bicyclic acid **3** was executed by means of a Wittig-type reaction of

(13) The dianion of ethyl 2-methylacetoacetate (Aldrich) was γ-alkylated with methallyl chloride (Aldrich) by using the procedure described for related compounds (ref 14a and 14b).

(14) (a) Sum, F. W.; Weiler, L. *J. Am. Chem. Soc.* **1979**, *101*, 4401. (b) Pinnick, H. W.; Chang, Y. H. *Tetrahedron Lett.* **1979**, 837.

the hemiketal acetate **39**, which may be considered a masked form of the corresponding seven-ring hydroxy ketone. Although the reaction is related to *C*-glycoside formation of carbohydrate aldehyde hemiacetals,[15] the synthesis of compound **41** was not totally obvious due to the more complex nature of the bicyclic system of the masked hydroxy ketone of **39**. Treatment of the hemiacetal **39** with (carbethoxymethylene)triphenylphosphorane (**40**) at 120 °C gave the desired ester **41** (69% chromatographed). The stereochemistry at C-1 is determined by the stereochemistry of positions C-4 and C-5 and by the prerequisite oxygen bridge formation between C-1 and C-5.

Isomerization of the terminal double bond of **41** gave the 7-nonenyl isomer **42** by treatment with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene.[16] Compound **42** contained approximately 5–10% of **41**, as shown by ^{1}H NMR spectroscopy. The two double bond isomers are separable by chromatography on $AgNO_3$-impregnated plates or columns.

Saponification of the acetoxy ester **41** gave the hydroxy acid **43** (91%). Saponification of the isomerized acetoxy ester **42** gave the desired bicyclic 7-nonenyl hydroxy acid **3** (91%). The compound contained a small amount (5–10%) of **43**, which is a reflection of the purity of the ester precursor **42**.

In summary, geraniol [(*E*)-**4**] has been converted to the bicyclic acid **3** in a 22-step total synthesis averaging 85% yield per step. We also described the earlier total synthesis of compound **3** starting with the ketal-ketone **5**. Publications related to the present paper should appear in the near future.[18a,b]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The IR spectra were recorded on a Beckman IR-8 spectrophotometer. ^{1}H NMR spectra were measured in the indicated solvent with tetramethylsilane as the internal standard, on a Varian T-60A spectrometer. The values are expressed in parts per million (δ). EI and CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph.

6,6-(Ethylenedioxy)-2-methylhept-1-ene (12). To a slurry of methyltriphenylphosphonium bromide (218 g, 0.61 M) in anhydrous THF (1.8 L) cooled to 0 °C was added *n*-BuLi (0.60 M). After stirring for 1 h, **5**[6] (91.3 g, 0.53 M) in anhydrous THF (200 mL) was added dropwise and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was filtered and the filter cake was washed with Et_2O. The solvent was removed via distillation at atmospheric pressure. The crude residue was purified via vacuum distillation to give **12** (33.95 g, 38%): bp, 75 °C (15 mm); NMR ($CDCl_3$) 4.67 (bs, 2 H, C=CH_2), 3.92 (s, 4 H, OCH_2CH_2O), 1.7 (s, 3 H, =CCH_3), 1.32 (s, 3 H, CH_3).

1-(Benzyloxy)-2-methyl-6-oxoheptane (14). To a solution of **12** (33.95 g, 200 mM) in hexane (132 mL), under a N_2 atmosphere, was added borane–methyl sulfide complex (7.05 mL) at 0 °C over a 0.5-h period, and the resulting solution was allowed to stir for 3 h at room temperature. The reaction mixture was then treated with 95% EtOH (68 mL) and 3 N NaOH (21.8 mL) and cooled to 0 °C, followed by the dropwise addition of 30% H_2O_2 (24.5 mL) to maintain a temperature of 25–35 °C. The reaction mixture was heated at reflux for 0.5 h, poured into ice water (500 mL), and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give **13** (33.35 g, 89%) as a colorless oil: NMR ($CDCl_3$) 3.93 (m, 5 H, OCH_2CH_2O and $CHCH_3$), 3.45 (br d, 2 H, $CHCH_2O$), 1.32 (s, 3 H, CH_3), 0.93 (d, 3 H, CH_3). The alcohol **13** was converted to benzyl ether **14** without further purification.

To a slurry of NaH (50%, benzene washed, 71.7 g, 1.49 M) in benzene (4 L) was added **13** (187.1%, 0.995 M) in benzene (1.5 L) and the resulting mixture was allowed to stir for 5 h at room temperature. Benzyl bromide (147.3 mL, 1.24 M) in benzene (1 L) was added and the reaction allowed to stir at reflux for 16 h. The solvent was removed in vacuo and the residue obtained was poured into ice water and partitioned between Et_2O and brine. The aqueous phase was extracted with Et_2O and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give the crude benzyl ketal.

The intermediate benzyl ketal (277 g, 1 M) in acetone (4.25 L) was treated with 10% HCl (400 mL) and allowed to stir at room temperature for 3 h. The reaction mixture was neutralized with saturated $NaHCO_3$ and filtered to remove salt, and the solvent was removed in vacuo. The residue was partitioned between Et_2O and water, the aqueous phase was extracted with Et_2O, and the combined Et_2O extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give crude **14** (248 g). Purification via silica gel chromatography using an EtOAc/hexane gradient as the eluent gave compound **14** (162 g, 70%), as a colorless oil: NMR ($CDCl_3$) 7.37 (s, 5 H, Ar H), 4.54 (s, 2 H, OCH_2), 3.3 (d, 2 H, $CHCH_2O$-) 2.42 (br t, 2 H, $COCH_2$) 2.13 (s, 3 H, CH_3CO), 0.95, (d, 3 H, CH_3CH).

Ethyl 8-(Benzyloxy)-3,7-dimethyl-2-octenoate (15, 80:20 *E*:*Z*). To a slurry of 99% NaH (22.8 g, 0.95 M) in benzene (2 L) was added distilled triethyl phosphonoacetate (241 g, 1.08 M) in benzene (1 L) and the temperature was maintained at 70 °C for 3 h. Compound **14** (88.7 g, 0.38 M) in benzene (0.5 L) was added and the temperature was maintained at 70 °C for 2 h. The reaction mixture was cooled to room temperature, brine was added, and the suspension was neutralized with 10% HCl and partitioned between Et_2O and brine. The aqueous phase was extracted with Et_2O and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give crude **15** (186 g). Purification via silica gel chromatography using an EtOAc/hexane gradient as the eluent gave compound **15** (94.6 g, 82%), a mixture of 80/20 *E*/*Z* isomers by NMR analysis: NMR ($CDCl_3$) 7.37 (s, 5 H, Ar H), 5.66 (m, 1 H, C=CH), 4.53 (s, 2 H, OCH_2), 4.18 (q, 2 H, $-OCH_2CH_3$), 3.32 (d, 2 H, $-CHCH_2O$-), 2.17 (br s, (*E*)-C=CCH_3), 1.88 (br s, (*Z*)-C=CCH_3), 1.3 (t, 3 H, CH_3CH_2) 0.95 (d, 3 H, CH_3CH).

8-(Benzyloxy)-3,7-dimethyl-2-octenol (16, 85:15 *E*:*Z*). To a slurry of LAH (47.3 g, 1.25 M) in Et_2O (3.3 L) at 0 °C was added compound **15** (94.6 g, 0.31 M) in Et_2O (1.4 L). The reaction was allowed to stir at 0 °C for 4 h. Wet Et_2O (750 mL) was added slowly, and the reaction mixture was then acidified with 1 N HCl. The organic phase was separated, the aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give crude **16** (77.6 g, 95%). Purification via silica gel chromatography using an EtOAc/hexane gradient as the eluent gave fractions of varying mixtures of isomers. A collection of fractions that gave compound **16** (17.7 g) as a colorless oil with an 85/15 *E*/*Z* isomer ratio by GC analysis was used in the next step: NMR ($CDCl_3$) 7.33 (s, 5 H, Ar H) 5.30 (br t, 1 H, C=CH), 4.50 (s, 2 H, $-OCH_2$), 4.13 (d, 2 H, =CCH_2OH), 3.3 (d, 2 H, $-CHCH_2O$-), 2.02 (br m, C=CCH_2), 1.73 (br s, (*Z*)-CH_3C=C), 1.67 (br s, (*E*)-CH_3C=C), 0.94 (d, 3 H, CH_3CH).

Similarly, treatment of compound **14** (17.8 g) as described above but using a Waters Prep 500 HPLC (EtOAc/hexane gradient) to effect the separation of *E*/*Z* isomers gave **16** (5.8 g) with a 97:3 ratio (GC/MS).

1-(Benzyloxy)-2,6-dimethyl-10-oxoundec-6-ene (19, 85:15 *E*:*Z*). Compound **16** (17.7 g, 67.6 mM) in collidine (13.35 mL, 101 mM) was treated with LiCl (2.88 g, 67.9 mM) in DMF (145 mL). The reaction mixture was cooled to 0 °C and then CH_3SO_2Cl (7.6 mL, 98.2 mM) was added neat. The thick suspension was allowed to stir at 0 °C for 0.75 h, and then at room temperature for 2 h. The reaction mixture was poured into ice water and

(15) Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 145.

(16) A similar double-bond isomerization has been described for davanone (ref 17).

(17) Naegeli, P.; Weber, G. *Tetrahedron Lett.* **1970**, 959.

(18) (a) A communication describing a related synthesis of **3** but avoiding the 8-nonenyl isomer **43** is in preparation. (b) Mitsubishi Chemical Laboratories, Ltd., Japan, will shortly publish the synthesis of **3** by a modification of the geraniol route.

extracted with hexane, and combined extracts were washed with saturated $CuSO_4$, brine, and dried (Na_2SO_4). The solvent was removed in vacuo to give **17** (19.7 g), which was used without further purification.

Ethyl acetoacetate (81.8 g, 0.62 M) was treated with sodium ethoxide prepared by the addition of sodium (14.18 g, 0.62 M) to absolute ethanol (400 mL) with cooling to give ethyl sodioacetoacetate (**18**). After being stirred at room temperature for 1 h, the reaction mixture was cooled to 0 °C and **17** (18.9 g, 67.5 mM) was added. After 1.5 h at 0 °C the reaction mixture was allowed to stir at room temperature for 2 h. The solvent was removed in vacuo, and the residue was poured into ice water, neutralized with 1 N HCl, and partitioned between Et_2O and brine. The aqueous phase was extracted with Et_2O and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give the crude β-keto ester containing residual ethyl acetoacetate which was then saponified.

The β-keto ester (25.25 g, 67.5 mM) was treated with 2 N NaOH/MeOH (675 mL) and after 10 min, H_2O (675 mL) was added. The reaction mixture was heated at reflux for 3 h. The solvent was removed in vacuo and the residue was treated with Et_2O and brine. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give the crude **19** (16 g). Purification via silica gel chromatography using 5% EtOAc/hexane as the eluent gave **19** (12.4 g, 61%) with a 85/15 *E*/*Z* isomer ratio by GC analysis: NMR ($CDCl_3$) 7.34 (s, 5 H, Ar H), 5.05 (br m, 1 H, C=CH), 4.49 (s, 2 H, -OCH_2), 3.27 (d, 2 H, -OCH_2CH), 2.1 (s, 3 H, CH_3CO), 1.68 (br s, (*Z*)-CH_3C=C), 1.63 (br s, (*E*)-CH_3C=C), 0.93 (d, 3 H, CH_3CH).

Similarly, treatment of compound **16** (5.8 g, 97% *E*) as described above gave **19** (4.1 g, 62% yield, 97/3 *E*/*Z*).

11-(Benzyloxy)-1-bromo-6,10-dimethyl-2-oxoundec-5-ene (6). LDA was prepared by the addition of 2.1 M *n*-BuLi in hexane (22.7 mL, 48.8 mM) to diisopropylamine (3.45 mL, 48.8 mM) in dry THF (125 mL). The base was cooled to −70 °C and methyl ketone **19** (12.4 g, 41 mM) in dry THF (300 mL) was added and allowed to stir for 1 h. Trimethylsilyl chloride (14 mL, 111 mM) was added to triethylamine (3.7 mL, 26.8 mM) in dry THF (50 mL) and centrifuged, and the supernatant was added to the lithio salt at −70 °C. After 4 h, $NaHCO_3$ (2.5 g), and saturated $NaHCO_3$ (250 mL) were added, the reaction mixture was partitioned between Et_2O and brine, the aqueous phase extracted with Et_2O, and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give a quantitative yield of the silyl enol ether (15.36 g, 41 mM) which was dissolved in dry THF (400 mL), treated with $NaHCO_3$ (4.1 g, 49 mM) followed by NBS (7.3 g, 41 mM) at −70 °C, and allowed to stir for 4 h. The reaction was allowed to reach room temperature, and then saturated $NaHCO_3$, Et_2O, and brine were added. The phases were separated, the aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give crude **6** (17 g) which was epoxidized without further purification.

(1*RS*,4*RS*,5*SR*)-4-[5-(Benzyloxy)-4-methylpentyl]-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (28). Bromo ketone **6** (15.6 g, 41 mM) in CH_2Cl_2 (250 mL) was treated with 85% MCPBA (8.35 g, 41 mM) in CH_2Cl_2 (200 mL) at 0 °C for 3 h. The reaction mixture was washed with brine, saturated Na_2SO_3, and brine and then dried (Na_2SO_4). The solvent was removed in vacuo to give epoxide **25**.

Epoxide **25** (16.2 g, 41 mM) in acetone (170.5 mL) was treated with 0.2 N HCl (18.75 mL) at 0 °C for 0.75 h. The reaction mixture was allowed to stir at room temperature for 18 h. The solvent was removed in vacuo and the residue obtained was treated with Et_2O, brine, and saturated $NaHCO_3$. The phases were separated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting bromo acetal **26** (16.9 g, 41 mM) was treated with distilled trimethyl orthoformate (51 mL, 660 mM) and 0.1 N H_2SO_4/MeOH at 0 °C for 0.5 h and then at 5 °C for 66 h. The solvent was removed in vacuo and the residue obtained was treated with Et_2O, saturated $NaHCO_3$, and brine. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give ketal **27** as a mixture of erythro and threo isomers.

Compound **27** (17.5 g, 41 mM) was treated with 85% KOH (22 g, 335 mM) in distilled Me_2SO (200 mL) at 65 °C for 1.5 h. The reaction mixture was allowed to stir at 55 °C for 18 h, followed by an additional 4 h at 65 °C. The reaction mixture was poured into cold brine and then partitioned between hexane and brine. The aqueous phase was reextracted with hexane (4×) and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give crude **28** (10.1 g). Purification via silica gel chromatography using an EtOAc/hexane gradient as the eluent gave **28** (2.2 g, 15.5% yield from compound **19**) as an 85/15 ratio of isomers.

Similarly treatment of **19** (97/3 *E*/*Z*) by the route described above gave **28** as a pale yellow oil containing 97% of the desired 1*RS*,4*RS*,5*SR* isomer as a pale yellow oil: NMR ($CDCl_3$) 7.37 (s, 5 H, Ar H), 4.50 (s, 2 H, -OCH_2), 3.9 (br m, 1 H, C_5-H), 3.88 (AB q, 2 H, C_2-CH_2), 3.43 (s, 3 H, OCH_3), 3.25 (d, 2 H, -OCH_2CH), 1.34 (s, 3 H, C_4-CH_3), 0.95 (d, 3 H, CH_3CH); MS, M^+ 348.

(1*RS*,4*RS*,5*SR*)-4-(5-Hydroxy-4-methylpentyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (7). A solution of benzyl ether **28** (80 mg) in 95% EtOH (100 mL) was hydrogenated in the presence of 10% Pd/C (25 mg) for 90 min. The catalyst was removed by filtration through a bed of Celite and washed with EtOH. The combined filtrate was evaporated in vacuo to give alcohol **7** (52 mg, 88%) as a yellow oil: NMR ($CDCl_3$) 3.4 (s, 3 H, OCH_3), 3.2–4.0 (overlapping m, 5 H, CH_2OH, C_2-CH_2, C_5-H), 1.33 (s, 3 H, C_4-CH_3), 0.92 (d, 3 H, CH_3CH); MS, M^+ 258.

6,10-Dimethyl-2-[(trimethylsilyl)oxy]-(5*E*)-1,5,9-undecatriene (21). Triphenylmethane indicator (50 mg) was added to diisopropylamine (distilled from LAH, 6.5 mL, 0.046 M) dissolved in THF (distilled from LAH, 60 mL). The solution was cooled to −10 °C (ice–methanol bath), and *n*-butyllithium in hexane (18.7 mL of 2.4 M, 0.044 M) was added while stirring at −10 °C. The resulting solution was kept at −10 °C for 20 min and then at −70 °C for an additional 20 min. While stirring at −70 °C, geranylacetone (6.2 g, 0.032 M) dissolved in anhydrous THF (6.0 mL) was added within 15 min to the above solution followed by the addition of a freshly prepared mixture of trimethylsilyl chloride (15 mL, 0.118 M) and triethylamine (2.6 mL, 0.018 M) in THF (20 mL). After keeping the reaction mixture at −70 °C for 1.5 h, solid $NaHCO_3$ was added, followed by a saturated aqueous $NaHCO_3$ solution (70 mL). After the addition of the $NaHCO_3$ solution, the cooling bath was removed and a water bath was substituted. The two layers were separated and the aqueous layer was reextracted with Et_2O. The Et_2O extracts were combined with the THF layer and the solution was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered, and evaporated in vacuo to afford crude **21** (8.7 g) a yellow oil: IR (neat) 1647, 1620, 1253, 849 cm^{-1}; NMR ($CDCl_3$) 5.10 (m, 2 H, C=CH), 4.02 (s, 2 H, $C=CH_2$), 2.03 (m, 8 H, CH_2CH_2), 1.68 (br s, 3 H, C=CCH_3), 1.62 (br s, 6 H, $C=C(CH_3)_2$).

1-Bromo-6,10-dimethyl-(5*E*)-5,10-undecadien-2-one ((5*E*)-22). Anhydrous solid $NaHCO_3$ (3.3 g) was added to crude **21** (8.7 g, 0.032 M) dissolved in THF (170 mL) with stirring. The mixture was cooled to −78 °C under nitrogen, and solid *N*-bromosuccinimide (6.04 g, 0.034 M) was added. The reaction mixture was stirred at −78 °C for 2 h and then poured into a stirred mixture of ice-cold 10% aqueous $NaHCO_3$ solution and Et_2O. The organic layer was separated, washed with 10% aqueous Na_2SO_4 solution and saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated in vacuo to give (5*E*)-**22**, a brown oil (8.6 g, 98.4%): IR (neat) 1724, 845 cm^{-1}; NMR ($CDCl_3$) 5.01 (m, 2 H, C=CH), 3.85 (s, 2 H, CH_2Br), 2.55 (m, 2 H, -$CH_2C(O)$), 2.28–1.96 (m, 6 H, $C=CCH_2$) 1.66 (m, 3 H, cis vinyl methyl); 1.61 (m, 6 H, trans vinyl methyls).

1-Bromo-6,10-dimethyl-9,10-epoxy-5(*E*)-undecen-2-one ((5*E*)-23). Water (250 mL) and saturated $NaHCO_3$–H_2O (250 mL) were added to (5*E*)-**22** (31.5 g, 0.115 M) dissolved in CH_2Cl_2 (500 mL). A solution of MCPBA (22.0 g, 0.127 M) dissolved in CH_2Cl_2 (500 mL) was added to the stirred mixture at 20 °C dropwise within 3 h. The CH_2Cl_2 layer was separated, washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to afford crude (5*E*)-**23** (33.3 g); NMR ($CDCl_3$) 5.08 (m, 1 H, C=CH); 3.87 (s, 2 H, CH_2Br), 2.68 (t, 1 H, 9-H), 1.67 (br s, 3 H, (6*E*)-CH_3), 1.30 (s, 3 H, (10*Z*)-CH_3), 1.27 (s, 3 H, (10*E*)-CH_3).

The crude product was used without further purification in the next step.

1-Bromo-6-methyl-2-oxo-5(*E*)-nonen-9-al ((5*E*)-24). Periodic acid (34.6 g, 3 × 0.051 M) dissolved in aqueous THF (240 mL, 5% by volume) was added to crude (5*E*)-**23** (14.7 g, 0.051 M) in aqueous THF (240 mL, 5% by volume) while stirring at 20 °C over a 3-min period, and the mixture was stirred at 20 °C for an additional 9 min. The reaction mixture was then added to a stirred mixture of ice-cold saturated $NaHCO_3$–H_2O (400 mL) and Et_2O (700 mL). The mixture was filtered, the organic layer separated, washed with 10% $NaHCO_3$–H_2O, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give crude (5*E*)-**24** (14.5 g): IR (neat) 2730 (CH of aldehyde), 1706 cm^{-1} (broad CO groups).

The crude reaction product was used without further purification in the next step.

1-Bromo-6-methyl-2-oxo-5(*E*)-nonen-9-oic Acid ((5*E*)-9). Jones reagent (20 mL) was added to (5*E*)-**24** (14.5 g, 0.059 M of 38% pure by NMR) in acetone (250 mL) within 5 min while stirring at 0 °C. The resultant solution was stirred for an additional 10 min at 0 °C and then added to a stirred solution of ice-cold saturated $NaHCO_3$–H_2O (350 mL). The acetone was removed in vacuo, CH_2Cl_2 (300 mL) was added, and the mixture was filtered. The organic phase was washed with H_2O and then added to the $NaHCO_3$–H_2O. The aqueous basic solution was washed once with CH_2Cl_2 and once with Et_2O, stirred at 0 °C, and acidified carefully with ice-cold 6 N HCl–H_2O to pH 2. The acidic solution was then extracted twice with CH_2Cl_2 and once with Et_2O. The extracts were washed separately with brine, combined, dried (Na_2SO_4), filtered, and evaporated in vacuo to give (5*E*)-**9** (3.92 g, 29%). The compound solidified on standing: mp 45–47 °C; IR (neat) 2700–2330 (OH), 1710 cm^{-1} (CO); NMR ($CDCl_3$) 8.67 (br, 1 H, $-CO_2H$), 5.17 (t, 1 H, C=CH), 3.88 (s, 2 H, CH_2Br), 1.67 (br s, 3 H, $C{=}CCH_3$). Anal. Calcd for $C_{10}H_{15}BrO_3$: C, 45.64; H, 5.75. Found: C, 45.82; H, 5.70.

***cis*/*trans*-2-[2-(Bromomethyl)-2-methoxytetrahydrofuran-5-yl]-2-methyl-5-oxotetrahydrofuran (30a and 30b).** MCPBA (1.40 g, 8.1 mM) in CH_2Cl_2 (20 mL) was added to (5*E*)-**9** (2.2 g, 8.4 mM) in CH_2Cl_2 (15 mL) at 2 °C dropwise, while stirring over a 15-min period. Stirring at 2 °C was continued for 3 h. Acetone (50 mL) and 0.2 N HCl–H_2O (10 mL) were added at 2 °C to the above stirred mixture and stirring was continued at approximately 5 °C for 16 h. The solvents were evaporated in vacuo with no external heating. The residue was extracted with CH_2Cl_2, and the extract was washed with brine containing enough $NaHCO_3$–H_2O to make it basic and then with saturated brine to a neutral pH. The extract was dried (Na_2SO_4), filtered, and evaporated in vacuo to give an oily solid (3.9 g). A small sample of the mixture was dissolved in CH_2Cl_2 and extracted twice with saturated $NaHCO_3$–H_2O. The extract was washed with NaCl–H_2O, dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude **29a**: IR (neat) 3300 (OH), 1754 cm^{-1} (CO); NMR ($CDCl_3$) 4.23 (m, 1 H, HC), 3,53 (s, 2 H, $-CH_2Br$), 2.05–3.00 (m, 8 H, CH_2CH_2), 1.38 (s, 3 H, CH_3).

The crude main batch of **29a** (3.8 g) was dispersed in trimethyl orthoformate (4.0 mL). The dispersion was stirred under nitrogen at 2 °C and 0.1 N H_2SO_4–methanol (1.4 mL of 0.27 mL concentrated H_2SO_4 in 100 mL of methanol) was added. The reaction mixture was stirred at 5 °C for 2 days, and then added dropwise to a stirred, ice-cold mixture of saturated $NaHCO_3$–H_2O (20 mL) and CH_2Cl_2 (20 mL). The organic layer was washed with saturated $NaHCO_3$–H_2O and then with NaCl–H_2O. It was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a mixture of the cis and trans bromo ketal lactones, **30a** and **30b** (approximately 60/40 by GC/MS, 1.94 g): IR (neat) 1770 (br), 1709 (sh), 1087, 1041 cm^{-1}; NMR ($CDCl_3$) 4.14 (m, 1 H, HC), 3.64 (s, 60% of 2 H, $-CH_2Br$), 3.49 (s, 40% of 2 H, CH_2Br), 3.29 (s, 40% of 3 H, $-OCH_3$), 3.23 (s, 60% of 3 H, OCH_3); GC/MS, two identical spectra, ratio 60/40; M^+ (292/294), $M^+ - OCH_3$ = 261/263.

(1*RS*,4*RS*,5*SR*)-4-(2-Carboxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (31). Potassium hydroxide pellets (6 g, 0.11 M) were added to the cis/trans mixture of the bromo ketal lactones **30a** and **30b** (3.27 g, 11.2 mM) in anhydrous dimethyl sulfoxide (25 mL). The mixture was stirred and heated at 45 °C under nitrogen for 3 days. It was then cooled to room temperature and CH_2Cl_2 (100 mL) was added. The organic layer was decanted and the KOH pellets were quickly rinsed with ice water (60 mL). The rinse was added to the organic extract and the organic phase was reextracted 2 times with ice water (2 × 20 mL) and then with NaCl–H_2O (20 mL). The dark, aqueous basic solution was cooled with water, stirred, and acidified with 6 N HCl–H_2O, and the acidic solution was extracted with CH_2Cl_2 (50 mL). The aqueous layer was reacidified with 2 N HCl–H_2O and reextracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 extracts were combined and washed free of acid with NaCl–H_2O, dried (Na_2SO_4), filtered, and evaporated in vacuo to give a mixture of the bicyclic acid **31** and the noncyclized trans bromo ketal lactone **30b**. The mixture (2 g) was dissolved in Et_2O (50 mL) and the Et_2O solution extracted with saturated $NaHCO_3$–H_2O. The combined $NaHCO_3$–H_2O extracts were reextracted with Et_2O. The combined Et_2O extract was evaporated in vacuo to give crude trans bromo ketal lactone **30b** (660 mg, 20%): IR (neat) 1754 cm^{-1} (br); NMR ($CDCl_3$) 4.62 (t, J = 8 Hz, 1 H, H-C), 3.5 (q, J = 12 Hz, 2 H, $-CH_2Br$), 1.37 (s, 3 H, CH_3).

The $NaHCO_3$–H_2O extract was cooled with ice water, stirred, acidified carefully with 6 N HCl–H_2O, and then extracted with CH_2Cl_2 and Et_2O. The extracts were washed separately free of mineral acid with saturated NaCl–H_2O, combined, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the bicyclic acid **31** (1.2 g, 46.6%), which solidified on standing. Crystallization from ether/petroleum ether gave pure **31**: mp 80–82 °C; IR (neat) 2800–2500 (OH), 1715 (br, CO) cm^{-1}; NMR ($CDCl_3$) 10.0 (br, 1 H, CO_2H), 3.93 (t, 1 H, C_5-H), 3.53 (q, J = 12 Hz, 2 H, C_2-CH_2), 3.43 (s, 3 H, $-OCH_3$), 1.37 (s, 3 H, C_4-CH_3); GC/MS of Me_3Si derivative (CI mode), $(M + 1)^+$ 303. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.18; H, 8.13.

(1*RS*,4*RS*,5*SR*)-4-(3-Hydroxypropyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (10). BH_3·THF (20 mL of 1 M solution) was added to **31** (3.13 g, 13.6 mM) in anhydrous THF (30 mL) while stirring at 2 °C under nitrogen within 3 min. Stirring was continued for 30 min at 2 °C and at room temperature for 2 h after which the solution was added dropwise, while stirring, to ice water (20 mL). The aqueous solution was extracted with CH_2Cl_2 and with Et_2O, and the combined extract was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the solution was washed with brine containing enough saturated $NaHCO_3$–H_2O to make it basic. The extract was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the bicyclic alcohol **10** (2.94 g, 100%) as an oil: IR (neat) 3330 (OH), 1060, 1040 cm^{-1}; NMR ($CDCl_3$) 3.92 (m, 1 H, C_5-H), 3.63 (m, 2 H, HO-CH_2-), 3.5 (q, 2 H, C_2-CH_2), 3.40 (s, 3 H, $-OCH_3$), 1.37 (s, 3 H, C_4-CH_3); GC/MS, M^+ 216. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.93; H, 9.56.

(1*RS*,4*RS*,5*SR*)-4-[3-[(Methylsulfonyl)oxy]propyl]-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (34). Triethylamine (4.0 mL, 27 mM distilled) was added to the alcohol **10** (2.94 g, 13.6 mM) in CH_2Cl_2 (30 mL). The resultant mixture was cooled with ice water and stirred under nitrogen, and methanesulfonyl chloride (1.8 mL, 22.40 mM) was added dropwise within 5 min. The reaction mixture was stirred at 5 °C under nitrogen for 16 h and then added dropwise to a stirred mixture of ice water (30 mL) and 2 N HCl–H_2O (4.0 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the mesylate **34** (3.29 g, 82%). Crystallization from ether/petroleum ether gave **34**: mp 50–54 °C; IR (neat) 1330, 1190, 1150, 1090, 1060 cm^{-1}; NMR ($CDCl_3$) 4.23 (m, 2 H, MsO-CH_2), 3.87 (t, 1 H, C_5-H) 3.53 (q, 2 H, C_2-CH_2), 3.02 (s, 3 H, CH_3S); GC/MS, M^+ 294.

(1*RS*,4*RS*,5*SR*)-1-Methoxy-4-methyl-4-(4-carbethoxy-4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (36a). To the bicyclic ketal mesylate **34** (458 mg, 1.56 mM) in anhydrous THF (4 mL) was added sodium iodide (254 mg, 1.6 mM) with the exclusion of moisture, under nitrogen, followed by the addition of ethyl 2,6-dimethyl-3-oxo-6-heptenoate (0.75 mL, 3.0 mM). A solution of lithium diisopropylamide in hexane (3 mL of 0.7 M = 2.1 mM) was added dropwise under nitrogen to the slowly stirred mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 24 h. The solvents were removed by evaporation with a fast stream of nitrogen at room temperature. Anhydrous DMF (4.0 mL) was added to the residue and the stirring at room temperature under nitrogen was continued for 72 h. CH_2Cl_2 (25 mL) and ice water (20 mL) were

added, and the organic layer was separated and washed with water containing enough 2 N HCl–H_2O to make it acidic. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the crude β-keto ester **36a** (1.3 g). This was chromatographed on a SilicAR CC-7 column (30 g) to give purified **36a** (418 mg, 65%): IR (neat) 1730 (ester CO), 1709 (keto CO) and 1644 cm^{-1} (olefinic double bond); NMR ($CDCl_3$) 4.67 (m, 2 H, CH_2=C), 4.17 (g, J = 7 Hz, 2 H, -OCH_2CH$_3$), 3.87 (m, 1 H, C_5-H), 3.50 (q, 2 H, C_2-CH_2), 3.40 (s, 3 H, -OCH_3), 1.72 (br s, 3 H, C=CCH_3), 1.33 (s, 3 H, CH_3CO$_2$), 1.32 (t, J = 7 Hz, 3 H, -OCH$_2$CH_3), 1.30 (s, 3 H, C_4-CH_3).

(1*RS*,4*RS*,5*SR*)-1-Methoxy-4-methyl-4-(4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (37). Aqueous NaOH (10 mL) was added to the β-keto ester **36a** (2.24 g, 5.7 mM) in methanol (10 mL) with stirring at 2 °C under nitrogen. After being stirred for 10 min, the mixture was allowed to warm to room temperature, and the stirring was continued for 4 days under nitrogen. The methanol was evaporated in vacuo and the aqueous residue was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give **37** (1.33 g, 72%): IR (neat) 1709 (keto CO), 1658 (double bond), 1060–1090 cm^{-1}; NMR ($CDCl_3$) 4.67 (m, 2 H, CH_2=C), 3.93 (m, 1 H, C_5-H); 3.50 (q, J = 12 Hz, 2 H, C_2-CH_2), 3.37 (s, 3 H, -OCH_3), 1.73 (br s, 3 H, C=CCH_3), 1.32 (s, 3 H, C_4-CH_3), 1.06 (d, J = 7 Hz, 3 H, -CHCH_3); GC/MS, M^+ 324.

The aqueous basic solution was cooled to 2 °C, stirred, and acidified carefully with ice-cold 6 N HCl–H_2O. The acidic solution was extracted with CH_2Cl_2 and with Et_2O, and the organic extracts were washed separately with brine, combined, dried (Na_2SO_4), filtered, and evaporated in vacuo to give **36b** (0.41 g, 20%): IR (neat) 3600–3300 (OH), 2800–3550 (OH), 1710 (CO), 1665 cm^{-1}; NMR ($CDCl_3$) 4.67 (m, 2 H, CH_2=C), 3.93 (m, 1 H, C_5-H), 3.50 (q, J = 12 Hz, 2 H, C_2-CH_2), 3.42 (s, 3 H, -OCH_3), 1.75 (br s, 3 H, C=CCH_3, 1.40 (s, 3 H, CH_3CO$_2$H), 1.35 (s, 3 H, C_4-CH_3).

The β-keto acid **36b** (0.41 g) was decarboxylated by refluxing in anhydrous toluene (80 mL) under nitrogen for 2 h to give additional ketone **37**.

(1*RS*,4*RS*,5*SR*)-1-Methoxy-4-methyl-4-(5-hydroxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (8). $NaBH_4$ (378 mg, 10 mM) was added in small portions within 3 min to **37** (1.33 g, 4.1 mM) in absolute ethyl alcohol (10 mL) while stirring at 0 °C under nitrogen. The mixture was stirred in the cold for 2 h and then added dropwise to ice water (15 mL) with stirring. The aqueous mixture was carefully acidified with 6 N HCl–H_2O and the acidic solution was extracted with Et_2O. The extract was washed with brine (10 mL) containing a few drops of saturated $NaHCO_3$–H_2O to make it basic. The Et_2O was evaporated in vacuo and the residue was dissolved in CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the bicyclic ketal alcohol **8** (1.25 g, 93%): IR (neat) 3350 (OH), 1090–1060 cm^{-1}; NMR ($CDCl_3$) 4.68 (br s, 2 H, CH_2=C), 3.91 (m, 1 H, C_5-H), 3.5 (q, J = 11 Hz, 2 H, C_2-CH_2), 3.38 (s, 3 H, -OCH_3), 1.72 (br s, 3 H, CH_2=CCH_3), 1.31 (s, 3 H, C_4-CH_3), 1.18 (d, J = 7 Hz, 3 H, -CHCH_3); GC/MS of Me_3Si derivative (CI mode), (M + 1)$^+$ = 399, 399 – Me_3SiO = 310 (BP).

(1*RS*,4*RS*,5*SR*)-1-Methoxy-4-methyl-4-(4-methyl-5-oxopentyl)-3,8-dioxabicyclo[3.2.1]octane (32). To a solution of CH_2Cl_2 (100 mL) and pyridine (1.2 g) was added CrO_3 (0.77 g, 7.7 mM), and the resulting suspension was stirred at room temperature under nitrogen for 1 h. Celite (5.5 g) was added, the suspension was cooled to −10 °C, and alcohol **7** (329 mg, 1.28 mM) in CH_2Cl_2 (40 mL) was added dropwise over 30 min and the resulting mixture was stirred 2 h at room temperature. The resulting crude reaction mixture was filtered, the filter cake containing Celite was washed well with CH_2Cl_2, and the filtrate was washed with saturated $NaHCO_3$ and brine and was dried (Na_2SO_4). The solids were filtered, and the solvent was removed in vacuo to give crude aldehyde **32** (0.32 g) which was used in the subsequent Grignard reaction without further purification: IR (neat) 1760 cm^{-1}; NMR ($CDCl_3$) 9.2 (d, 1 H, CHO), 3.4 (s, 3 H, C_1-OCH_3), 3.2–4.0 (m, 3 H, C_5-H, C_2-CH_2), 1.33 (s, C_4-CH_3).

(1*RS*,4*RS*,5*SR*)-1-Methoxy-4-methyl-4-(5-hydroxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (8). Anhydrous THF (10 mL) and Mg turnings (0.05 g) were placed in a 25-mL three-necked flask under nitrogen followed by the dropwise addition of 4-bromo-2-methyl-1-butene (0.30 g, 2.02 mM) in THF (5 mL). After the formation of the Grignard reagent, the reaction was cooled to 0 °C for 30 min and crude aldehyde **32** (0.32 g) in THF (7 mL) was added dropwise and stirred at 0 °C for 30 min. The reaction was allowed to warm to room temperature, stirred an additional 3 h, and evaporated in vacuo. The residue was partitioned between Et_2O and brine, the aqueous phase reextracted with Et_2O, and the combined organic phase washed with brine, dried (Na_2SO_4), and filtered, and the filtrate was evaporated in vacuo to give a crude yellow oil (0.243 g) which was purified by chromatography on SilicAR CC-7 using an EtOAc:hexane gradient to give **8** (0.121 g) as a yellow oil.

(1*RS*,4*RS*,5*SR*)-1-Methoxy-4-methyl-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (38). A mixture of anhydrous pyridine (1.5 mL) and acetic anhydride (3.0 mL) was added to the ketal alcohol **8** (1.25 g, 3.83 mM) at room temperature under nitrogen. The mixture was stirred at room temperature for 16 h after which the solution was evaporated while stirring under high vacuum at 45 °C for 1 h. The residue obtained was dissolved in CH_2Cl_2 and the resulting solution was washed with brine containing 2 N HCl–H_2O. The solution was then washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give **38** (1.4 g, 99.3%): IR (neat) 1739 (CO), 1242 (acetate), 1090–1030 cm^{-1}; NMR ($CDCl_3$) 4.68 (br, 3 H, CH_2=C and -CHOAc), 3.91 (m, 1 H, C_5-H), 3.5 (q, J = 11 Hz, 2 H, C_2-CH_2), 3.38 (s, 3 H, -OCH_3), 2.03 (s, 3 H, -OCOCH_3), 1.72 (br s, 3 H, C=CCH_3), 1.31 (s, 3 H, C_4-CH_3), 1.18 (d, J = 7 Hz, 3 H, -CHCH_3). GC/MS, M^+ 368.

(1*RS*,4*RS*,5*SR*)-1-Hydroxy-4-methyl-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (39). H-Cl-H_2O (1 N, 4 mL) was added to **38** (1.4 g, 3.8 mM) in acetone (12 mL). The mixture was stirred and heated at 55 °C for 4 h. The acetone was evaporated in vacuo at room temperature, and the residue was extracted with CH_2Cl_2 and washed with brine containing enough saturated $NaHCO_3$–H_2O to make it basic and then with brine. The solution was dried (Na_2SO_4), filtered, and evaporated in vacuo to give **39** (1.23 g, 91%): IR (neat) 3330 (OH), 1725 (CO), 1242 cm^{-1} (acetate); NMR ($CDCl_3$) 4.80 (m, 1 H, H-C-OAc), 4.72 (br, 2 H, CH_2=C), 3.97 (m, 1 H, C_5-H), 3.58 (q, 2 H, C_2-CH_2), 2.07 (s, 3 H, -OCOCH_3), 1.75 (br s, 3 H, C=CCH_3), 1.35 (s, 3 H, C_4-CH_3), 0.87 (d, J = 7 Hz, 3 H, -CHCH_3); GC/MS of Me_3Si derivative, 366 (M^+ – HOAc).

Ethyl (1*RS*,4*SR*,5*RS*)-4-(5-Acetoxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (41). (Carbethoxymethylene)triphenylphosphorane (**40**) (3.6 g, 10.3 mM) was added to **39** (1.23 g, 3.47 mM). The mixture was heated under nitrogen to 120 °C, stirred at this temperature for 2 days, and then cooled to room temperature, after which additional Wittig reagent **40** (1.2 g, 3.4 mM) was added. The mixture was heated again under nitrogen to 120 °C and stirred at this temperature for two more days. The reaction mixture was cooled to room temperature and purified by chromatography (SilicAR CC-7) to give **41** (1.01 g, 69%): IR (neat) 1725 (CO), 1242 cm^{-1} (acetate); NMR ($CDCl_3$) 4.83 (m, 1 H, HC-OAc), 4.67 (m, 2 H, CH_2=C), 4.13 (q, J = 7 Hz, 2 H, -COOCH_2CH$_3$), 3.83 (m, 1 H, C_5-H), 3.58 (q, J = 11 Hz, 2 H, C_2-CH_2), 2.60 (s, 2 H, -CH$_2$CO$_2$C$_2$H$_5$), 2.03 (s, 3 H, -OCH_3), 1.72 (br s, 3 H, C=CCH_3), 1.30 (s, 3 H, C_4-CH_3), 1.25 (t, J = 7 Hz, 3 H, -COOCH$_2$CH_3), 0.88 (d, J = 7 Hz, 3 H, -CHCH_3).

Ethyl (1*RS*,4*SR*,5*RS*)-4-(5-Acetoxy-4,8-dimethyl-7-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (42). p-TsOH·H_2O (8.2 mg) was added to benzene (12 mL), the mixture was stirred and refluxed in a Dean–Stark apparatus, and the ester **41** (85 mg, 0.2 mM), dissolved in benzene (6 mL), was added at room temperature, and the resultant mixture was stirred and refluxed 18 h. The reaction mixture was added to saturated $NaHCO_3$–H_2O (10 mL) and Et_2O (20 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give **42** (80.4 mg, 95%): IR (neat) 1724 (CO), 1242 (acetate), 1087 1060, 1020 cm^{-1}; NMR ($CDCl_3$) 5.12 (t, 1 H, C=CH), 4.13 (q, J = 7 Hz, 2 H, -COOCH_2CH$_3$), 3.90 (m, 1 H, C_5-H), 3.58 (q, J = 11 Hz, 2 H, C_2-CH_2), 2.65 (s, 2 H, -CH_2CO$_2$C$_2$H$_5$), 2.03 (s, 3 H, -OCOCH_3), 1.75 (br s, 3 H, (CH_3)$_2$C=C), 1.67 (br s, 3 H, (CH_3)$_2$C=C), 1.35 (s, 3 H, C_4-CH_3), 0.92 (d, J = 7 Hz, 3 H, -CHCH_3); GC/MS (CI mode), (M + 1)$^+$ 425.

(1*RS*,4*SR*,5*RS*)-4-(5-Hydroxy-4,8-dimethyl-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic Acid Hemihydrate (3). NaOH–H_2O (2 N, 2.0 mL) was added to **42** (79 mg, 0.19 mM) in methanol (2.0 mL) while stirring under nitrogen at 2 °C. After 10 min of stirring, it was allowed to come to room temperature and stirred under nitrogen for 72 h. The methanol was evaporated in vacuo at room temperature and the residue was extracted with Et_2O. The aqueous basic solution was cooled with ice water, stirred, acidified with 6 N HCl–H_2O, and extracted with Et_2O. It was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the bicyclic hydroxy acid **3** (70 mg, 91%): IR (neat) 3500–3300, 2500–2300 (OH), 1720 (CO), 1090, 1050, 1010 cm^{-1} (ether bonds); NMR ($CDCl_3$) 5.43 (br m, 2 H, -OH and -CO_2H), 5.12 (t, 1 H, C=CH), 3.90 (m, 1 H, H-C), 3.58 (q, J = 11 Hz, 2 H, -C_2-CH_2), 3.33 (m, 1 H, -C*H*OH), 2.65 (br s, -CH_2CO_2H), 1.75 and 1.67 (2 × br s, 2 × 3 H, vinyl methyls), 1.35 (s, 3 H, C_4-CH_3), 0.92 (d, J = 7 Hz, 3 H, -CHCH_3); GC/MS of bis Me_3Si derivative, M^+ 498. Anal. Calcd for $C_{20}H_{34}O_5 \cdot {}^1/_2H_2O$: C, 66.08; H, 9.74. Found: C, 65.81; H, 9.29.

(1*RS*,4*SR*,5*RS*)-4-(5-Hydroxy-4,8-dimethyl-8-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic Acid Monohydrate (43). NaOH–H_2O (2 N, 5.0 mL) was added to **41** (1.06 g, 2.5 mM) in methanol (5.0 mL) while stirring at 0 °C under nitrogen. The cooling bath was removed after 15 min and the reaction mixture was stirred at room temperature for 3 days. The methanol was evaporated in vacuo at room temperature and the residue was extracted with Et_2O. The aqueous basic solution was cooled with ice water, stirred, acidified with 6 N HCl–H_2O, and extracted with Et_2O. This extract was washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give 608 mg (69%) of crude acid **43** which was purified by column chromatography on SilicAR CC-7 to give the pure acid **43** (305 mg): IR ($CHCl_3$) 3000, 2800–2500 (sh), 1750, 1720, 1650, 730 cm^{-1}; NMR ($CDCl_3$) 6.10 (m, 2 H, CO_2H, and HO), 4.70 (m, 2 H, C=CH_2), 3.86–3.31 (m, 4 H, -CH(OH)-, C_2-CH_2, C_5-H), 2.63 (m, 2 H, CH_2CO_2H), 1.71 (br s, 3 H, CH_3C=C), 1.30 (s, 3 H, C_4-CH_3), 0.88 (d, J = 6 Hz, 3 H, -CHCH_3); MS (CI), bis Me_3Si derivative. $M^+ + 1$ = 493, $M^+ - 1$ = 491, M – Me_3SiO = 409 (base peak). Anal. Calcd for $C_{20}H_{34}O_5 \cdot H_2O$: C, 64.49; H, 9.74. Found: C, 64.00; H, 9.28.

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Registry No. **3**, 67441-54-7; (*E*)-**4**, 106-24-1; **5**, 15580-05-9; (±)-(*E*)-**6**, 90460-03-0; (±)-(*Z*)-**6**, 90460-04-1; **7**, 77878-45-6; **8**, 77878-47-8; (*E*)-**9**, 79756-30-2; (±)-**10**, 79756-34-6; **12**, 38237-34-2; (±)-**13**, 90432-82-9; (±)-**13** (benzyl ether), 90432-92-1; (±)-**14**, 90432-83-0; (±)-(*E*)-**15**, 90432-84-1; (±)-(*Z*)-**15**, 90432-85-2; (±)-(*E*)-**16**, 90460-05-2; (±)-(*Z*)-**16**, 90460-06-3; (±)-(*Z*)-**17**, 90432-87-4; (*E*)-**4**, 106-24-1; (±)-(*E*)-**18**, 90432-86-3; (±)-(*E*)-**19**, 90432-88-5; (±)-(*Z*)-**19**, 90432-89-6; (*E*)-**20**, 3796-70-1; (*E*)-**21**, 79756-27-7; (*E*)-**22**, 79756-28-8; (±)-(*E*)-**23**, 90432-90-9; (*E*)-**24**, 79772-32-0; (*E*)-**25**, 77878-39-8; **26**, 77878-41-2; **27**, 77878-43-4; **28**, 77878-62-7; **29**, 79756-31-3; **30**, 90528-01-1; (±)-**31**, 79756-33-5; (±)-**32**, 77878-46-7; **33**, 20038-12-4; (±)-**34**, 90432-91-0; **36a**, 79756-36-8; (±)-**37**, 90528-02-2; **38**, 77878-48-9; **39**, 77878-49-0; **41**, 77878-50-3; **42**, 77878-51-4; **43**, 79756-39-1; H_2C=C(CH_3)-$CH_2CH_2COCH(CH_3)CO_2Et$, 18034-04-3; Ph_3P=$CHCO_2Et$, 1099-45-2; ethyl acetoacetate, 141-97-9.

Kinetics and Mechanism of the Reaction of Ketones with Lithium Reagents in Cyclohexane

Munther A. Al-Aseer and Stanley G. Smith*

Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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The kinetics of the reaction of *sec*-BuLi and *n*-BuLi with several substituted phenyl *sec*-butyl ketones in cyclohexane at 25.0 °C have been examined by stopped-flow infrared spectroscopy. Experiments in which reacting solutions of the ketones were scanned over the carbonyl region of the infrared spectrum revealed the presence of an intermediate which was characterized as a reversibly formed complex between ketone and alkyllithium aggregate. The rates of disappearance of the ketones in the presence of excess alkyllithium exhibited complex dependence on reagent concentration. Further, the dependence of the pseudo-first-order rate constant on lithium reagent concentration varied with each compound. These results are accommodated by a mechanism in which product is formed by rearrangement of the ketone–alkyllithium aggregate complex and by reaction of uncomplexed ketone with alkyllithium monomer.

The addition of alkyllithium reagents to ketones is a widely used reaction in organic synthesis. In contrast to the corresponding Grignard reagent reactions with ketones which give high ratios of reduction to addition products, the use of alkyllithiums leads to the predominant formation of the addition product.[1]

The mechanism of this reaction has been the subject of several reports by Smith and co-workers. For example, the reactions of methyllithium with 2,4-dimethyl-4′-(methylthio)benzophenone[2a] and 4-(methylthio)acetophenone[2b] in ether was found to be $^1/_4$ order with respect to methyllithium which supports a dissociative mechanism in which the tetrameric methyllithium is in rapid equilibrium with a small concentration of monomer which is

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