The Convergent Synthesis of Polyether Ionophore Antibiotics: The Synthesis of the A Ring Carbamonensin Spiro Ether[1]

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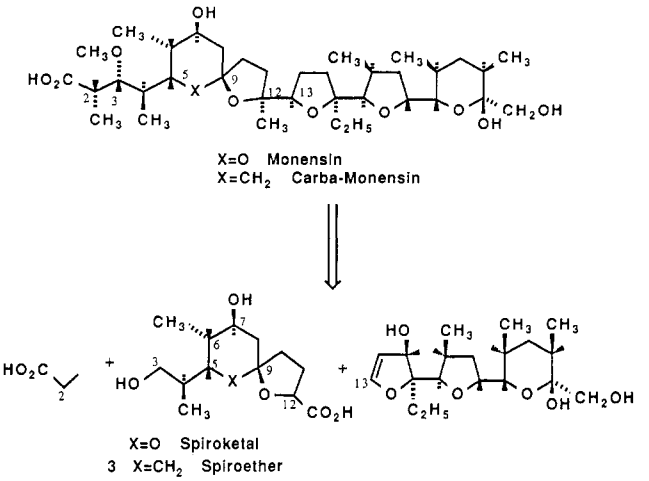
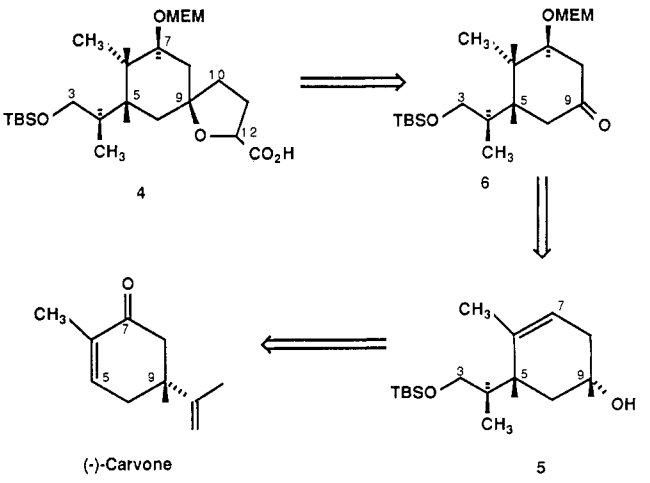
The spiro ether **3**, a versatile intermediate for the synthesis of the A ring carbamonensin and other nonnatural analogues of polyether ionophore antibiotics, is prepared in 20 steps from (*R*)-(−)-carvone. Key steps include the ester enolate Claisen rearrangement of the propionate **8**, the regio- and stereoselective hydroboration of the olefin **5** via the protected bicyclic hemiacetal **34** and the stereoselective Grignard reaction of the ketone **6** bearing a β-leaving group.

The polyether antibiotics[4] are a class of fascinating, stereochemically complex organic molecules. As ionophores, these compounds possess the ability to form lipid soluble complexes with monovalent and divalent cations.[5] Via these species, the ionophores catalyze the transport of cations across lipid barriers.[6] This exchange of cations is responsible for most of their diverse biological activities.[7] Their most important commercial applications so far have been in the field of veterinary medicine.[8] The ionophores, such as monensin and lasalocid, represent the most successful class of anticoccidials, and their use to improve feed utilization in ruminants has been of extensive economic benefit. In human medicine, several carboxylic acid ionophores have shown interesting activity, particularly as cardiovascular agents.[9] Because of their biological importance and their molecular complexity it is not surprising that the synthesis of these molecules has become the concern of numerous research groups over the last few years.[10]

Scheme I. Retrosynthetic Analysis for Carbamonensin



Scheme II. Basic Design for Spiro Ether 4 Synthesis



We here describe the preparation of the spiro ether subunit **3** of the ring A carbamonensin. To transport cations across lipophilic cell membranes, monensin forms a complex in which the hydrophilic oxygen functions are coordinated around the cation, forming a hydrophilic "inside" and a lipophilic "outside". From the X-ray structure[11] it is known that the monensin–cation complex still has one of its hydrophilic oxygens, the oxygen bridging C5 and C9, on the outside and the presence of such an

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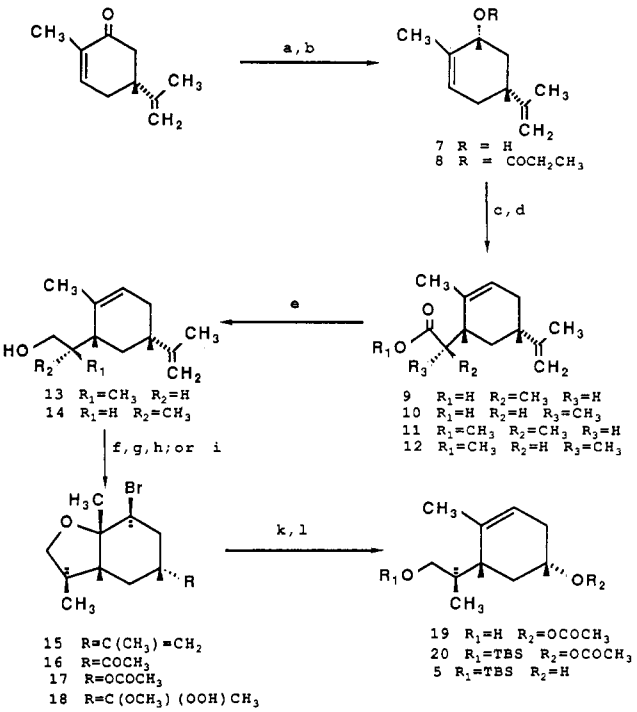
"outside polar group" might be expected to impede transport of the ion complex. This "imperfect structure" occurs because nature is restricted to a small set of starting molecules.[12] Our plan was to develop a monensin-like structure that has a lipophilic carbon atom in place of the outside lipophobic oxygen of natural monensin. As a result, ion complex transport across cell membranes should be enhanced, and this should reflect in biological activity. To accomplish this structural change it was necessary that the monensin spiro ketal subunit be replaced by a spiro ether system. In other ionophores such as dianemycin, laidlomycin, mutalomycin, and lonomycin, where the same spiro ketal unit is present, only one of the spiro ketal oxygens as well acts as a ligand.[13] A basic design was therefore sought for the synthesis of a spiro ether building block that could be used for the construction of the ring A carbamonensin as well as for other potentially important nonnatural analogues of other polyether antibiotics.

The synthetic route chosen for the construction of ring A carbamonensin is based on the recently developed building-block approach to the polyethers which utilizes the ester enolate Claisen rearrangement[14] to join prefabricated tetrahydrofuran and tetrahydropyran ring systems (Scheme I). This method was already used in the total synthesis of lasalocid A[10b] and its enantiomer[15] and in an approach toward the synthesis of monensin.[16]

The suitably protected spiro ether 4 (Scheme II), with its challenging array of six asymmetric centers, is a particularly attractive synthetic target. Disconnection of the C9,10 bond[17] generates the cyclohexanone derivative 6 for which the cyclohexanol 5 is a suitable precursor. To avoid potentially tedious resolutions of one of the required intermediates, (*R*)-(−)-carvone was chosen as a chiral starting material[18] (Scheme II). It was believed that the remote asymmetric centers could be controlled by the preexisting chirality at C9[17] and the isopropylidene group would serve as a suitable protected oxygen functionality. This approach provides for the use of methodology already developed in these laboratories; namely, the stereoselection provided by the ester enolate Claisen rearrangement[14] allows the introduction of the C5[17] side chain, and an intermediate bicyclic system[16a] leading to ketone 6 provides

Scheme III. Synthesis of the Homoallylic Alcohol 5[a]



[a] (a) LAH, ether, −78 °C; 98%; (b) CH_3CH_2COCl, pyr, CH_2Cl_2, 0 °C → room temperature; 99%; (c) (i) LDA, THF, HMPA, −78 °C; (i2) TBSCl, THF, −78 °C → room temperature; (iii) 50 °C, 6 h; 71%; or (i) LHMDS, THF, −78 °C; (ii) *t*-$BuMe_2SiCl$, HMPA, −78 °C → room temperature; (iii) 50 °C, 6 h; 58%; (d) CH_2N_2, ether; 96%; (e) LAH, ether; 99%; (f) NBS, acetone, 0 °C; 85%; (g) OsO_4 (cat.), $NaIO_4$, THF, H_2O; 90%; (h) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2; 92%; (i) O_3, CH_3OH, CH_2Cl_2; (ii) $(CH_3CO)_2O$, $N(C_2H_5)_3$, DMAP, CH_2Cl_2; (iii) $(CH_3CO)_2O$, pyr, DMAP, CH_2Cl_2; 72%; (j) Zn, H_2O, C_2H_5OH, 80 °C; 87%; (k) *t*-$BuMe_2SiCl$, imidazole, DMF; 100%; (l) LAH, ether, 0 °C; 96%.

easy control of the asymmetry at C6 and C7 through regio- and stereoselective hydroboration. While the stereochemistry at C12[17] was believed not to be crucial for the further transformation to the A ring carbamonensin by ester enolate Claisen rearrangement,[14] equatorial attack of a carbon nucleophile should introduce the desired configuration at C9.[17]

I. Synthesis of the Homoallylic Alcohol 5 (Scheme III). After having decided on the homoallylic alcohol 5 as one of our key intermediates, we investigated two approaches for its construction from (−)-carvone. The first is shown in Scheme III. (−)-*cis*-Carveol (7),[19] available on large scale by treatment of (−)-carvone with lithium tetrahydridoaluminate (LAH) at −78 °C, was converted to its propionate 8. Application of the ester enolate Claisen rearrangement procedure[14] to 8 allowed the introduction of the side chain at C5.[17] The use of lithium diisopropylamide (LDA) in HMPA/THF afforded in 71% yield a 10:1 mixture of the isomeric acids 9 and 10, as could be determined from the ^1H NMR spectrum of the mixture of the corresponding methyl esters 11 and 12. That the major component of the isomeric mixture was the desired acid 9 could be concluded from ample precedent.[20]

The rearrangement of the *Z* silyl ketone acetal takes place through a preferred boatlike transition state, and thus the major product obtained from enolization in the

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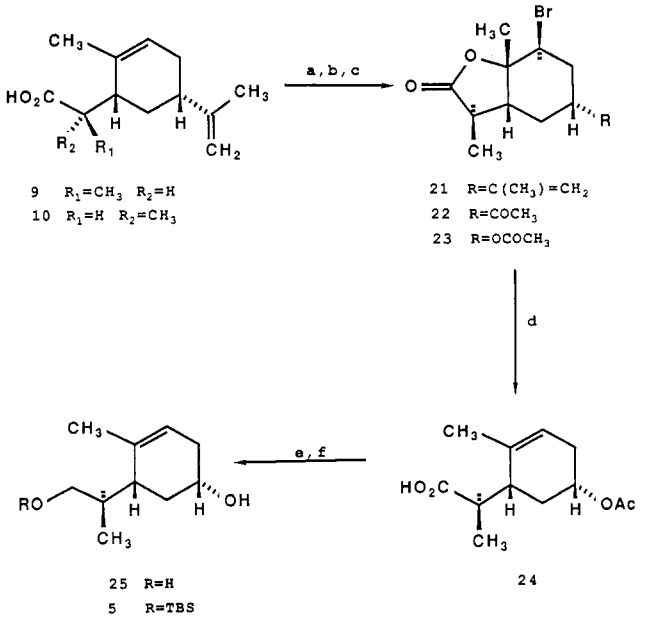
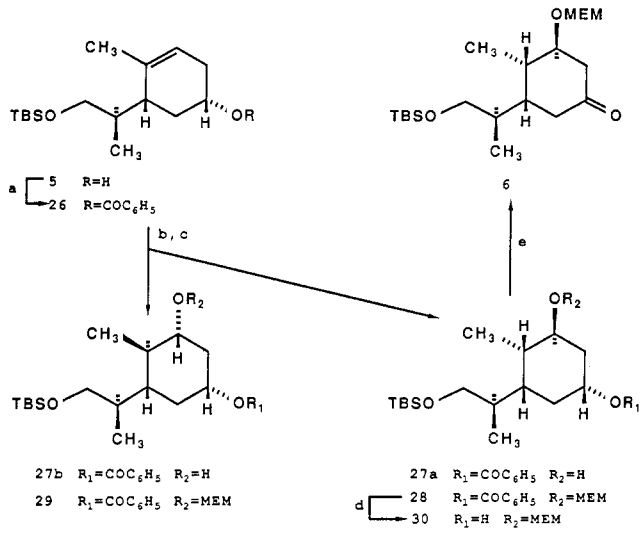
Scheme IV. Second Approach to the Homoallylic Alcohol 5[a]



[a] (a) NBS, acetone, 0 °C; 82%; (b) OsO_4 (cat.), $NaIO_4$, THF, H_2O; 95%; (c) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2; 90%; (d) Zn, C_2H_5OH, 80 °C; 95%; (e) LAH, ether; 100%; (f) *t*-$BuMe_2SiCl$, $N(C_2H_5)_3$, DMAP, CH_2Cl_2; 83%.

Scheme V. Hydroboration of the Monocyclic Olefin 26[a]



[a] (a) C_6H_5COCl, pyr, CH_2Cl_2; 98%; (b) (i) BH_3, THF, 0 °C; (ii) 1 N NaOH, 30% H_2O_2; 95%; (c) $CH_3OCH_2OCH_2Cl$, (*i*-Pr)$_2$NEt, CH_2Cl_2, 40 °C; 69% of **28** and 23% of **29**; (d) LAH, ether, 0 °C; 91%; (e) (i) $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 → −50 °C; (ii) Et_3N, −50 °C → room temperature; 88%.

presence of HMPA has the *R* configuration at C4.[17] A comparable stereochemical result was obtained with lithium hexamethyldisilazide (LiHMDS) in THF instead of LDA in THF/HMPA,[21] but rearrangement products **9** and **10** were isolated as a 9:1 mixture in only 58% yield.

Having attached the side chain at C5, we now planned to convert the C9-isopropylidene[17] group into a hydroxy group and in preparation for this degradation the C6,7[17] double bond was protected as a bromo ether.[22] Treatment of the mixture of the diastereomeric acids **9** and **10** with 2 equiv of LAH in ether at room temperature led in 99% yield to a 10:1 mixture of the alcohols **13** and **14**. Reaction of this mixture in acetone with 1.05 equiv of *N*-bromosuccinimide (NBS) at 0 °C for 15 min produced stereoselectively in 85% yield the bromo ether **15**. Interestingly, the 2*S* alcohol **14** did not react under these reaction conditions and was recovered in 7% yield.

Conversion of the bromo ether **15** to the acetate **17** was achieved in high yield by catalytic oxidation with osmium tetraoxide in the presence of sodium periodate[23] followed by Baeyer–Villiger rearrangement with peroxytrifluoroacetic acid.[24,25] Alternatively the acetate **17** can be synthesized in 72% isolated yield from the bromo ether **15** by a sequence recently developed by Schreiber and Liew.[26] Ozonolysis in the presence of methanol afforded the α-methoxy hydroperoxide **18**, which undergoes Criegee rearrangement[27] upon treatment with acetic anhydride to provide after reacetylation the acetate **17**. As a byproduct the ketone **16** could be isolated in 11% yield. The bromo ether **17** was then transformed into the olefin **19** by the Boord reaction,[28] and a protection–deprotection sequence gave the intermediate **5** in excellent yields.

The second approach to the homoallyl alcohol **5** is outlined in Scheme IV. Here the C6,7[17] double bond of the acid **9** was protected by bromolactonization[29] with NBS in acetone. As the only product the bromo lactone **21** was isolated in 82% yield as one single isomer. The isopropylidene group in **21** was then converted into a methylcarbonyloxy group by the sequence described above in the bromo ether series and the acid **24** was obtained in excellent yield after the zinc reduction.[28]

Selective protection of the primary hydroxy group of the diol **25**, obtained by LAH reduction of the acid **24**, was achieved by the method of Chaudhary and Hernandez.[30] The homoallyl alcohol **5** was isolated in 83% yield as well of 7% disilylated product and 6% starting material **25**.

II. Synthesis of the β-Alkoxy Ketone 6 (Scheme VIII). With the appropriately functionalized intermediate **5** in hand, the construction of the β-alkoxy ketone **6** was pursued. It was our plan first to investigate the stereochemical outcome of the hydroboration reaction of a monocyclic system, such as the benzoyl-protected alcohol **26**. Bearing in mind the small difference in steric hindrance between the α- and the β-side of the olefin **26** it was not surprising that treatment of **26** with BH_3 in THF at 0 °C afforded after oxidative workup a 2.5:1 mixture of the 6*S*,7*S* alcohol **27a** and the 6*R*,7*R* alcohol **27b**[17] in 95% yield[31] (Scheme V). Protection of this mixture with (2-methoxyethoxy)methyl chloride[32] (MEMCl) provided after chromatographic separation on silica gel the desired ether

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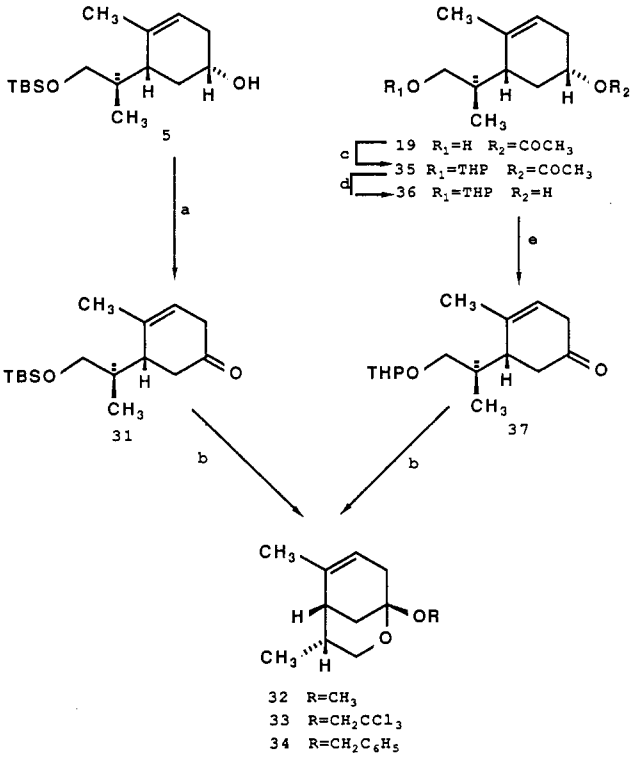
Scheme VI. Synthesis of the Protected Hemiacetals[a]



[a] (a) (i) $(COCl)_2$, Me_2SO, CH_2Cl_2, −50 °C; (ii) Et_3N, −50 °C → room temperature; 81% (over three steps from **19**); (b) for conditions, see Table I. (c) DHP, PPTS, CH_2Cl_2; 99%; (d) LAH, ether, 0 °C; 100%; (e) (i) $(COCl)_2$, Me_2SO, CH_2Cl_2; −50 °C; (ii) Et_3N, −50 °C → room temperature; 91%.

28 and its isomer **29** in 69% and 23% yield, respectively. Debenzoylation of **28** using LAH reduction followed by Swern oxidation[33] yields the desired β-alkoxy ketone **6** in good yield.

To improve the stereoselectivity of the hydroboration reaction other boranes were tested. Surprisingly, treatment of **26** with thexylborane[34] in THF at 0 °C afforded in a very slow reaction a 1:5 mixture of the alcohols **27a** and **27b**.[35] No reaction at all was observed when 9-BBN was used as the hydroborating agent even at 65 °C.

Due to low stereoselectivity in the hydroboration reaction an alternative route to intermediate **6** was pursued. Although the rigidity of a bicyclic system itself can mediate control of relative stereochemistry, in this instance we planned to use a suitably protected bicyclic hemiacetal such as **34** for this purpose (Scheme VI). Therefore, the homoallyl alcohol **5** was converted by swern oxidation[33] in good yield to the rather unstable β,δ-unsaturated ketone **31**.[36,37] All attempts to obtain the free hydroxy ketone by cleavage of the silyl ether **31** with fluoride failed.[38,39]

Scheme VII. Fluoride-Catalyzed Cyclization of Ketone 31

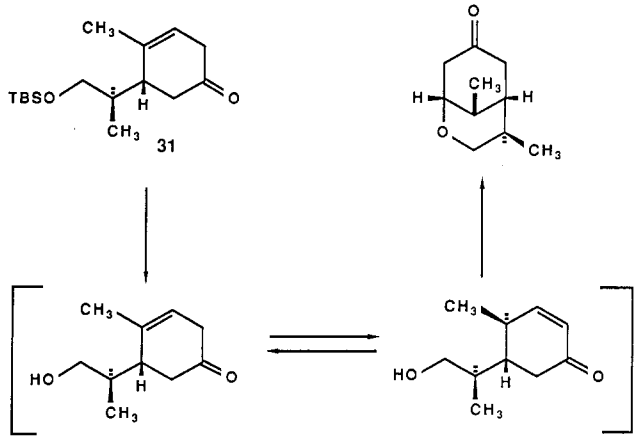


Table I. Synthesis of the Protected Bicyclic Hemiacetals

starting material	conditions	product	yield, %
31	CH_3OH, $BF_3{\cdot}OEt_2$[a]	**32**	23
31	CH_2OH, IR-120[b]	**32**	48
31	$C_6H_5CH_2OH$, PPTS[c]	**34**	59
37	CH_3OH, PPTS[d]	**32**	86
37	CCl_3CH_2OH, PPTS[e]	**33**	65
37	$C_6H_5CH_2OH$, PPTS[c]	**34**	91

[a] equiv of $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 30 min; then excess CH_3OH, 0 °C. [b] 40 wt % Amberlite IR-120, CH_3OH, room temperature. [c] 10 mol % PPTS, excess $C_6H_5CH_2OH$, $CHCl_3$, 61 °C. [d] 10 mol % PPTS, excess CH_3OH, CH_2Cl_2, 40 °C. [e] 15 mol % PPTS, excess CCl_3CH_2OH, CH_2Cl_2, 40 °C.

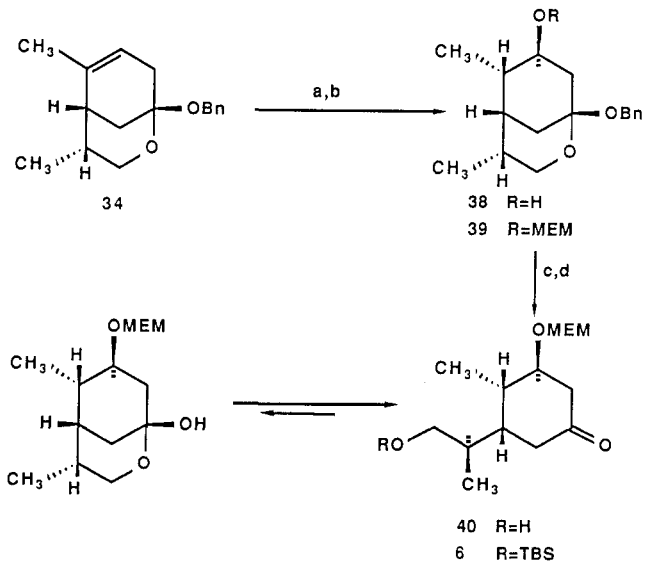
Under these reaction conditions isomerization of the β,δ-unsaturated cyclohexanone to the hydroxyenone which underwent an intramolecular Michael-type cyclization was the only observed result[40] (Scheme VII).

Frustrated by these results, we were constrained to use a one-step procedure in which the initially formed hydroxy ketone, which is in equilibrium with its hemiacetal form, is immediately converted to the protected hemiacetal. These experiments are summarized in Table I.

Starting from the β,δ-saturated ketone **31**, best results are obtained with pyridinium *p*-toluenesulfonate (PPTs) as acid catalyst;[41] with this reagent the β,δ-unsaturated hydroxy ketone intermediate seemed to be most stable. To further improve the yield, another protecting group for the hydroxy ketone was chosen. The alcohol **19** could be converted in a protection[42] -deprotection sequence to the homoallylic alcohol **36**, which afforded after Swern oxidation[43] the THP-protected hydroxy ketone **37**. Treatment of **37** with excess benzyl alcohol in refluxing $CHCl_3$ catalyzed by PPTs provided the protected hemiacetal **34** in excellent yield. Under similar conditions ketone **37** could also be converted into **32** or **33** in good yields.[44]

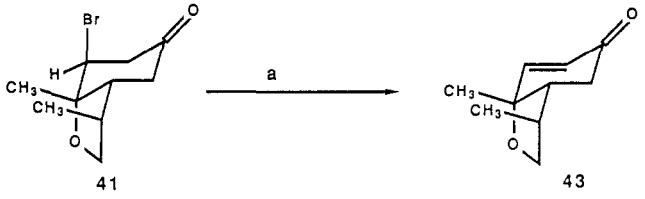
(33) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(34) For a review about applications of thexylborane, see: Brown, H. C.; Negishi, E. *Synthesis* **1974**, 77.
(35) After 4 h the mixture of **27a** and **27b** was isolated in only 9% yield besides 87% starting material.
(36) Similar results could be obtained by oxidation with Pyridinium chlorochromate (PCC) on alumina in benzene: Cheng, Y.-S.; Lui, W.-L.; Chen, S. *Synthesis* **1980**, 223.
(37) Compound **31** could be stored in the refrigerator (−15 °C) for several weeks without decomposition. On standing at room temperature **31** was completely isomerized to the α,β-unsaturated ketone after 4 weeks.
(38) The following conditions had been tried. (1) 2.5 equiv of tetrabutylammonium fluoride, THF: Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (2) HF–pyridine, pyridine, THF: (a) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (b) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (3) 3 equiv of $LiBF_4$, CH_2CH_2/CH_3CN (3:2): Metcalf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35.
(39) For a similar observation, see: Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta* **1986**, *69*, 1273.
(40) For an example of fluoride-catalyzed addition of thiols to α,β-unsaturated carbonyl compounds, see: Kuwajima, I.; Murofushi, T., Nakamura, E., *Synthesis* **1976**, 602. Another similar cyclization of a β,δ-unsaturated hydroxy ketone is described by: Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986.
(41) PPTS in CH_3OH/CH_2Cl_2 can also be used for simple deprotection of silylethers.
(42) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(43) Oxidation with PCC–alumina, molecular sieves (4-Å), and benzene gave the ketone **37** in only 71% yield (see also ref 36).
(44) For another important example for protection of a hemiacetal moiety, especially of the anomeric center of carbohydrates, see: Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603.

Scheme VIII. Synthesis of the β-Alkoxy Ketone 6[a]



[a] (a) (i) BH_3, THF, Et_3N, 0 °C → room temperature; (ii) 2 N NaOH, 30% H_2O_2, 35 °C; >91%; (b) (i) KH, THF, 0 °C → room temperature; (ii) $CH_3OCH_2CH_2OCH_2Cl$; 88%; (c) 10% Pd/C, H_2, EtOH; 99%; (d) *t*-$BuMe_2SiCl$, imidazole, DMF; 86%.

Scheme IX. Elimination of Bromo Ketone 41 by Grignard Reagent 42[a]



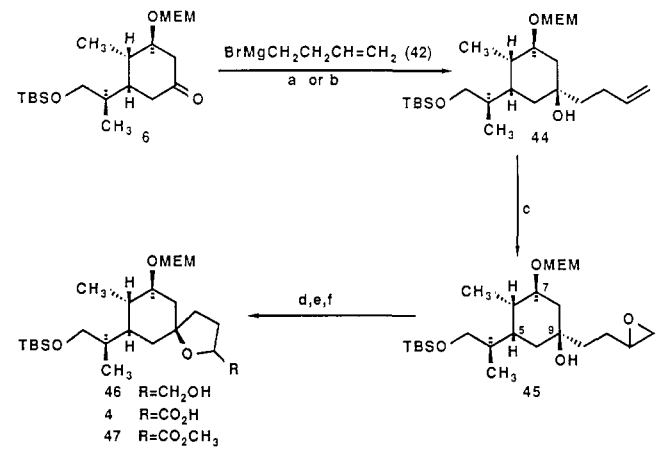
[a] (a) $BrMgCH_2CH_2CH{=}CH_2$ (41), ether, −20 °C.

Having developed good access to protected bicyclic hemiacetals we now focused our attention on its further conversion to the desired β-alkoxy ketone **6**. It was expected that cyclohexanones with an axial alkoxy substituent in β position would be rather unstable toward basic or acidic conditions necessary for deketalization of the bicyclic system. Therefore, the benzyl-protected hemiacetal **34** was chosen for further manipulations.

Hydroboration of **34** occurred with complete regio- and stereoselectivity from the convex face of the bicyclic acetal[45] (Scheme VIII). After protection of the alcohol **38** as its MEM ether,[32] hydrogenolytic cleavage[46] of the benzyl acetal[39] afforded the corresponding hydroxy ketone **40**, which was converted to the silyl ether **6** in excellent yield. As could be seen from the 500-MHz NMR, in $CDCl_3$ 40% of the hydroxy ketone **40** exists in its hemiacetal form, suggesting an energy difference of approximately 0.25 kcal/mol.

III. Formation of the Spiro Ether 4 (Scheme X). The final stages of the spiro ether synthesis (Scheme X) involved the introduction of a suitably functionalized C_4 chain by Grignard addition to the cyclohexanone **6**.[47] Literature precedence[48] as well as model studies (see below)

Scheme X. Synthesis of the Spiro Ether 4[a]



[a] (a) THF, −15 °C; 55%; (b) ether, −15 °C; 51%; (c) MCPBA, NaOAc, CH_2Cl_2; 100%; (d) (±)-camphor-10-sulfonic acid, CH_2Cl_2, 0 °C; (100%); (e) for conditions, see Table II; (f) CH_2N_2, ether.

Table II. Oxidant of the Alcohol 46

oxidant	yield of 48,[a] %
Pt, O_2[b]	NR[g]
(i) $(COCl)_2$, Me_2SO; (ii) Ag_2O[c]	[h]
$RuCl_3{\cdot}3H_2O$ (cat.), $NaIO_4$[d]	30
RuO_4[e]	47
PDC[f]	56

[a] Yields are given after esterification of the crude acid **4** with diazomethane and chromatographic separation. [b] Pt, O_2, acetone, aqueous $NaHCO_3$, 50 °C. [c] (i) $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 → −40 °C; then Et_3N, −60 °C → room temperature 90%. (ii) Ag_2O, 1 N NaOH, EtOH, H_2O. [d] $RuCl_3{\cdot}3H_2O$ (cat.), $NaIO_4$, CCl_4, CH_3CN, H_2O. [e] RuO_4, CCl_4 added to **46** in acetone, 0 °C, 10 min. [f] PDC, DMF. [g] No reaction. [h] Decomposition.

indicate that β-elimination is an important side reaction of the addition of organometallics to ketones bearing a β-leaving group. On treatment of the cyclohexanone derivative **41**,[49] having an axial leaving group in the 3-position, with 1 equiv of the Grignard reagent **42**, no 1,2-addition was observed under various conditions. The β-elimination product **43** could be isolated in good yields[50] (Scheme IX) as the only product.

Fortunately reaction of ketone **6** with the Grignard reagent **42** in THF at −15 °C gave the desired alcohol **44** in 55% yield (Scheme X). The remainder of the material consisted of products resulting from β-elimination (15%) or reduction (20%).[51,52] The 1,2-addition was completely stereoselective from the sterically less hindered "equatorial" side.[53] A sharp and concentration independent absorption at 3500 cm^{-1} in the IR spectrum confirmed the presence of an intramolecular hydrogen bond[54]

(45) Complete regio- and stereoselectivity was also observed in the hydroboration of the bicyclic olefins **32** and **33**.

(46) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.

(47) The synthesis of substituted tetrahydrofurans by addition of a C_4-Grignard reagent to a ketone or aldehyde was first described by: Renfrow, W. B.; Oakes, D.; Lauer, C.; Walter, T. A. *J. Org. Chem.* **1961**, *26*, 935.

(48) (a) McLamore, W. M.; Harfenist, M.; Bavley, A.; P'An, S. Y. *J. Org. Chem.* **1954**, *19*, 570. (b) Fuson, R. C.; Hess, E. H.; Killam, H. S. *J. Org. Chem.* **1958**, *23*, 645. (c) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019. (d) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.

(49) The bromo ketone **41** can easily be synthesized from the acetate **17** (Scheme III) by diisobutylaluminum hydride reduction followed by Swern oxidation. See ref 50.

(50) Ireland, R. E.; Courtney, L., unpublished results.

(51) The reduction product consisted mainly of the alcohol **27a** (Scheme IV) derived from axial attack of the hydride. Swern oxidation of this material afforded the starting material **6** in good yield.

(52) Similar results are obtained with ether as solvent: 1,2-addition (54%), β-elimination (13%), and reduction (14%).

(53) (a) Jasserand, D.; Granger, R.; Girard, J. P.; Chapat, J. P.; Rossi, J. C. *Bull. Soc. Chim. Fr.* **1973**, 2442. (b) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521. (c) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

between the C9-hydroxyl and the C7 ether oxygen.[17] The yield of addition could not be improved at the expense of reduction by complexing the Grignard reagent with lithium perchlorate, tetrabutylammonium bromide, or HMPA.[55] Although no more reduction was observed under these conditions, β-elimination was the main reaction.

Completion of the synthesis of the spiro ether **4** followed an earlier strategy developed by Kishi and co-workers.[56] Thus, treatment of the bishomoallylic alcohol **44** with *m*-chloroperbenzoic acid[57] in CH_2Cl_2 at room temperature afforded a 1:1 mixture of the epimeric epoxides **45**, which was directly converted in quantitative yield to the tetrahydrofuran **46** under acidic conditions. Unforseen difficulties arose in the final oxidation of the primary alcohol **46** to its acid **4**. After an initial disappointment with Adam's catalyst[58] a series of other oxidation methods was tested. These experiments are summarized in Table II. Best results were obtained with pyridinium dichromate (PDC) in DMF.[60] After esterification of the crude acid **4** with diazomethane the methyl ester **47** was isolated in 56% yield as a 3:2 mixture epimeric at C12.[17] Since the asymmetry at the carbomethoxy center will be lost during enolization in the Claisen rearrangement joining this subunit to the polyether backbone, each of the two diastereomers as well as their mixture can, in principle, be converted to the desired unnatural polyether ionophore antibiotic.

Experimental Section

(−)-*cis*-Carveol (7). To a stirred suspension of 6.05 g (0.15 M) of lithium tetrahydridoaluminate in 350 mL of ether at −78 °C under an argon atmosphere was added dropwise over a 1 h period of solution of 23.10 g (0.154 M) of (−)-carvone in 40 mL of ether. After being stirred for an additional 1 h at −78 °C, the reaction was allowed to warm up to 0 °C over a 15-min period and was cautiously treated with 6.0 mL of water, 4.5 mL of 5 N aqueous NaOH, and then 20.0 mL of water. The mixture was stirred for 0.5 h, filtered, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 23.45 g (quant) of crude (−)-*cis*-carveol (**7**). Distillation [124–128 °C (40 mmHg)] of the crude product gave 22.90 g (98%) of a clear liquid containing 97% (−)-carveol (**7**) and 3% (−)-*trans*-carveol. The (−)-carveol mixture obtained was used in the next step without further purification: R_f 0.32 (silica gel, 1:1 ether/petroleum ether): $[\alpha]^{23}_D$ −26.6° (neat, 1 dm) ($[\alpha]^{25}_D$ −25.8° (neat, 1g)); IR ($CHCl_3$) 3600, 3450, br, 1640, 1455, 1435, 1370, 1025, 995, 915, 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 6 H, 2 CH_3C), 3.8–4.2 (m, 1 H, CC*H*CH_2), 4.71 (s, 2 H, H_2C=C), 5.4–5.6 (m, 1 H, CH_2CH=C).

(−)-*cis*-Carvyl Propionate (8). To a stirred solution of 23.00 g (0.151 M) of the (−)-carveol mixture (**7**) in 450 mL of dry dichloromethane cooled to 0 °C (ice bath) under an argon atmosphere was added first 23.0 mL (0.232 M) of dry pyridine and then dropwise over a 0.5-h period of 16.0 mL (0.184 M) of propionyl chloride. The solution was stirred for 1 h at 0 °C and for an additional 1 h at room temperature. After filtration, the reaction mixture was washed with two 100-mL portions of 1 N aqueous HCl, 100 mL of water, and 100 mL of saturated NaCl, dried over $MgSO_4$, and then concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) on 20 cm of silica gel with 1:15 ether/petroleum ether afforded 31.17 g (99%) of the ester **8**, which contained 3% of its trans isomer: R_f 0.48 (silica gel, 1:15 ether/petroleum ether); evaporative distillation 85 °C (0.11 mmHg); $[\alpha]^{22}_D$ −46.13° (neat, 1 dm); IR ($CHCl_3$) 1720, 1640, 1450, 1360, 1270, 1185, 1080, 1015, 925, 895 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.16 (t, 3 H, J = 7.5 Hz, CH_3CH_2), 1.61 (s, 3 H, CH_3C), 1.71 (s, 3 H, CH_3C), 2.34 (t, 2 H, J = 7.5 Hz, CH_3CH_2C), 4.71 (s, 2 H, CH_2=C), 5.2–5.7 (m, 2 H, CC*H*CH_2 and CH_2CH=C). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.08; H, 9.65.

2(*R*)-[2-Methyl-5(*S*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionic Acid (9). To a stirred solution of 96.9 mmol of lithium diisopropylamide [from 15.0 mL (107.0 mmol) of diisopropylamine and 96.9 mmol of *n*-butyllithium in hexane] in 50 mL of THF were added at −40 °C 100 mL of dry THF and 45 mL of dry HMPA. After the reaction was cooled to −78 °C (dry ice/acetone) a solution of 18.00 g (86.4 mmol) of the propionate **8** in 20 mL of dry THF was added dropwise over 20 min. After 15 min, 17.40 g (115.4 mmol) of *tert*-butyldimethylchlorosilane in 10 mL of dry THF was added rapidly with vigorous stirring. The mixture was stirred for 10 min at −78 °C and then allowed to warm to room temperature over a 45-min period. After heating to 50 °C for 6 h, the reaction mixture was diluted with 300 mL of 2 N NaOH and stirred for 15 min. The organic phase was separated and extracted with three 150-mL portions of 2 N NaOH, and then the combined aqueous base phases were washed with 2 × 250 mL of ether, acidified with concentrated HCl (pH ~2), and extracted with 3 × 500 mL of ether. The combined ethereal extracts were washed with 250 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 12.80 g (71%) of a 10:1 mixture of the diastereomeric acids **9** and **10** a colorless oil: R_f 0.41 (silica gel, 1:1 ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 0.95 and 1.15* (2 d, 3 H, J = 7 Hz, CH_3CH), 1.69 (br s, 6 H, $w_{1/2}$ = 6 Hz, CH_3C), 4.69 (br s, 2 H, $w_{1/2}$ = 3 Hz, CH_2=C), 5.4–5.6 (m, 1 H, CH_2CH=C), 10.05 (br s, 1 H, $w_{1/2}$ = 18 Hz, COOH).

Methyl 2(*R*)-[2-Methyl-5(*R*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionate (11). A sample of 380 mg (1.824 mmol) of the 10:1 mixture of the diastereomeric acids **9** and **10** was esterified with ethereal diazomethane. Chromatography of the crude product on silica gel with 1:15 ether/petroleum ether afforded 389 mg (96%) of the methyl ester. ^1H NMR analysis revealed a ratio of 10:1 for the 2*R* methyl ester **11** and the 2*S* methyl ester **12**: R_f 0.47 (silica gel, 1:15 ether/petroleum ether); evaporative distillation 100 °C (0.14 mmHg); $[\alpha]^{22}_D$ +23.8° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 1718, 1639, 1445, 1430, 1378, 1192, 1168, 1150, 1094, 1040, 893 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 0.96 and 1.16 (2 d, 3 H, J = 7 Hz, CH_3CH), 1.38 (t, 1 H, J = 12 Hz, CHC*H*HCH, α-H), 1.60 and 1.64* (2 br s, 3 H, CH_3C), 1.70 and 1.72* (2 br s, 3 H, CH_3C), 2.57 (br s, 1 H, $w_{1/2}$ = 24 Hz, CH_2CHCH_2), 2.79 (d, 1 H, J_d = 3 Hz, J = 7 Hz, CH_3CHCH), 3.65* and 3.94 (s, 3 H, CH_3O), 4.70 (br s, 2 H, CH_2=C), 5.51* and 5.58 (br d, 1 H, J = 6 Hz, CH_2CH=C). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.64; H, 9.87.

2(*R*)-[2-Methyl-5(*S*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propan-1-ol (13). To a stirred suspension of 4.53 g (119.4 mmol) of lithium tetrahydroaluminate in 150 mL of ether at room temperature under an argon atmosphere was added dropwise over a 1-h period a solution of 12.44 g (59.72 mmol) of the 10:1 mixture of the diastereomeric acids **9** and **10** in 50 mL of ether. After the addition was completed, the reaction mixture was stirred for an additional 2.5 h at room temperature and then cautiously treated with 4.5 mL of water, 3.4 mL of 5 N aqueous NaOH, and 14.6 mL of water. After filtration and drying ($MgSO_4$), removal of the solvent under reduced pressure afforded 11.43 g (99%) of an oil consisting of a ca. 10:1 mixture of the 2*R* alcohol **13** and its 2*S* isomer **14**: R_f 0.14 (silica gel, 1:4 ether/petroleum ether); evaporative distillation 95 °C (0.005 mmHg); $[\alpha]^{22}_D$ +43.4 (*c* 2.15, $CHCl_3$); IR ($CHCl_3$) 3620, 1635, 1445, 1375, 1020, 840 cm^{-1}; ^1H NMR ($CDCl_3$) 0.68 and 0.98* (2 d, 3 H, J = 7 Hz, CH_3CH), 1.68 (br s, 6 H, CH_3C), 3.30 (dd, 1 H, J = 11 Hz, J' = 8 Hz, OC*H*HCH), 3.55 (dd, 1 H, J = 11 Hz, J' = 6 Hz, OCH*H*CH), 4.65 (br s, 2 H, C=CH_2), 5.48 (br s, 1 H $w_{1/2}$ = 9 Hz, CH_2CH=C). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.17; H, 11.40.

(54) Aaron, H. S. In *Topics in Stereochemistry*; Allinger, N. L.; Eliel, E. L., Eds.; Wiley: New York, 1979; Vol. 11, p 1.
(55) (a) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. (b) Chastrette, M.; Amouroux, R. *Bull. Soc. Chim. Fr.* **1970**, 4348. (c) Chastrette, M.; Amouroux, R. *J. Chem. Soc., Chem. Commun.* **1970**, 470.
(56) Fukuyama, T.; Vranesic, B.; Negri, D. P. Kishi, Y. *Tetrahedron Lett.* **1978**, 2741.
(57) No epoxidation was observed with *tert*-butyl hydroperoxide/vanadyl acetylacetonate: Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta*, **1979**, *12*, 63.
(58) Heyns, K.; Paulsen, H. *Angew. Chem.* **1957**, *69*, 600.
(59) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(60) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(61) When the compound was obtained as a diastereoisomeric mixture the characteristics of the major isomer are marked with an asterisk.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-(2-propenyl)-9-oxabicyclo[4.3.0]nonane (15). To a stirred solution of 11.236 g (57.822 mmol) of the above 10:1 mixture of the diastereomeric alcohols **13** and **14** in 120 mL of acetone at 0 °C was added 10.800 g (60.678 mmol) of *N*-bromosuccinimide, and the resulting solution was stirred for 15 min at 0 °C under an argon atmosphere. The reaction mixture was then poured into 200 mL of 10% $NaHSO_3$ and extracted with three 250-mL portions of ether. The organic extracts were washed with 2 × 200 mL of saturated aqueous NaCl and dried ($MgSO_4$), and then the solvent was removed under pressure. Flash chromatography (i.d. 5 cm) on 30 cm of silica gel with 1:12 ether/petroleum ether afforded 13.406 g (85%) of the bromide **15**, as one single isomer: R_f 0.43 (silica gel, 1:4 ether/petroleum ether); evaporative distillation 150 °C (0.008 mmHg); $[\alpha]^{22}_D$ −16.6° (*c* 1.93, $CHCl_3$); IR ($CHCl_3$) 1640, 1445, 1430, 1370, 1160, 1150, 1005, 980, 895 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 0.96 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.08 (1 H, *J* = 11 Hz, CHCHHCH, α-H), 1.42 (s, 3 H, CH_3C), 1.77 (br s, 3 H, CH_3C=C), 2.53 (m, 1 H, CH_2CHCH_2), 2.75 (m, 1 H, $CHCHCH_2$), 3.49 (t, 1 H, *J* = 9 Hz, OCHHCH), 3.98 (t, 1 H, *J* = 9 Hz, OCHHCH), 4.37 (t, 1 H, *J* = 4.5 Hz, $CCHCH_2$), 4.71 (br s, 1 H, $w_{1/2}$ = 4.5 Hz, HHC=C), 4.74 (br s, 1 H, $w_{1/2}$ = 4.5 Hz, HHC=C). Anal. Calcd for $C_{13}H_{21}BrO$: C, 57.15; H, 7.75; Br, 29.25. Found: C, 57.24; H, 7.82; Br, 29.31.

Elution with 1:1 ether/petroleum ether gave 742 mg (7%) of an oil consisting of a ca. 1:10 mixture of the 2*R* alcohol **13** and its 2*S* isomer **14**.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-acetyl-9-oxabicyclo[4.3.0]nonane (16). To a stirred solution of 13.190 g (48.276 mmol) of the olefin **15** in 250 mL of THF and 100 mL of water was added 6.3 mL (0.483 mmol) of a solution of 2.5 wt % OsO_4 in *tert*-butyl alcohol. The solution turned black and then 31.00 g (144.93 mmol) of sodium metaperiodate was added, and the reaction mixture was stirred for 4.5 h at room temperature under an argon atmosphere. The mixture was filtered, and the filter cake was washed with three 100-mL portions of ether. The filtrate was washed with 200 mL of water, 200 mL of 10% $NaHSO_3$, and 200 mL of saturated NaCl and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, flash chromatography (i.d. 5 cm) of the crystalline residue on 30 cm of silica gel with 1:1:2 ether/dichloromethane/petroleum ether afforded 11.934 g (90%) of the ketone **16** as a white solid. A small portion of this solid was crystallized from ether/hexane: mp 100 °C; R_f 0.38 (silica gel, 1:1:2 ether/dichloromethane/petroleum ether); $[\alpha]^{22}_D$ −32.5° (*c* 1.96, $CHCl_3$); IR ($CHCl_3$) 1700, 1445, 1425, 1380, 1350, 1140, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.34 (s, 3 H, CH_3C), 2.12 (s, 3 H, CH_3COO), 3.42 (t, 1 H, *J* = 9 Hz, OCHHCH), 3.90 (t, 1 H, *J* = 9 Hz, OCHHCH), 4.27 (t, 1 H, *J* = 4.5 Hz, $CCHCH_2$). Anal. Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96; Br, 29.04. Found: C, 52.44; H, 6.95; Br, 29.03.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-acetoxy-9-oxabicyclo[4.3.0]nonane (17). To a stirred suspension of 2.20 mL (83.96 mmol) of a 90% aqueous H_2O_2 solution in 30 mL of dichloromethane was added at 0 °C 13.0 mL (92.04 mmol) of trifluoroacetic anhydride over a 5-min period. After being stirred for 30 min at 0 °C under an argon atmosphere, this solution was added dropwise over a 45-min period via a cannula to a rapidly stirred suspension of 11.813 g (42.925 mmol) of the ketone **16** and 30.0 g (211 mmol) of dry Na_2HPO_4 in 200 mL of dichloromethane. During the addition, the reaction temperature was maintained between 25 and 30 °C with a water bath. After being stirred for 2.5 h at room temperature under an argon atmosphere, the reaction mixture was filtered, and the filter cake was washed with two 250-mL portions of dichloromethane. The filtrate was washed with 200 mL of saturated aqueous $NaHCO_3$ and 200 mL of saturated aqueous NaCl. The aqueous phases were extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) on 30 cm of silica gel of the crude product with 1:4 ether/petroleum ether afforded 11.496 g (92%) of the acetate **17** as a colorless oil: R_f 0.36 (silica gel, 1:4 ehter/petroleum ether); evaporative distillation 135 °C (0.008 mmHg); $[\alpha]^{23}_D$ −46.3° (*c* 2.09, $CHCl_3$); IR ($CHCl_3$) 1720, 1450, 1430, 1380, 1360, 1245, 1150, 1110, 1030, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.23 (1 H, *J* = 12 Hz, CHCHHCH), 1.39 (s, 3 H, CH_3C), 2.05 (s, 3 H, CH_3C), 2.76 (m, 1 H, $CHCHCH_2$), 3.53 (t, 1 H, *J* = 9 Hz, OCHHCH$_2$), 4.02 (t, 1 H, *J* = 9 Hz, OCHHCH), 4.33 (t, 1 H, *J* = 4.5 Hz, $CCHCH_2$), 5.22 (m, 1 H CH_2CHCH_2). Anal. Anal. Calcd for $C_{12}H_{19}BrO_3$: C, 49.50; H, 6.58; Br, 27.44. Found: C, 49.39; H, 6.53; Br, 27.33.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-acetoxy-9-oxabicyclo[4.3.0]nonane (17) (via the α-Alkoxy Hydroperoxide 18). To a stirred solution of 2.459 g (8.996 mmol) of the olefin **15** in 15 mL of dichloromethane was added 3 mL of methanol. A stream of ozone was passed through the solution at −78 °C until a light blue color persisted (12 min). The solution was purged with a stream of nitrogen, then poured into 100 mL of water, and extracted with three 150-mL portions of ether. The organic phases were washed with 100 mL of saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 2.98 g of crude α-alkoxy hydroperoxide **18** as a colorless oil: R_f = 0.28 (silica gel, 1:1 ether/petroleum ether).

To a stirred solution of 2.98 g (ca. 8.996 mmol) of the above α-alkoxy hydroperoxide **18** in 25 mL of dichloromethane were added 6.30 mL (45.20 mmol) of triethylamine, 2.50 mL (26.45 mmol) of acetic anhydride, and 50 mg (0.367 mmol) of (*N*,*N*-dimethylamino)pyridine. After 16 h at 40 °C under an argon atmosphere, the reaction mixture was poured into 100 mL of 1 N aqueous HCl and extracted with three 200-mL portions of ether. The organic phases were washed with 100 mL of water, 100 mL of saturated aqueous $NaHCO_3$, and 100 mL of saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 2.70 g of a mixture of (6*R*)-1(*S*),7(*R*)-dimethyl-2(*S*)-bromo-4(*R*)-acetoxy-9-oxabicyclo[4.4.0]nonane (**17**) (R_f 0.52 (silica gel, 1:1 ether/petroleum ether)) and (6*R*)-1(*S*),7-(*R*)-dimethyl-2(*S*)-bromo-4(*R*)-hydroxy-9-oxabicyclo[4.3.0]nonane.

To a stirred solution of 2.70 g (ca. 8.996 mmol) of the above mixture in 25 mL of dichloromethane were added 2.90 mL (37.33 mmol) of pyridine, 1.70 mL (17.98 mL) of acetic anhydride, and 20 mg (0.147 mmol) of (*N*,*N*-dimethylamino)pyridine. After 2.5 h at room temperature under an argon atmosphere, the reaction mixture was poured into 100 mL of 1 N HCl, and the resulting aqueous solution was extracted with three 200-mL portions of ether. The combined organic phases were washed with 100 mL of water, 100 mL of saturated $NaHCO_3$, and 100 mL of saturated NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) of the residue on 20 cm of silica gel with 1:3 ether/petroleum ether afforded first 1.874 g (72% over three steps from **15**) of (6*R*)-1(*S*),7(*R*)-dimethyl-2-(*S*)-bromo-4(*R*)-acetoxy-9-oxabicyclo[4.3.0]nonane (**17**). For analytical data, see above.

There was then eluted 282 mg (11%) of (6*R*)-1(*S*),7(*R*)-dimethyl-2(*S*)-bromo-4(*R*)-acetyl-9-oxabicyclo[4.3.0]nonane (**16**). For analytical data, see above.

4-Methyl-5(*R*)-[1-hydroxy-2(*R*)-propyl]-3-cyclohexen-1-(*S*)-yl Acetate (19). To a solution of 11.024 g (37.858 mmol) of the bromide **17** in 140 mL of ethanol and 14 mL of water was added 4.950 g (75.723 mmol) of zinc. The resulting suspension was heated at reflux for 16 h and then filtered through a pad of Celite, which was then thoroughly washed with ether. The filtrate was evaporated to ca. 30 mL and diluted with 150 mL of water, and the resulting aqueous solution was then extracted with three 250-mL portions of ether. The combined organic phases were washed with 150 mL of saturated NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) on 25 cm silica gel with 2:1 ether/petroleum ether afforded 6.997 g (87%) of the alcohol **19** as a white solid. A small portion of this solid was crystallized from ether/hexane: mp 70–71 °C; R_f 0.33 (silica gel, 2:1 ether/petroleum ether); $[\alpha]^{22}_D$ +4.9 °C (*c* 1.86, $CHCl_3$); IR ($CHCl_3$) 3620, 1710, 1450, 1435, 1380, 1360, 1250, 1025, 970, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.70 (br s, 3 H, $w_{1/2}$ = 4 Hz, CH_3C), 2.01 (s, 3 H, CH_3COO), 3.32 (dd, 1 H, *J* = 11 Hz, *J'* = 8 Hz, HOCHHCH), 3.55 (dd, 1 H, *J* = 11 Hz, *J'* = 6 Hz, HOCHHCH), 3.82 (m, 1 H, CH_2CHCH_2), 5.33 (br s, 1 H, $w_{1/2}$ = 12 Hz, CH_2CH=C). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.91; H, 9.50.

Elution with 24:1 ether/ethanol afforded 470 mg (7%) of 2-(*R*)-[2-methyl-5(*S*)-hydroxy-2-cyclohexen-1(*R*)-yl]propan-1-ol (**25**) as a white solid. A small portion of this solid was crystallized from ether/hexane: mp 83–83.5 °C; R_f 0.06 (silica gel, 2:1 ether/petroleum ether); $[\alpha]^{26}_D$ +74.7° (*c* 1.93, $CHCl_3$); IR ($CHCl_3$) 3590,

3400, 1440, 1370, 1080, 1050, 1020, 975, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 7 Hz, CH_3CH), 1.70 (br s, 3 H, $w_{1/2}$ = 4 Hz, CH_3C), 3.1–4.0 (m, 3 H, $HOCH_2CH$ and CH_2CHCH_2), 5.36 (br s, 1 H, $w_{1/2}$ = 10 Hz, CH_2CH=C). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.56; H, 10.56.

4-Methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)-oxy)-2(*R*)-propyl]-3-cyclohexen-1(*S*)-yl Acetate (20). To a stirred solution of 663 mg (3.123 mmol) of the alcohol **19** in 5 mL of DMF were added 532 mg (7.814 mmol) of imidazole and 565 mg (3.749 mmol) of *tert*-butyldimethylchlorosilane. After 14 h at room temperature, the product was isolated by ether extraction. Flash chromatography (i.d. 2 cm) on 20 cm silica gel with 1:10 ether/petroleum ether afforded 1.015 g (100%) of the silyl ether **20**, as a colorless oil: R_f 0.32 (silica gel, 1:10 ether/petroleum ether); evaporative distillation 135 °C (0.08 mmHg); $[\alpha]^{25}_D$ −11.1° (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 1710, 1460, 1450, 1375, 1355, 1250, 1085, 1035, 1020, 1000, 970, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, $(CH_3)_2Si$), 0.92 (s, 9 H, $(CH_3)_3C$), 1.01 (d, 3 H, J = 7 Hz, CH_3CH), 1.40 (1 H, J = 12 Hz, CHC*H*CHCH), 1.70 (s, 3 H, CH_3C), 2.05 (s, 3 H, CH_3COO), 3.32 (dd, 1 H, J = 10 Hz, J' = 7.5 Hz, OC*H*HCH), 3.48 (dd, 1 H, J = 10 Hz, J' = 5 Hz OCH*H*CH), 4.87 (m, 1 H, CH_2CHCH_2), 5.32 (br s, 1 H, $w_{1/2}$ = 12 Hz, CH_2CH=C). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.25; H, 10.46.

4-Methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)-oxy)-2(*R*)-propyl]-3-cyclohexen-1(*S*)-ol (5). To a stirred suspension of 231 mg (6.087 mmol) of lithium tetrahydridoaluminate in 20 mL of ether at 0 °C was added dropwise over a 5-min period a solution of 994 mg (3.044 mmol) of the ester **17** in 10 mL of ether. After 1 h at 0 °C, the product was isolated as described above. Flash chromatography (i.d. 2 cm) of the residue on 20 cm of silica gel with 1:1 ether/petroleum ether afforded 829 mg (96%) of the alcohol **5** as a colorless oil: R_f 0.28 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 110 °C (0.08 mmHg); $[\alpha]^{25}_D$ +32.4° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3660, 3420, 1470, 1370, 1260, 1100, 1050, 1010, 990, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, $(CH_3)_2Si$), 0.90 (s, 9 H, $(CH_3)_3C$), 1.00 (d, 3 H, J = 7 Hz, CH_3CH), 1.30 (1 H, J = 12 Hz, CHC*H*HCH), 1.68 (br s, 3 H, CH_3C), 3.33 (dd, 1 H, J = 10 Hz, J' = 7 Hz, OC*H*HCH), 3.46 (dd, 1 H, J = 10 Hz, J' = 5 Hz, OCH*H*CH), 3.80 (m, 1 H, CH_2CHCH_2), 5.32 (br s, 1 H, $w_{1/2}$ = 10 Hz, CH_2CH=C). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.58; H, 10.46.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-(2-propenyl)-8-oxo-9-oxabicyclo[4.3.0.]nonane (21). To a stirred solution of 3.605 g (17.307 mmol) of a 10:1 mixture of the epimeric acids **9** and **10** in 50 mL of acetone was added at once at 0 °C (ice/water bath) 3.389 g (19.039 mmol) of *N*-bromosuccinimide, and the resulting solution was stirred for 1.75 h at 0 °C under an argon atmosphere. The reaction mixture then was poured into 150 mL of 10% aqueous $NaHSO_3$ and extracted with three 250-mL portions of ether. The organic extracts were washed with 150 mL of saturated aqueous NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. After isolation of the product as described above, flash chromatography (i.d. 5 cm) on 15 cm of silica gel of the solid residue with 1:1:8 ether/dichloromethane/petroleum ether afforded 4.061 g (82%) of the bromide **21**, as one single isomer. A small portion of this solid was crystallized from ether/hexane: mp 99–99.5 °C; R_f 0.28 (silica gel, 1:1:8 ether/dichloromethane/petroleum ether); $[\alpha]^{25}_D$ +9.6° (*c* 2.57, $CHCl_3$); IR ($CHCl_3$) 1750, 1630, 1435, 1370, 1145, 1030, 965, 910, 890 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (1 H, J = 12 Hz, CHC*H*HCH) 1.18 (d, 3 H, J = 7 Hz, CH_3CH), 1.65 (s, 3 H, CH_3C), 1.73 (br s, 3 H, $w_{1/2}$ = 3 Hz, CH_3C=C), 1.75 (m, 1 H, CHC*H*HCH), 1.97 (ddd, 1 H, J = 14 Hz, J' = 12 Hz, J'' = 3.5 Hz, CHCH*H*CH), 2.06 (m, 1 H, CHCH*H*CH), 2.48 (m, 1 H, symmetric five-line system, $CHCH_2$), 2.60 (tt, 1 H, J = 12 Hz, J' = 3 Hz, CH_2CHCH_2), 3.14 (quint, J = 7 Hz, CH_3CHCH), 4.51 (t, 1 H, J = 3.5 Hz, $CCHCH_2$), 4.71 (br s, 1 H, $w_{1/2}$ = 4 Hz *H*HC=C), 4.78 (br s, 1 H, $w_{1/2}$ = 4 Hz, H*H*C=C). Anal. Calcd for $C_{13}H_{19}BrO_2$: C, 54.37, H, 6.67; Br, 27.82. Found: C, 54.35; H, 6.57; Br, 27.71.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-acetyl-8-oxo-9-oxabicyclo[4.3.0]nonane (22). To a stirred solution of 6.152 g (21.42 mmol) of the olefin **21** in 120 mL of THF and 60 mL of water was added 5.5 mL (0.433 mmol) of a solution 2.5 wt % OsO_4 in *tert*-butyl alcohol. The solution turned black, then 13.75 g (64.29 mmol) of sodium metaperiodate was added, and the reaction mixture was stirred well for 3 h at room temperature under an argon atmosphere. After isolation of the product as described above, flash chromatography (i.d. 5 cm) on 20 cm of silica gel of the solid residue with 1:1:1 ether/dichloromethane/petroleum ether afforded 5.897 g (95%) of the ketone **22** as a white solid. A small portion of this solid was crystallized from ether/hexane: mp 117–118 °C; R_f 0.39 (silica gel, 1:1:1 ether/dichloromethane/petroleum ether); $[\alpha]^{25}_D$ −3.5° (*c* 2.03, $CHCl_3$); IR ($CHCl_3$) 1755, 1695, 1440, 1370, 1345, 1140, 1095, 1070, 1040, 1025, 945, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (1 H, J = 12 Hz, CHC*H*HCH), 1.20 (d, 3 H, J = 7 Hz, CH_3CH), 1.65 (s, 3 H, CH_3C), 1.91 (ddd, 1 H, J = 14 Hz, J' = 6 Hz, J'' = 3.5 Hz, CHC*H*HCH), 2.08 (ddd, 1 H, J = 14, J' = 11 Hz, J'' = 3.5 Hz, CHCH*H*CH), 2.20 (s, 3 H, CH_3CO), 2.50 (m, 1 H, symmetric five-line system, $CHCH_2$), 3.04 (tt, 1 H, J = 12 Hz, J' = 3.5 Hz, CH_2CHCH_2), 3.14 (quint, 1 H, J = 7 Hz, CH_3CHCH), 4.51 (t, 1 H, J = 3.5 Hz, $CCHCH_2$). Anal. Calcd for $C_{12}H_{17}O_3Br$: C, 49.84, H, 5.93; Br, 27.63. Found: C, 49.89; H, 5.90; Br, 27.61.

(6*R*)-1(*S*),7(*R*)-Dimethyl-2(*S*)-bromo-4(*R*)-acetyl-8-oxo-9-oxabicyclo[4.3.0]nonane (23). To a stirred suspension of 1.0 mL (38.2 mmol) of a 90% aqueous H_2O_2 solution in 15 mL of dichloromethane was added a 0 °C (ice/water bath) 6.0 mL (42.48 mmol) of trifluoroacetic anhydride over a 5-min period. After being stirred for 30 min at 0 °C under an argon atmosphere, this solution was added dropwise over a 30-min period via a cannula to a rapidly stirred suspension of 5.794 g (20.036 mmol) of the ketone **22** and 20.0 g (140.85 mmol) of dry Na_2HPO_4 in 120 mL of dichloromethane. During the addition, the reaction temperature was maintained between 25 and 30 °C with a water bath. After the reaction mixture was stirred for 3 h at room temperature under an argon atmosphere the product was isolated as described above. Flash chromatography (i.d. 5 cm) on 25 cm of silica gel of the crude product with 1:1:1 ether/dichloromethane/petroleum ether afforded 5.513 g (90%) of the acetate **23** as a colorless oil: R_f 0.51 (silica gel, 1:1:1 ether/dichloromethane/petroleum ether); evaporative distillation 180 °C (0.004 mmHg); $[\alpha]^{26}_D$ −25.5° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 1755, 1715, 1440, 1360, 1300, 1240, 1145, 1095, 1030, 995, 980, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, 3 H, J = 7 Hz, CH_3CH), 1.63 (s, 3 H, CH_3C), 2.05 (s, 3 H, CH_3COO), 2.10 (m, 1 H, CHC*H*HCH), 2.18 (ddd, 1 H, J = 13 Hz, J' = 9 Hz, J'' = 3.5 Hz, CHCH*H*CH), 2.29 (m, 1 H, CHCH*H*CH), 2.57 (m, 1 H, symmetric five-line system, $CHCH_2$), 3.12 (quint, 1 H, J = 7 Hz, CH_3CHCH), 4.45 (t, 1 H, J = 4 Hz, $CCHCH_2$), 5.26 (m, 1 H, symmetric eight-line system, CH_2CHCH_2). Anal. Calcd for $C_{12}H_{17}BrO_4$: C, 47.23; H, 5.62; Br, 26.19. Found: C, 47.38; H, 5.64; Br, 26.24.

2(*R*)-[2-Methyl-5(*S*)-acetoxy-2-cyclohexen-1(*R*)-yl]-propionic Acid (24). To a stirred solution of 2.006 g (6.573 mmol) of the bromide **23** in 40 mL of ethanol and 4 mL of water was added 860 mg (13.156 mmol) of zinc. The resulting suspension was heated at reflux for 20 h and then filtered through a pad of Celite, which was thoroughly washed with ether. The filtrate was evaporated to ~10 mL and diluted with 100 mL of 1 N HCl, and then the resulting aqueous solution was extracted with three 150-mL portions of ether. The combined organic phases were washed with 100 mL of saturated NaCl and dried ($MgSO_4$). Evaporation under reduced pressure gave 1.409 g (95%) of the acid **24** as a colorless oil: R_f 0.32 (silica gel, 1:1:1 ether/dichloromethane/petroleum ether); ^1H NMR ($CDCl_3$) δ 1.16 (d, 3 H, J = 7 Hz, CH_3CH), 1.68 (br s, 3 H, $w_{1/2}$ = 5 Hz, CH_3C=C) 2.02 (s, 3 H, CH_3COO), 4.82 (m, 1 H, CH_2CHCH_2), 5.30 (br s, 1 H, $w_{1/2}$ = 12 Hz, CH_2CH=C).

2(*R*)-[2-Methyl-5(*S*)-hydroxy-2-cyclohexen-1(*R*)-yl]-propan-1-ol (25). To a stirred suspension of 950 mg (25.033 mmol) of lithium tetrahydridoaluminate in 40 mL of ether at room temperature under an argon atmosphere was added dropwise over a 1-h period a solution of 1.409 g (6.227 mmol) of the crude acid **24** in 20 mL of ether. After, the addition was completed, the reaction mixture was stirred for an additional 2 h at room temperature. Isolation of the product in the manner described above afforded 1.057 g (100%) of the diol **25** as a white solid. For analytical data, see above.

4-Methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)-oxy)-2(*R*)-propyl]-3-cyclohexen-1(*S*)-ol (5). To a stirred so-

lution of 640 mg (3.759 mmol) of the diol **25** in 25 mL of dichloromethane were added 580 μL (4.161 mmol) of triethylamine, 595 mg (3.948 mmol) of *tert*-butyldimethylchlorosilane, and 18 mg (0.147 mmol) of 4-(dimethylamino)pyridine. After 15 h at room temperature under an argon atmosphere, the crude product was isolated in the standard manner. Flash chromatography (i.d. 5 cm) of the residue on 15 cm of silica gel with 1:2 ether/petroleum ether afforded first 110 mg (7%) of 1-methyl-4(*S*)-[((1,1-dimethylethyl)dimethylsilyl)oxy]-6(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-1-cyclohexene as a colorless oil: R_f 0.76 (silica gel, 1:1 ether/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H, $(CH_3)_2Si$), 0.10 (s, 6 H, $(CH_3)_2Si$), 0.92 (s, 18 H, $2(CH_3)_3C$), 1.01 (d, 3 H, J = 7 Hz, CH_3CH), 1.69 (br s, 3 H, $w_{1/2}$ = 5 Hz, CH_3C=C), 3.30 (dd, 1 H, J = 10.5 Hz, J' = 8 Hz, OC*H*HCH) 3.49 (dd, 1 H, J = 10.5 Hz, J' = 5 Hz, OCH*H*CH), 3.75 (m, 1 H, CH_2CHCH_2), 5.32 (br s, 1 H $w_{1/2}$ = 10 Hz, CH_2CH=C).

There was then eluted with 1:1 ether/petroleum ether 884 mg (83%) of the alcohol **5** as a colorless oil. For analytical data, see above.

Elution with 50:1 ether/ethanol gave 39 mg (6%) of unreacted starting material **25**.

4-Methyl-5(*R*)-[1-(((1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-3-cyclohexen-1(*S*)-yl Benzoate (26). To a stirred solution of 480 mg (1.687 mmol) of the alcohol **5** in 15 mL of dichloromethane were added 340 μL (4.204 mmol) of pyridine and 235 μL (2.025 mmol) of benzoyl chloride. After 24 h at room temperature, the product was isolated in the standard manner. Flash chromatography (i.d. 5 cm) of the residue on 15 cm of silica gel with 1:15 ether/petroleum ether afforded 644 mg (98%) of the ester **26**, as a colorless oil: R_f 0.39 (silica gel, 1:15 ether/petroleum ether); evaporative distillation 150 °C (0.07 mmHg); $[\alpha]^{15}_D$ +5.4° (*c* 1.68; $CHCl_3$); IR ($CHCl_3$) 1700, 1600, 1580, 1445, 1310, 1270, 1250, 1175, 1110, 1090, 1070, 1020, 1005, 960, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6 H, $(CH_3)_2Si$), 0.96 (s, 9 H, $(CH_3)_3C$), 1.04 (d, 3 H, J = 7 Hz, CH_3CH), 1.75 (br s, 3 H, $w_{1/2}$ = 5 Hz, CH_3C=C), 3.37 (dd, 1 H, J = 10 Hz, J' = 7.5 Hz, OC*H*HCH), 3.54 (dd, 1 H, J = 10 Hz, J' = 5 Hz, OCH*H*CH), 5.13 (m, 1 H, CH_2CHCH_2), 5.39 (br s, 1 H, $w_{1/2}$ = 11 Hz, CH_2CH=C, 7.49 (m, 3 H, $C_5H_2H_3$), 8.05 (m, 2 H, $C_5H_2H_3$). Anal. Calcd for $C_{23}H_{36}O_3Si$: C, 71.09; H, 9.34. Found: C, 71.25; H, 9.39.

3-Hydroxy-4-methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]cyclohexan-1(*R*)-yl Benzoate (Mixture of 27a and 27b). To a stirred solution of 420 mg mL (3.4 mmol) of a 1 M solution of borane in THF. After 3 h at 0 °C, the solution was treated with 3.5 mL of water, 3.5 mL of 1 N aqueous NaOH, and then 3.5 mL of 30% aqueous H_2O_2. After 1 h at room temperature, the solution was poured into 50 mL of water and extracted with three 100-mL portions of ether. The organic phases were washed with 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on 30 g of silica gel with 1:1 ether/petroleum ether afforded 416 mg (95%) of an oil consisting of a 5:2 mixture of the 3*S*,4*S* alcohol **27a** and its 3*R*,4*R* isomer **27b**: R_f 0.30 (3*S*) diastereomer) and 0.25 (3*R*,4*R* diastereomer) (silica gel, 1:1 ether/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6 H, $(CH_3)_2Si$), 0.91 (s, 9 H, $(CH_3)_3C$), 0.97 (d, 3 H, J = 7 Hz, CH_3CH), 3.1–3.8 (m, 2.3 H, OCH_2CH and $CHCHCH_2$ (minor diastereomer)), 3.99 (br s, 0.7 H, $w_{1/2}$ = 6 Hz, $CHCHCH_2$ (major diastereomer)), 4.91 (m, 0.3 H, CH_2CHCH_2 (minor diastereomer)), 5.29 (m, 0.7 H, CH_2CHCH_2 (major diastereomer)), 7.45 (m, 3 H, $C_5H_2H_3$), 8.02 (m, 2 H, $C_5H_2H_3$).

3(*S*)-[((2-Methoxyethoxy)methyl)oxy]-4(*S*)-methyl-5-(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-cyclohexan-1(*R*)-yl Benzoate (28) and 3(*R*)-[((2-Methoxyethoxy)methyl)oxy]-4(*R*)-methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]cyclohexan-1(*R*)-yl Benzoate (29). To a stirred solution of 338 mg (0.831 mmol) of a unseparated diastereomeric mixture of the above alcohols **27a** and **27b** in 10 mL of dichloromethane were added 290 μL (1.665 mmol) of *N*,*N*-diisopropylethylamine and 145 μL (1.270 mmol) of (2-methoxyethoxy)methyl chloride. After 15 h at room temperature, another 290 μL (1.665 mmol) of *N*,*N*-diisopropylethylamine and 145 μL (1.270 mmol) of (2-methoxyethoxy)methyl chloride were added. After 15 h heating at reflux under an argon atmosphere, the reaction mixture was poured into 50 mL of water, and then the resulting suspension was extracted with three 100-mL portions of ether. The organic phases were washed with 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Chromatography of the residue on 60 g of silica gel with 1:1:4 ether/dichloromethane/petroleum ether afforded first 282 mg (69%) of the ester **28** as a colorless oil: R_f 0.29 (silica gel, 1:1:4 ether/dichloromethane/petroleum ether); evaporative distillation: 195 °C (0.003 mmHg); $[\alpha]^{25}_D$ +7.7° (*c* 1.51, $CHCl_3$); IR ($CHCl_3$) 1725, 1620, 1600, 1485, 1465, 1380, 1330, 1295, 1265, 1130, 1115, 1060, 1010, 855 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.93 (d, 3 H, J = 7 Hz, CH_3CH), 1.34 (q, 1 H, J = 12 Hz, CHC*H*HCHC, α-H), 1.49 (m, 1 H, symmetric nine-line system, $CHCH(CH_3)CH_2$), 1.638 (dt, 1 H, J_d = 2.5 Hz, J_t = 12.5 Hz, CHC*H*HCH–O, α-H), 1.84 (m, 1 H, $CHCH(CH_3)CH$), 2.03 (br d, 1 H, J = 12 Hz, CHCH*H*CHC, β-H), 2.08 (m, 1 H, $CHCH(CH)CH_2$), 2.15 (br d, 1 H, J = 12.5 Hz, CHCH*H*CH–O, β-H), 3.37 (s, 3 H, CH_3O), 3.38 (dd, 1 H, J = 10 Hz, J' = 6 Hz, OC*H*HCH), 3.56 (t, 2 H, J = 4.5 Hz, OCH_2CH_2O), 3.66 (dd, 1 H, J = 10 Hz, J' = 4 Hz, OCH*H*CH), 3.74 (m, 1 H, symmetric ten-line system, OCH_2CH_2O), 3.81 (br, 1 H, J = 3 Hz, $CHCHCH_2$), 4.57 (d, 1 H, J = 7 Hz, OC*H*HO), 4.59 (d, 1 H, J = 7 Hz, OCH*H*O), 5.22 (m, 1 H, symmetric seven-line system, CH_2CHCH_2), 7.41 (br t, 2 H, J = 7.5 Hz, $C_6H_2H_2H$), 7.53 (br t, 1 H, J = 7.5 Hz, $C_6H_2H_2H$), 8.02 (br d, 2 H, J = 7.5 Hz, $C_5H_2H_2H$). Anal. Calcd for $C_{27}H_{46}O_6Si$: C, 65.55; H, 9.37. Found: C, 65.60; H, 9.41.

There was then eluted 96 mg (23%) of the diastereomeric ether **29** as a colorless oil: R_f 0.21 (silica gel, 1:1:4 ether/dichloromethane/petroleum ether); evaporative distillation: 200 °C (0.002 mmHg); $[\alpha]^{26}_D$ –22.0° (*c* 1.36, $CHCl_3$); IR ($CHCl_3$) 1700, 1595, 1580, 1455, 1440, 1335, 1310, 1270, 1250, 1170, 1105, 1090, 1060, 1030, 1020, 980, 945,l 905, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6 H, $(CH_3)_2Si$), 0.87 (s, 9 H, $(CH_3)_3C$), 0.95 (d, 3 H, J = 7 Hz, CH_3CH), 1.04 (d, 3 H, J = 6.5 Hz, CH_3CH), 1.15 (m, 1 H, $CHCH(CH_3)CH$), 1.27 (q, 1 H, J = 12 Hz, CHC*H*HCHC, α-H), (q, 1 H, J = 12 Hz, CHC*H*HCH–O, α-H), 1.49 (m, 1 H, symmetric ten-line system, $CHCH(CH_3)CH_2$), 2.07 (m, 1 H, CHCH*H*CH, β-H), 2.52 (m, 1 H, CHC*H*HCH, α-H), 3.21 (dt, 1 H, J_d = 4 Hz, J_t = 10.5 Hz, $CHCHCH_2$), 3.37 (s, 3 H, CH_3O), 3.38 (dd, 1 H, J = 10 Hz, J' = 7 Hz, OC*H*HCH), 3.54 (t, 2 H, J = 4.5 Hz, OCH_2CH_2O), 3.59 (dd, 1 H, J = 10 Hz, J' = 5 Hz, OCH*H*CH), 3.73 (m, 2 H, OCH_2CH_2O), 4.71 (d, 1 H, J = 7 Hz, OC*H*HO), 4.85 (d, 1 H, J = 7 Hz, OCH*H*O), 4.90 (m, 1 H, symmetric nine-line system, CH_2CHCH_2), 7.42 (br t, 2 H, J = 7.5 Hz, $C_6H_2H_2H$), 7.53 (br t, 1 H, J = 7.5 Hz, $C_6H_2H_2H$), 8.02 (br d, 2 H, J = 7.5 Hz, $C_6H_2H_2H$). Anal. Calcd for $C_{27}H_{46}O_6Si$: C, 65.55; H, 9.37. Found: C, 65.47; H, 9.33.

3(*S*)-[((2-Methoxyethoxy)methyl)oxy]-4(*S*)-methyl-5-(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-1(*R*)-cyclohexanol (30). To a stirred suspension of 60 mg (1.581 mmol) of lithium tetrahydridoaluminate in 5 mL of ether at 0 °C was added over a 5-min period a solution of 192 mg (0.388 mmol) of the ester **28** in 5 mL of ether. After 1.5 h at 0 °C, the product was isolated as described above. Chromatography of the residue of 30 g of silica gel with 3:1:1 ether/dichloromethane/petroleum ether afforded 138 mg (91%) of the alcohol **30** as a colorless oil: R_f 0.18 (silica gel, 3:1:1 ether/dichloromethane/petroleum ether); evaporative distillation 180 °C (0.01 mmHg); $[\alpha]^{25}_D$ –0.6° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 3600, 3440, 1455, 1380, 1365, 1250, 1090, 1040, 980, 960, 935, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.81 (d, 3 H, J = 7 Hz, CH_3CH), 0.88 (s, 9 H, $(CH_3)_3C$), 0.91 (d, 3 H, J = 6.5 Hz, CH_3CH), 1.11 (q, 1 H, J = 12 Hz, CHC*H*HCHC, α-H), 1.44 (m, 1 H, $CHCH(CH_3)CH_2$), 1.46 (dt, 1 H, J_d = 2.5 Hz, J_t = 12 Hz, CHC*H*HCH–O, α-H), 1.70 (m, 1 H, $CHCH(CH_3)CH$), 1.89 (br d, 1 H, J = 12 Hz, CHCH*H*CH, β-H), 2.01 (m, 2 H, $CHCH(CH)CH_2$ and CHCH*H*CH, β-H), 3.39 (s, 3 H, CH_3O), 3.41 (dd, 1 H, J = 10 Hz, J' = 7 Hz, OC*H*HCH), 3.55 (t, 2 H, J = 4.5 Hz, OCH_2CH_2O), 3.66 (dd, 1 H, J = 10 Hz, J' = 3 Hz, OCH*H*CH), 3.69 (m, 2 H, symmetric seven-line system, OCH_2CHCH_2O), 3.75 (br, 1 H, J = 3 Hz, $CHCHCH_2$), 3.86 (m, 1 H, symmetric seven-line system, CH_2CHCH_2), 4.73 (s, 2 H, OCH_2O). Anal. Calcd for $C_{20}H_{42}O_5Si$: C, 61.49; H, 10.84. Found: C, 61.29; H, 10.76.

3(*S*)-[((2-Methoxyethoxy)methyl)oxy]-4(*S*)-methyl-5-(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-cyclohexan-1-one (6). To a stirred solution of 55 μL (0.630 mmol) of oxalyl chloride in 5 mL of dichloromethane at −60 °C was added 90 μL (1.268 mmol) of dimethyl sulfoxide. After 5 min, a solution of 122 mg (0.312 mmol) of the alcohol **30** in 5 mL of dichloromethane was added to the reaction mixture over a 10-min period. After 15 min at −50 °C, the reaction mixture was treated with 0.44 mL (3.152 mmol) of triethylamine, stirred for 5 min at −50 °C, and allowed to warm to room temperature. The mixture was poured into 50 mL of water and extracted with three 100-mL portions of ether. The organic phases were washed with 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on 20 g of silica gel with 2:1 ether/petroleum ether afforded 107 mg (88%) of the ketone **6** as a colorless oil: R_f 0.25 (silica gel, 2:1 ether/petroleum ether); evaporative distillation 170 °C (0.01 mmHg); $[\alpha]^{29}_D$ +5.9° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$) 1700, 1455, 1405, 1385, 1360, 1330, 1250, 1150, 1130, 1090, 1040, 970, 915, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si), 0.86 (s, 9 H, $(CH_3)_3C$), 0.95 (d, 3 H, *J* = 6.5 Hz, CH_3CH), 0.99 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.53 (m, 1 H, $CHCH(CH_3)CH_2$), 2.04–2.18 (m, 2 × 1 H, $CHCHHCH$, α-H), 2.24 (m, 1 H, $CHCH(CH)CH_2$), 2.39–2.54 (m, 2 × 1 H, $CHCHHCH$, β-H), 3.36 (dd, 1 H, *J* = 10 Hz, *J'* = 6.5 Hz, $OCHHCH$), 3.37 (s, 3 H, CH_3O), 3.53 (m, 2 H, OCH_2CH_2O), 3.58 (dd, 1 H, *J* = 10 Hz, *J'* = 3.5 Hz, $OCHHCH$), 3.66 (m, 2 H, OCH_2CH_2O), 4.02 (q, 1 H, *J* = 3 Hz, $CHCHCH_2$), 4.71 (d, 1 H, *J* = 7 Hz, $OCHHO$), 4.73 (d, 1 H, *J* = 7 Hz, $OCHHO$). Anal. Calcd for $C_{20}H_{40}O_5Si$: C, 61.81; H, 10.37. Found: C, 61.88; H, 10.22.

4-Methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)-oxy)-2(*R*)-propyl]-3-cyclohexen-1-one (31). To a stirred solution of 290 μL (3.32 mmol) of oxalyl chloride in 8 mL of dichloromethane at −60 °C was added 510 μL (7.19 mmol) of dimethyl sulfoxide. After 5 min, a solution of 430 mg (1.507 mmol) of the crude alcohol **5** (from 320 mg of **19**) in 6 mL of dichloromethane was added to the reaction mixture over a 5-min period. After 15 min at −50 °C, the reaction mixture was treated with 1.05 mL (7.52 mmol) of triethylamine and, after 5 min at −50 °C, allowed to warm to room temperature. The mixture was then worked up as described above. Flash chromatography (i.d. 5 cm) of the residue on 20 cm of silica gel with 1:4 ether/petroleum ether afforded 343 mg (81% over three steps from **19**) of the ketone **31** as a colorless oil: R_f 0.59 (silica gel, 1:1 ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, $(CH_3)Si$), 0.91 (s, 9 H, $(CH_3)_3C$), 0.95 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.80 (m, 1 H, $CHCH(CH_3CH_2)$, 1.85 (br s, 3 H, $w_{1/2}$ = 5 Hz, $CH_3C{=}C$), 2.51 (br s, $w_{1/2}$ = 3 Hz), 2.81 (br s, 2 H, $w_{1/2}$ = 6 Hz), 3.44 (d, 2 H, *J* = 6 Hz, OCH_2CH), 5.53 (br s, 1 H, $w_{1/2}$ = 6 Hz, $CH_2CH{=}C$).

4-Methyl-5(*R*)-[1-((2-tetrahydropyranyl)oxy)-2(*R*)-propyl]-3-cyclohexen-1(*S*)-yl Acetate (35). To a stirred solution of 6.22 g (29.30 mmol) of the alcohol **19** and 5.40 mL (59.19 mmol) of 3,4-dihydro-2*H*-pyran in 60 mL of dichloromethane was added 370 mg (1.472 mmol) of pyridinium *p*-toluenesulfonate. After 5 h at room temperature under an argon atmosphere the reaction mixture was poured into 150 mL of water and extracted with three 250-mL portions of ether. The combined organic phases were washed with 150 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) of the residue on 25 cm of silica gel with 1:4 ether/petroleum ether afforded 8.602 (99%) of the ether **35** as a colorless oil: R_f 0.29 (silica gel, 1:4 ether/petroleum ether); evaporative distillation 140 °C (0.06 mmHg); $[\alpha]^{25}_D$ −11.9° (*c* 2.29, $CHCl_3$); IR ($CHCl_3$) 1710, 1445, 1430, 1375, 1365, 1355, 1250, 1130, 1110, 1070, 1050, 1020, 965, 900, 860, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 and 1.05 (2 d, 3 H, *J* = 7 Hz, CH_3CH), 1.69 (br s, 3 H, $w_{1/2}$ = 4 Hz, $CH_3C{=}C$), 2.01 (s, 3 H, CH_3COO), 2.9–4.0 (m, 4 H, OCH_2CH_2 and OCH_2CH), 4.51 (br s, 1 H, $w_{1/2}$ = 6 Hz, $OCHCH_2$), 4.83 (m, 1 H, symmetric 13-line system, CH_2CHCH_2), 5.31 (br s, 1 H, $w_{1/2}$ = 10 Hz, $CH_2CH{=}C$). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.92; H, 9.46.

4-Methyl-5(*R*)-[1-((2-tetrahydropyranyl)oxy)-2(*R*)-propyl]-3-cyclohexen-1(*S*)-ol (36). To a stirred suspension of 1.38 g (36.36 mmol) of lithium tetrahydridoaluminate in 100 mL of ether at 0 °C was added dropwise over a 30-min period a solution of 5.395 g (18.201 mmol) of the ester **35** in 25 mL of ether. After the addition was completed, the reaction mixture was stirred for an additional 2 h at 0 °C, and then the product was isolated as described above. Removal of the solvent under reduced pressure afforded 4.63 g (100%) of the alcohol **36** as a colorless oil: R_f 0.12 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 140 °C (0.08 mmHg); $[\alpha]^{25}_D$ +44.1° (*c* 1.38, $CHCl_3$); IR ($CHCl_3$) 3580, 3420, 1440, 1430, 1370, 1345, 1125, 1105, 1060, 1050, 1015, 970, 895, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.65 (br s, 3 H, $w_{1/2}$ = 5 Hz, $CH_3C{=}C$), 2.9–4.0 (m, 5 H, OCH_2CH_2, OCH_2CH, and CH_2CHCH_2), 4.51 (br s, 1 H, $w_{1/2}$ = 6 Hz, $OCHCH_2$) 5.30 (br s, 1 H, $w_{1/2}$ = 10 Hz, $CH_2CH{=}C$). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.93; H, 10.27.

4-Methyl-5(*R*)-[1-((2-tetrahydropyranyl)oxy)-2(*R*)-propyl]-3-cyclohexen-1-one (37). To a stirred solution of 3.20 mL (36.682 mmol) of oxalyl chloride in 80 mL of dichloromethane at −60 °C was added a solution of 5.80 mL (81.733 mmol) of dimethyl sulfoxide in 15 mL of dichloromethane over a 10-min period. After 2 min, a solution of 4.637 g (18.201 mmol) of the alcohol **36** in 20 mL of dichloromethane was added to the reaction mixture over a 10-min period. After 15 min at −50 °C, the reaction mixture was treated with 12.70 mL (90.99 mmol) of triethylamine, stirred for 5 min at −50 °C, and allowed to warm to room temperature. The mixture was poured into 150 mL of water and extracted with three 250-mL portions of ether. The combined organic phases were washed with 150 mL of saturated aqueous NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) of the residue on 20 cm of silica gel with 1:1 ether/petroleum ether afforded 4.189 g (91%) of the ketone **37** as a colorless oil: R_f 0.35 (silica gel, 1:1 ether/petroleum ether); evaporative distillation of 125 °C (0.09 mmHg); $[\alpha]^{25}_D$ −134.2° (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 1700, 1445, 1430, 1375, 1340, 1130, 1110, 1070, 1050, 1020, 965, 900, 860, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 and 1.00 (2 d, 3 H, *J* = 7 Hz, CH_3CH), 1.83 (br s, 3 H, $w_{1/2}$ = 5 Hz, $CH_3C{=}C$), 2.51 (br s, 3 H, $w_{1/2}$ = 4 Hz), 2.79 (br s, 2 H, $w_{1/2}$ = 7 Hz), 3.0–4.0 (m, 4 H, OCH_2CH and OCH_2CH_2), 4.46 (br s, 1 H, $w_{1/2}$ = 6 Hz, $OCHCH_2$), 5.51 (br s, 1 H, $w_{1/2}$ = 6 Hz, $CH_2CH{=}C$). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.66.

(5*R*)-1(*S*)-Methoxy-4(*R*),6-dimethyl-2-oxabicyclo[3.3.1]-non-6-ene (32). A stirred solution of 801 mg (3.174 mmol) of the ketone **37** and 80 mg (0.318 mmol) of pyridinium *p*-toluenesulfonate in 20 mL of dichloromethane and 5 mL of methanol was heated at reflux under a Dean–Stark trap. After 24 h the reaction mixture was poured into 100 mL of saturated aqueous $NaHCO_3$ and extracted with three 100-mL portions of ether. The organic phases were washed with 100 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (i.d. 2 cm) of the residue on 20 cm of silica gel with 1:4 ether/petroleum ether afforded 498 mg (86%) of the acetal **32** as a colorless oil: R_f 0.50 (silica gel, 1:1 ether/petroleum ether); IR ($CHCl_3$) 1455, 1435, 1370, 1360, 1330, 1165, 1125, 1115, 1100, 1035, 995, 970, 910, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.70 (br s, 3 H, $w_{1/2}$ = 5 Hz, $CH_3C{=}C$), 2.03 (m, 2 H), 2.25 (br s, 2 H, $w_{1/2}$ = 6 Hz), 3.31 (s, 3 H, CH_3O), 3.40 (dd, 1 H, *J* = 11 Hz, *J'* = 4 Hz, $OCHHCH$), 3.84 (dd, 1 H, *J* = 11 Hz, *J'* = 5 Hz, $OCHHCH$), 5.35 (br s, 1 H, $w_{1/2}$ = 5 Hz, $CH_2CH{=}C$).

(5*R*)-1(*R*)-(2,2,2-Trichloroethoxy)-4(*R*),6-dimethyl-2-oxabicyclo[3.3.1]non-2-ene (33). A stirred solution of 178 mg (0.705 mmol) of the ketone **37** and 25 mg (0.099 mmol) of pyridinium *p*-toluenesulfonate in 10 mL of dichloromethane and 1.0. mL of 2,2,2-trichloroethanol was heated at reflux under a Dean–Stark trap. After 24 h under an argon atmosphere, the product was isolated as described above. Flash chromatography (i.d. 2 cm) of the residue on 15 cm of silica gel with 1:30 ether/petroleum ether afforded 137 mg (65%) of the acetal **33** as a colorless oil: R_f 0.36 (silica gel, 1:30 ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 1.09 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.72 (br s, 3 H, $w_{1/2}$ = 5 Hz, CH_3C), 3.43 (dd, 1 H, *J* = 11.5 Hz, *J'* = 5.5 Hz, $OCHHCH$), 3.83 (dd, 1 H, *J* = 11.5 Hz, *J'* = 5.5 Hz, $OCHHCH$), 4.10 (d, 1 H, *J* = 10.5 Hz, $OCHHCCl_3$), 4.30 (d, 1 H, *J* = 10.5 Hz, $OCHHCCl_3$), 5.33 (br s, 1 H, $w_{1/2}$ = 7 Hz, $CH_2CH{=}C$).

(5*R*)-1(*R*)-(Benzyloxy)-4(*R*),6-dimethyl-2-oxabicyclo-[3.3.1]non-2-ene (34) (from 31). A stirred solution of 197 0.674 mmol) of the ketone **31** and 17 mg (0.067 mmol) of pyridinium

p-toluenesulfonate in 15 mL of chloroform and 3.5 mL of benzyl alcohol was heated at reflux under a Dean–Stark trap. After 22 h under an argon atmosphere, the product was isolated in the manner described above. Flash chromatography (i.d. 2 cm) of the residue on 15 cm of silica gel with 1:15 ether/petroleum ether afforded 106 mg (59%) of the acetal **34** as a colorless oil: R_f 0.27 (silica gel, 1:15 ether/petroleum ether); evaporative distillation 130 °C (0.05 mmHg); $[\alpha]^{27}_D$ −74.4° (*c* 1.67, $CHCl_3$); IR ($CHCl_3$) 1590, 1440, 1360, 1335, 1160, 1125, 1100, 1030, 990, 975, 960, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.52 (br s, 3 H, $w_{1/2}$ = 6 Hz, CH_3C), 3.49 (dd, 1 H, *J* = 11.5 Hz, *J′* = 5 Hz, OC*H*HCH), 3.90 (dd, 1 H, *J* = 11.5 Hz, *J′* = 5 Hz, OCH*H*CH), 5.39 (br s, 1 H, $w_{1/2}$ = 10 Hz, $CH_2CH{=}C$), 7.2–7.4 (m, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.94; H, 8.59.

(5*R*)-1(*R*)-(Benzyloxy)-4(*R*),6-dimethyl-2-oxabicyclo-[3.3.1]non-2-ene (34) (from 37). A stirred solution of 3.195 g (12.661 mmol) of the ketone **37** and 318 mg (1.265 mmol) of pyridinium *p*-toluenesulfonate in 100 mL of chloroform and 26.2 mL of benzyl alcohol was heated at reflux under a Dean–Stark trap. After 17 h under an argon atmosphere, the product was isolated as described above. Flash chromatography (i.d. 5 cm) of the residue on 30 cm of silica gel with 1:1:15 ether/dichloromethane/petroleum ether afforded 5.083 g of a colorless oil consisting of a ~1:1 mixture of the acetal **34** (R_f 0.30 (silica gel, 1:1:15 ether/dichloromethane/petroleum ether)) and benzyl (2-tetrahydropyranyl ether (R_f 0.26 (silica gel, 1:1:15 ether/dichloromethane/petroleum ether)).

(5*S*)-1(*S*)-(Benzyloxy)-3(*S*)-hydroxy-4(*S*),6(*R*)-dimethyl-8-oxabicyclo[3.3.1]nonane (38). To a stirred solution of 5.083 g (ca. 12.66 mmol) of the above oil, containing ca. 50% of **34**, in 80 mL of THF at 0 °C were added first 1.0 mL of triethylamine and then over a 30-min period 38.0 mL (38.0 mmol) of a 1 M solution of borane in THF. After 30 min at 0 °C and 2 h at room temperature under an argon atmosphere, the solution was cautiously treated with 15.0 mL of water. After the evolution of hydrogen ceased (ca. 15 min), 25.0 mL of 2 N NaOH and 15.0 mL of 30% aqueous H_2O_2 were added to the reaction mixture. After 1 h at 35 °C, the solution was poured into 150 mL of water and then extracted with three 250-mL portions of ether. The combined organic phases were washed with 150 mL of saturated aqueous NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) of the residue on 25 cm of silica gel with 3:1:1 ether/dichloromethane/petroleum ether afforded 3.193 g (91% over two steps from **37**) of the alcohol **38** as a colorless oil: R_f 0.31 (silica gel, 3:1:1 ether/dichloromethane/petroleum ether); evaporative distillation 160 ° (0.01 mmHg); $[\alpha]^{27}_D$ +54.6° (*c* 1.58, $CHCl_3$); IR ($CHCl_3$) 3570, 3430, 1440, 1365, 1340, 1295, 1135, 1090, 1050, 1015, 980, 940, 870 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, 3 H, *J* = 7 Hz, CH_3CH), CC*H*HCH–O, β-H), 1.4–1.5 (m, 1 H, CHC*H*(CH_3)CH), 1.45 (dd, 1 H, *J* = 13.5 Hz, *J′* = 3.5 Hz, CC*H*HCHC, β-H), 1.68 (br s, 1 H, $w_{1/2}$ = 17 Hz, CHC*H*CH_2C), 1.85 (m, 1 H, $CH_2CH(CH_3)$CH), 2.24 (dt, 1 H, J_d = 13.5 Hz, J_t = 3.5 Hz, CCH*H*CHC, α-H), 2.44 (ddd, 1 H, *J* = 12 Hz, *J′* = 5.5 Hz, *J″* = 3 Hz, CCH*H*CH–O, α-H), 3.38 (t, 1 H, *J* = 11.5 Hz, OC*H*HCH, β-H), 3.54 (m, 1 H, CHC*H*CH_2), 3.66 (dd, 1 H, *J* = 11.5 Hz, *J′* = 7 Hz, OCH*H*CH, β-H), 4.57 (d, 1 H, *J* = 11.5 Hz, OC*H*HC), 4.65 (d, 1 H, *J* = 11.5 Hz, OCH*H*C), 7.2–7.4 (m, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.71; H, 8.79.

(5*R*)-1(*S*)-(Benzyloxy)-3(*S*)-[((2-methoxyethoxy)-methyl)oxy]-4(*S*),6(*R*)-dimethyl-8-oxabicyclo[3.3.1]nonane (39). To a stirred suspension of 742 mg (18.50 mmol) of potassium hydride in 50 mL of THF at 0 °C under an argon atmosphere was added a solution of 3.181 g (11.51 mmol) of the alcohol **38** in 10 mL of THF over a 10-min period. After 10 min at room temperature, 2.15 mL (18.83 mmol) of (2-methoxyethoxy)methyl chloride was added. The resulting mixture was stirred for 90 min at room temperature, poured into 150 mL of saturated aqueous $NaHCO_3$, and extracted with three 250-mL portions of ether. The combined organic phases were washed with 150 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (i.d. 5 cm) of the residue on 25 cm of silica gel with 1:1 ether/petroleum ether afforded 3.704 g (88%) of the ether **39** as a colorless oil: R_f 0.26 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 180 °C (0.005 mmHg); $[\alpha]^{26}_D$ +73.6° (*c* 1.51, $CHCl_3$); IR ($CHCl_3$) 1445, 1375, 1345, 1320, 1295, 1170, 1150, 1130, 1095, 1040, 980, 960, 940, 915, 900, 875, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.04 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.35 (dd, 1 H, *J* = 12 Hz, *J′* = 10–.5 Hz, CC*H*HCH–O, β-H), 1.46 (dd, 1 H, *J* = 13.5 Hz, *J′* = 3 Hz, CC*H*HCHC, β-H), 1.57 (m, 1 H, symmetric 11-line system, CHC*H*(CH_3)CH), 1.70 (br s, 1 H, $w_{1/2}$ = 9 Hz, CHC*H*CH_2C), 1.88 (m, 1 H, $CH_2CH(CH_3)$CH), 2.23 (dt, 1 H, J_d = 13.5 Hz, J_t = 3.5 Hz, CCH*H*CHC, α-H), 2.54 (ddd, 1 H, *J* = 12 Hz, *J′* = 5.5 Hz, *J″* = 3 Hz, CCH*H*CH–O, α-H), 3.36 (t, 1 H, *J* = 11.5 Hz, OC*H*HCH, β-H), 3.39 (s, 3 H, CH_3O), 3.50 (dt, 1 H, J_d = 5 Hz, J_t = 10.5 Hz, CHC*H*CH_2), 3.55 (br t, 2 H, *J* = 4.5 Hz, OCH_2CH_2O), 3.67 (dd, 1 H, *J* = 11.5 Hz, *J′* = 7 Hz, OCH*H*CH, α-H), 3.71 (br t, 2 H, *J* = 4.5 Hz, O*C*H_2CH_2O), 4.57 (d, 1 H, *J* = 11.5 Hz, OC*H*HC), 4.64 (d, 1 H, *J* = 11.5 Hz, OCH*H*C), 4.70 (d, 1 H, *J* = 7 Hz, OC*H*HO), 4.81 (d, 1 H, *J* = 7 Hz, OCH*H*O), 7.2–7.4 (m, 5 H, C_6H_5). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.30; H, 8.83.

3(*S*)-[((2-Methoxyethoxy)methyl)oxy]-4(*S*)-methyl-5-(*R*)-[1-hydroxy-2(*R*)-propyl]cyclohexan-1-one (40). To a stirred solution of 1.413 g (3.877 mmol) of the acetal **39** in 30 mL of ethanol was added 80 mg of 10% palladium on carbon. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 4.5 h. The catalyst was then removed by filtration and washed with three 50-mL portions of ether. Removal of the solvent from the combined filtrates afforded 1.049 g (99%) of the alcohol **40** as a colorless oil: R_f 0.12 (silica gel, 1:1 ether/dichloromethane); IR ($CHCl_3$) 3570, 3430, 1695, 1440, 1365, 1315, 1120, 1090, 1025, 970, 905, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.01 (d, 3 H, *J* = 7 Hz, CH_3H), 3.2–3.8 (m, 6 H), 3.37 (s, 3 H, CH_3O), 4.03 (br, 1 H, *J* = 3 Hz, CHC*H*CH_2), 4.72 (s, 2 H, OCH_2O).

3(*S*)-[((2-Methoxyethoxy)methyl)oxy]-4(*S*)-methyl-5-(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]cyclohexan-1-one (6). To a stirred solution of 1.049 (ca. 3.877 mmol) of the above alcohol in 10 mL of DMF were added 660 mg (9.694 mmol) of imidazole and 701 mg (4.651 mmol) of *tert*-butyldimethylchlorosilane. After 15 h at room temperature under an argon atmosphere, the product was isolated in the standard manner. Flash chromatography (i.d. 5 cm) of the residue on 15 cm of silica gel with 2:1 ether/petroleum ether afforded 1.299 g (86% over two steps from **39**) of the ether **6** as a colorless oil. For analytical data, see above.

1(*S*)-(4-Buten-1-yl)-3(*S*)-[((2-methoxyethoxy)methyl)-oxy]-4(*S*)-methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]cyclohexan-1-ol (44). To a stirred solution of 21.3 mL (9.37 mmol) of 0.44 M solution of 1-buten-4-ylmagnesium bromide (**42**) in THF in 40 mL of THF at −15 °C was added dropwise over a 30-min period a solution of 1.211 g (3.116 mmol) of the ketone **6** in 10 mL of THF. The resulting mixture was stirred for 1 h at −15 °C under an argon atmosphere, treated with 5 mL of water, and then poured into 100% of 1% aqueous H_2SO_4. This mixture was then extracted with three 250-mL portion of ether, and the combined organic phases were washed with 100 mL of water, 100 mL saturated aqueous $NaHCO_3$, and 100 mL of saturated aqueous NaCl and then dried ($MgSO_4$). After evaporation of the solvent at reduced pressure, flash chromatography (i.d. 5 cm) of the residue on 30 cm of silica gel with 1:2 ether/petroleum ether afforded first 156 mg (15%) of an oil, consisting of β-elimination products (R_f 0.49 and 0.37) and 758 mg (55%) of the alcohol **44** as a colorless oil: R_f 0.25 (silica gel, 1:2 ether/petroleum ether); evaporative distillation 160 °C (0.008 mmHg); $[\alpha]^{26}_D$ +0.6° (*c* 1.51, $CHCl_3$); IR ($CHCl_3$) 3510, 1635, 1455, 1400, 1380, 1355, 1250, 1090, 1030, 910, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.76 (d, 3 H, *J* = 7 Hz, CH_3CH), 0.88 (s, 9 H, $(CH_3)_3C$), 0.92 (d, 3 H, *J* = 6.5 Hz, CH_3CH), 1.18 (t, 1 H, *J* = 13 Hz, CC*H*HCHC, α-H), 1.4–1.5 (m, 3 H, CCH_2CH_2 and CHC*H*(CH_3)CH_2), 1.54 (dd, 1 H, *J* = 14.5 Hz, *J′* = 3 Hz, CC*H*HCH–O, α-H), 1.65 (br d, 1 H, *J* = 13 Hz, CCH*H*CHC, β-H), 1.73 (br d, 1 H, *J* = 14.5 Hz, CCH*H*CH–O, β-H), 1.84 (m, 1 H, CHC*H*(CH_3)CH), 2.07–2.21 (m, 3 H, CH_2CH_2CH and CHC*H*(CH)CH_2), 3.33 (dd, 1 H, *J* = 9.5 Hz, *J′* = 7.5 Hz, OC*H*HCH), 3.38 (s, 3 H, CH_3O), 3.54 (t, 2 H, *J* = 4.5 Hz, OCH_2CH_2O), 3.65–3.76 (m, 3 H, OCH_2CH_2O and OCH*H*CH), 3.84 (br, 1 H, *J* = 3 Hz, CHC*H*CH_2), 3.98 (s, 1 H, OH), 4.75 (d, 1 H, *J* = 7 Hz, OC*H*HO), 4.77 (d, 1 H, *J* = 7 Hz,

OCH*H*O), 4.91 (dd, 1 H, J = 10 Hz, J' = 1.5 Hz, *H*HC=CH, H cis), 5.01 (dd, 1 H, J = 17 Hz, J' = 1.5 Hz, H*H*C=CH, H trans), 5.82 (ddt, 1 H, J_d = 17 Hz, J_d = 10 Hz, J_t = 6.5 Hz, CH_2CH=CH_2. Anal. Calcd for $C_{24}H_{48}O_5Si$: C, 64.82; H, 10.88. Found: C, 64.72; H, 10.80.

Elution with 1:1 ether/dichloromethane afforded 239 mg (20%) of the alcohol **30**. For analytical data, see above.

1(*S*)-(3(*R*),4- and 1(*S*)-(3(*S*),4-Epoxy-1-butyl)-3(*S*)-[((2-methoxyethoxy)methyl)oxy]-4(*S*)-methyl-5(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]cyclohexan-1-ol (45). To a stirred solution of 648 mg (1.457 mmol) of the bishomoallylic alcohol **44** and 1.195 g (14.57 mmol) of sodium acetate in 15 mL of dichloromethane was added 503 mg (2.915 mmol) of *m*-chloropenbenzoic acid. The reaction mixture was stirred for 15 h at room temperature under an argon atmosphere, quenched by the addition of 50 mL of 10% aqueous $Na_2S_2O_5$, and then extracted with three 100-mL portion of ether. The combined organic phases were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 671 mg (100%) of an oil consisting of a ca. 1:1 mixture of the oxiranes **45** epimeric at C3′: R_f 0.21 (silica gel, 1:1:1 ether/dichloromethane/petroleum ether).

(5*R*)-2(*R*)- and (5*R*)-2(*S*)-(Hydroxymethyl)-7(*S*)-[((2-methoxyethoxy)methyl)oxy]-8(*S*)-methyl-9(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-1-oxaspiro-[4.5]decane (46). To a stirred solution of 671 mg (ca. 1.457 mmol) of the above oxirane **45** in 15 mL of dichloromethane at 0 °C was added 7 mg (0.028 mmol) of 10-camphorsulfonic acid. After 1 h at 0 °C under an argon atmosphere, the reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ and then extracted with three 100-mL portions of ether. The combined organic phases were washed with 50 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 670 mg (100%) of an oil that consisted of a ca. 1:1 mixture of the alcohols **46** epimeric at C2. Chromatography of 249 mg of the above oil on silica gel with ether afforded first 62 mg (25%) of the less polar isomer of the alcohol **46** as a colorless oil: R_f 0.19 (silica gel, ether); evaporative distillation 180 °C (0.01 mmHg); $[\alpha]^{26}_D$ −19.5° (c 1.02, $CHCl_3$); IR ($CHCl_3$) 3650, 3410, 1445, 1370, 1115, 1080, 1030, 980, 960, 935, 910, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.78 (d, 3 H, J = 7.5 Hz, C*H*$_3$CH), 0.87 (s, 9 H, $(CH_3)_3C$), 1.31 (t, 1 H, J = 13 Hz, CC*H*HCHC, α-H), 1.56 (dd, 1 H, J = 15 Hz, J' = 3.5 Hz, CC*H*HCH–O, α-H) 2.14 (br s, 1 H, $w_{1/2}$ = 22 Hz, CHC*H*(CH)CH$_2$), 3.3–3.4 (m, 1 H, CHC*H*HOH), 3.33 (dd, 1 H, J = 9.5 Hz, J' = 7.5 Hz, OC*H*HCH), 3.37 (s, 3 H, CH_3O), 3.54 (br t, 2 H, J = 4.5 Hz, OCH$_2$C*H*O), 3.63–3.80 (m, 5 H), 4.09 (br s, 1 H, $w_{1/2}$ = 18 Hz, CH$_2$C*H*CH$_2$), 4.72 (d, 1 H, J = 7.5 Hz, OC*H*HO), 4.80 (d, 1 H, J = 7.5 Hz, OCH*H*O). Anal. Calcd for $C_{24}H_{48}O_6Si$: C, 62.57; H, 10.50. Found: C, 62.68; H, 10.44.

There was then eluted 104 mg (42%) of an oil that consisted of a ca. 1:1 mixture of the alcohols **46** epimeric at C2.

There was then eluted 66 mg (27%) of the more polar isomer of the alcohol **46** as a colorless oil: R_f 0.12 (silica gel, ether); evaporative distillation 180 °C (0.01 mmHg); $[\alpha]^{26}_D$ +7.3° (c 0.83, $CHCl_3$); IR ($CHCl_3$) 3420, 1445, 1310, 1085, 1035, 1005, 980, 850 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.78 (d, 3 H, J = 7 Hz, C*H*$_3$CH), 0.87 (s, 9 Hz, $(CH_3)_3C$), 0.91 (d, 3 H, J = 7 Hz, C*H*$_3$CH), 1.27 (t, 1 H, J = 13.5 Hz, CC*H*HCHC, α-H), 1.51 (dd, 1 H, J = 15 Hz, J' = 3.5 Hz, CC*H*HCH–O, α-H), 2.08 (br s, 1 H, $w_{1/2}$ = 20 Hz, CHC*H*(CH)-CH$_2$), 3.25–3.45 (m, 2 H, CHC*H*HOH), 3.54 (t, 2 H, J = 4.5 Hz, OCH$_2$C*H*$_2$O), 3.55–3.80 (m, 5 H), 4.07 (br s, 1 H, $w_{1/2}$ = 20 Hz, CH$_2$C*H*CH$_2$), 4.74 (d, 1 H, J = 7 Hz, OC*H*HO), 4.79 (d, 1 H, J = 7 Hz, OCH*H*O). anal. Calcd for $C_{24}H_{48}O_6Si$: C, 62.57; H, 10.50. Found: C, 62.54; H, 10.37.

(5*S*)-2(*R*)- and (5*R*)-2(*S*)-Carboxy-7(*S*)-[((2-methoxyethoxy)methyl)oxy]-8(*S*)-methyl-9(*R*)-[1-(((1,1-dimethylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-1-oxaspiro[4.5]decane (4). To a stirred solution of 309 mg (0.671 mmol) of the above alcohol **46** in 5 mL of DMF was added 1.515 g (4.027 mmol) of pyridinium dichromate. After 7 h at room temperature under an argon atmosphere, the reaction mixture was poured into 50 mL of 1% aqueous H_2SO_4 and then extracted with three 100-mL portions of ether. The combined organic phases were washed with 50 mL of saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 257 mg (81%) of an oil that consisted of a ca. 3:2 mixture of the acids **4** epimeric at C2.

(5*S*)-2(*R*)- and (5*R*)-2(*S*)-Carbomethoxy-7(*S*)-[((2-methoxyethoxy)methyl)oxy]-8(*S*)-methyl-9(*R*)-[1-(((1,1-dimetyhylethyl)dimethylsilyl)oxy)-2(*R*)-propyl]-1-oxaspiro-[4.5]decane (47). A sample of 214 mg (0.451 mmol) of the above acid **4** was esterified with etheral diazomethane. Chromatography of the crude product on 20 g of silica gel with 1:1:1 ether–dichloromethane/petroleum ether afforded 152 mg (56% over two steps from **46**) of an oil that consisted of a ca. 3:2 mixture of the esters **47** epimeric at C2. Chromatography of 88 mg of this oil on silica gel with 2:1 ether/petroleum ether afforded first 45 mg of the less polar isomer of the ester **47** as a colorless oil: R_f 0.24 (silica gel, 2:1 ether/petroleum ether); evaporative distillation 180 °C (0.015 mmHg); $[\alpha]^{27}_D$ +11.2° (c 0.65, $CHCl_3$); IR ($CHCl_3$) 1735, 1720, 1450, 1425, 1370, 1355, 1275, 1245, 1165, 1120, 1080, 1035, 980, 950, 935, 910, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.80 (d, 3 H, J = 7.5 Hz, C*H*$_3$CH), 0.88 (s, 9 H, $(CH_3)_3C$), 0.91 (d, 3 H, J = 6.5 Hz, C*H*$_3$CH), 1.19 (t, 1 H, J = 13 Hz, CC*H*HCHC, α-H), 1.41 (m, 1 H, CHC*H*(CH$_3$)CH$_2$), 1.60 (dd, 1 H, J = 14.5 Hz, J' = 3.5 Hz, CC*H*HCH–O, α-H), 1.86 (m, 1 H, CHC*H*(CH$_3$)CH), 2.22 (m, 1 H, symmetric eight-line system, CHC*H*(CH)CH$_2$), 3.30 (br t, 1 H, J = 9 Hz, OC*H*HCH), 3.38 (s, 3 H, CH_3O), 3.56 (t, 3 H, J = 4.5 Hz, OCH$_2$C*H*$_2$O), 3.6–3.8 (m, 4 H, OC*H*$_2$CH$_2$O, OCH*H*CH, and CHC*H*CH$_2$), 3.67 (s, 3 H, CH_3OOC), 4.53 (dd, 1 H, J = 8.5 Hz, J' = 4.5 Hz, CH$_2$C*H*COO), 4.73 (d, 1 H, J = 7 Hz, OC*H*HO), 4.91 (d, 1 H, J = 7 Hz, OCH*H*O). Anal. Calcd for $C_{25}H_{48}O_7Si$: C, 61.44; H, 9.90. Found: C, 61.38; H, 9.93.

There was then eluted 21 mg of an oil that consisted of a ca. 1:2 mixture of the esters **47** epimeric at C2.

There was then eluted 20 mg of the more polar isomer of the ester **47** as a colorless oil: R_f 0.18 (silica gel, 2:1 ether/petroleum ether); evaporative distillation 180 °C (0.015 mmHg); $[\alpha]^{27}_D$ +26.1° (c 0.59, $CHCl_3$); IR ($CHCl_3$) 1740, 1715, 1450, 1425, 1370, 1280, 1170, 1120, 1080, 1035, 975, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3 H, CH_3Si), 0.045 (s, 3 H, CH_3Si), 0.81 (d, 3 H, J = 7.5 Hz, C*H*$_3$CH), 0.89 (s, 9 H, $(CH_3)_3C$), 0.93 (d, 3 H, J = 6.5 Hz, C*H*$_3$CH), 1.27 (t, 1 H, J = 13.5 Hz, CC*H*HCHC, α-H), 1.43 (m, 1 H, CHC*H*(CH$_3$),CH$_2$), 1.56 (dd, 1 H, J = 14.5 Hz, J' = 3.5 Hz, CC*H*HCH–O, α-H), 2.24 (m, 1 H, symmetric eight-line system, CHC*H*(CH)CH$_2$), 3.26 (t, 1 H, J = 9.5 Hz, OC*H*HCH), 3.38 (s, 3 H, CH_3O), 3.53 (t, 2 H, J = 4.5 Hz, OCH$_2$C*H*$_2$O), 3.6–3.8 (m, 3 H, OC*H*$_2$CH$_2$O and CHC*H*CH$_2$), 3.67 (s, 3 H, CH_3OOC), 3.84 (dd, 1 H, J = 9.5 Hz, J' = 4 Hz, OCH*H*CH), 4.53 (dd, 1 H, J = 8.5 Hz, J' = 5.5 Hz, CH$_2$C*H*COO), 4.75 (d, 1 H, J = 7 Hz, OC*H*-HO), 4.79 (d, 1 H, J = 7 Hz, OCH*H*O). Anal. Calcd for $C_{25}H_{48}O_7Si$: C, 61.44; H, 9.90. Found: C, 61.44; H, 9.94.