Effect of Added Sodium Acetate. Three samples of salt T1-Br (18 mg), each admixed with a different quantity of sodium acetate (0.31, 3.1, and 31 mg; 0.1, 1, and 10 equiv, respectively) were dissolved in 95:5 HOAc/MeCN (3 mL). The ampules were sealed and held at 76 °C for 27 days (648 h). Workup of the reactions (see above) showed only two products by GC, bromide B1-Br and acetate B1-OAc. The latter comprised 14%, 34%, and 87% of the product for the three respective acetate concentrations.

Four samples of salt T3-Br (18 mg) and silver acetate (6.5 mg), each admixed with a different quantity of sodium acetate (0.031, 3.1, and 31 mg; 0, 0.1, 1, and 10 equiv., respectively), were dissolved in 75:25 HOAc/MeCN (3 mL). The ampules were sealed and held at 76 °C for 5.5 h. Workup as before showed only bromide B3-Br and acetate B3-OAc. The latter comprised 13 ± 3% of the product in every case.

The UV spectra of salt T2-Br (5×10^{-5} M) was taken in 75:25 HOAc/MeCN: λ_{max} 252 nm (log ϵ 4.03). Addition of 1 or 10 equiv of sodium acetate showed λ_{max} 252 nm in each case, with log ϵ 4.03 and 4.01, respectively.

Acknowledgment. We thank Professors D. S. Crumrine and K. Olsen and Beth Gillece-Castro and Kate Martin, all of this department, for technical assistance. We also thank the referees for their incisive comments.

Registry No. B1-Br, 23526-72-9; B1-OAc, 90364-56-0; B1-OTFA, 109010-22-2; T1-Br·SbF_6, 90270-04-5; T1-OAc·SbF_6, 90270-06-7; T1-OTFA·SbF_6, 108920-12-3; B2-Br, 23526-73-0; B2-OAc, 109009-40-7; T2-Br·SbF_6, 104714-31-0; T2-OAc·SbF_6, 109009-42-9; T2-OTFA·SbF_6, 109009-44-1; B2-OTFA, 108920-10-1; B3-Br, 7605-11-0; B3-OAc, 1207-28-9; T3-Br·SbF_6, 104648-80-8; T3-OAc·SbF_6, 108920-14-5; B4-Br, 23526-75-2; B4-OAc, 1207-27-8; T4-Br·SbF_6, 104714-33-2; T4-OAc·SbF_6, 109009-46-3; $Ph_3C^+ \cdot SbF_6^-$, 437-18-3.

Convergence with Mutual Kinetic Resolution. 1. Studies Defining Methodology for the Taxol C/D Ring Fragment and Synthesis of the A Ring Fragment

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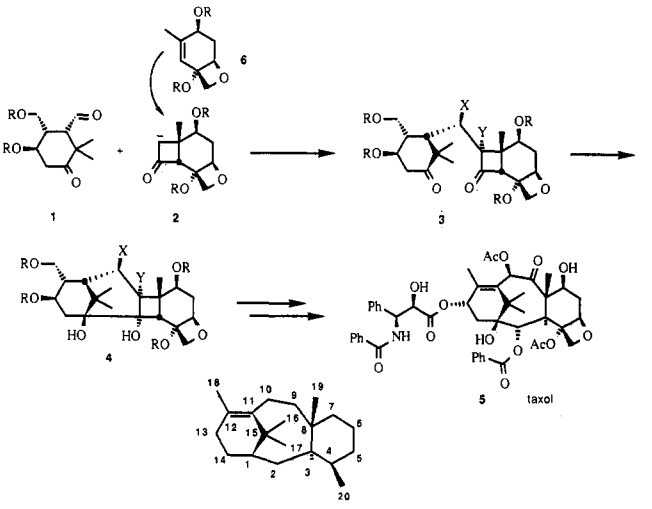
4-Exo-tet cyclization gives the alkoxyoxetane of the taxol C/D ring fragment if the tertiary alcohol is protected. Cycloaddition of dichloroketene and 1-[(*tert*-butyldimethylsilyl)oxy]-2-methylcyclohex-2-ene, a model for the allylic ether **6**, succeeds in the presence of DME. The synthesis of the A ring fragment relies on the Diels–Alder reaction of 1-ethoxy-3-[(trimethylsilyl)oxy]-2-methyl-1,3-butadiene with ethyl (*E*)-2-acetoxyacrylate and the axial conjugate addition of a vinyl Normant reagent.

Mutual kinetic resolution[1] in the aldol reaction of a cyclobutanone enolate[2] makes it possible in principle to couple A and C/D ring precursors **1** and **2** of the taxol skeleton for a convergent approach[3] to taxol[4,5] (Scheme I). This strategy complements the photochemical route outlined recently.[6] Our earliest experiments[2] were carried out with structurally simplified *racemic* A ring (aldehyde) and C/D ring (enolate) partners and gave within the limits of detection (^{1}H NMR at 300 MHz) only a single diastereomer in the aldol coupling reaction; efforts directed at generating fully functionalized A and C/D ring precursors are described herein. Model studies for generating the alkoxyoxetane unit[7] in the C/D ring precursor **2** and carrying out the [2 + 2] cycloaddition of dichloroketene[8] with an allyic ether precede the synthesis of complete A ring fragment.

Since **6** can aromatize with the formal loss of two water molecules, the alkoxyoxetane **8**, at a lower oxidation level, became the target of the model study. Using a ketone at C-4 (taxol numbering) as a precursor to the alkoxyoxetane unit was viewed a possible structural simplification.

As the first step in elaborating 3-methyl-2-cyclohexen-1-one, the methodology of Rubottom[9] afforded the ketol

Scheme I



9 (73% overall). Conversion of the ketol *tert*-butyldimethylsilyl ether **10** (obtained from **9** in quantitative yield

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(1) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300.

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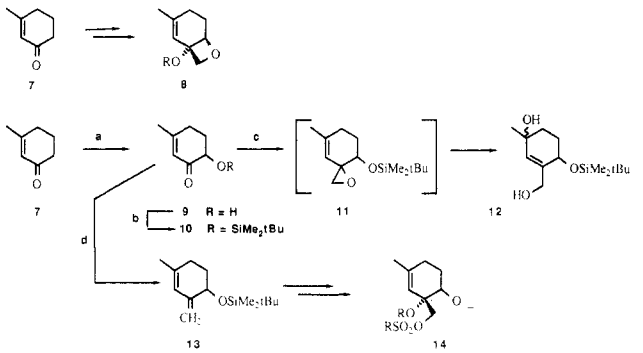
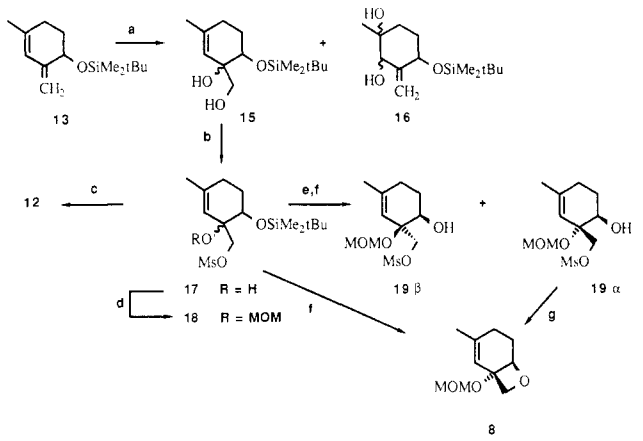
Scheme II[a]



[a] Reagents: (a) (1) LDA, Me_3SiCl, (2) MCPBA, (3) n-Bu_4NF; (b) t-$BuMe_2SiCl$, imidazole; (c) Me_2SCH_2; (d) (1) Me_3SiCH_2MgCl, (2) oxalic acid.

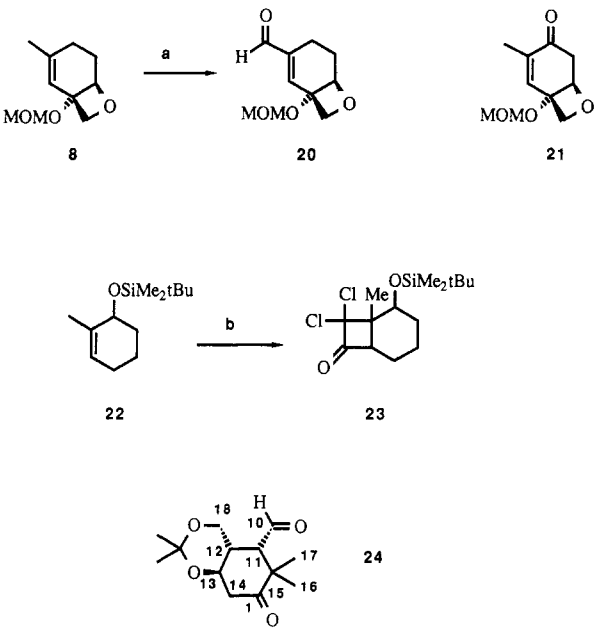
Scheme III[a]



[a] Reagents and conditions: (a) OsO_4, N-methylmorpholine N-oxide; (b) MsCl, pyridine; (c) n-Bu_4NF; (d) MOMCl, $Et_2N(i\text{-}Pr)$; (e) n-Bu_4NF, THF, 25 °C; (f) n-Bu_4NF, THF, reflux; (g) NaH, ether, reflux.

by using *tert*-butyldimethylchlorosilane and imidazole in *N*,*N*-dimethylformamide[10]) to the epoxide **11** with dimethylsulfonium methylide[11] (Scheme II) would provide the correct oxidation level at the three contiguous carbon atoms bearing oxygen. The manipulation of functionality and stereochemistry could then be examined. However, all attempts to produce **11** resulted instead in the isolation of the tertiary allylic alcohol **12**, resulting formally from ring opening of the epoxide by water with allylic rearrangement.

Scheme IV[a]



[a] Reagents and conditions: (a) SeO_2, dioxane, water, reflux 3 h; (b) Cl_3COCl, Zn–Cu, DME, ether.

Peterson olefination[12] of the silylated ketol **10** cleanly led to the diene **13** (72% overall). In this process, [(trimethylsilyl)methyl]magnesium chloride added smoothly to the ketone of **10**. Surprisingly, the elimination of trimethylsilanol proceeded rapidly under acidic (oxalic acid as catalyst in anhydrous methanol) but not at all under basic (potassium hydride in tetrahydrofuran) conditions.

Osmylation of **13** should give a 1,2-diol, although regio- and stereochemical questions remained. Exposure of the diene to osmium tetroxide (generated by using *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide in acetone)[13] produced a mixture of stereoisomers of **15** and **16** (2.3:1 **15**/**16**, 63%) (Scheme III).

Although **15** and **16** were chromatographically separable, the stereoisomers of **15** were not, so **15** as a mixture of stereoisomers was carried forward. Selective mesylation (methanesulfonyl chloride in pyridine;[14] 95%) afforded the primary mesylate **17** as a mixture of stereoisomers.

Following a strategy similar to that outlined recently,[6] attempted formation of the 2-hydroxyoxetane by tetra-*n*-butylammonium fluoride-mediated desilylation[10] of the C-5 *tert*-butyldimethylsilyl ether gave instead the allylic alcohol **12** (39%), presumably because deprotonation of the tertiary hydroxyl by fluoride ion[15] leads to the putative epoxide **11** (Scheme II). Protection of the tertiary allylic

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alcohol as the methoxymethyl ether to give **18** (chloromethyl methyl ether in diisopropylethylamine;[16] 94%) and then desilylation (tetra-*n*-butylammonium fluoride) in refluxing tetrahydrofuran produced the desired oxetane **8** (60%) along with the unchanged **19β** (27%). Although desilylation (tetra-*n*-butylammonium fluoride in tetrahydrofuran) at room temperature gave the alcohol **19** as a mixture of stereoisomers (80%), subsequent deprotonation (sodium hydride in tetrahydrofuran) also afforded **8** (56%).

Starting with 3-methyl-2-cyclohexen-1-one, this sequence provided the desired alkoxyoxetane in 5% yield after 10 steps. The 4-exo-tet[17,18] cyclization succeeded only when the tertiary allylic alcohol was protected, a result in agreement with the findings of Berkowitz.[6]

The alkoxyoxetane **8** was treated with selenium dioxide in refluxing aqueous dioxane[19] to investigate allylic oxidation as a means of introducing the oxygen atom at C-7 (taxol numbering). However, the allylic oxidation gave the aldehyde **20** (38%) rather than the enone **21** (Scheme IV).

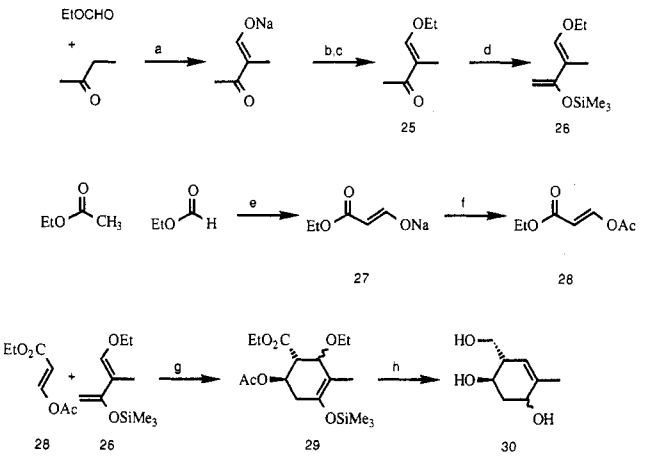
We attribute this observation to torsional factors.[20] In a single-crystal X-ray diffraction study, an oxetane displayed a dihedral angle (the angle between the planes defined by O1, C2, C3 and O1, C4, C3; oxetane numbering) of 16°.[21] Therefore, fusion to a cyclohexane (which normally displays a 60° dihedral angle between equatorial and axial substituents) puckers the oxetane (i.e., would like to increase the dihedral angle from about 16° to 60°; note that the oxetane and cyclohexane dihedral angles are defined differently). At the minimum, partial double-bond character is developing between C-7 and C-8 (taxol numbering) in the transition state for selininic acid formation during allylic oxidation at C-7, and that may be expected to pucker the cis-fused oxetane even further (as it would the saturated ring in cis-fused 1,4,4a,5,6,7,8,8a-octahydronaphthalene[20]). To avoid this geometrical change, allylic oxidation occurs at the exocyclic position.

The final sequence anticipated in the formation of the C/D ring fragment **2** is the [2 + 2] cycloaddition of the olefin **6**, bearing two allylic ether substituents, with dichloroketene.[22] Ample precedent indicates that the product of the reaction should result from a Claisen rearrangement.[23] However, a recent paper describes the cycloaddition of dichloroketene, generated by the reaction of trichloroacetyl chloride in refluxing ether with zinc–copper couple, to an allylic ether in the presence of 1,2-dimethoxyethane.[24] In our hands, this procedure succeeded (30%) with the model allylic silyl ether **22** as a substrate, and products resulting from the Claisen rearrangement were not observed (Scheme IV).

The desired C/D ring fragment is regarded as synthetically accessible in light of these results. Our finding that the alkoxyoxetane can be produced by a 4-exo-tet cyclization if the tertiary alcohol is protected is consonant with the reports of Berkowitz.[6,7] The necessary [2 + 2] cycloaddition of dichloroketene with an allylic ether occurs when the reductive dehalogenation of trichloroacetyl chloride is carried out in the presence of 1,2-dimethoxyethane.

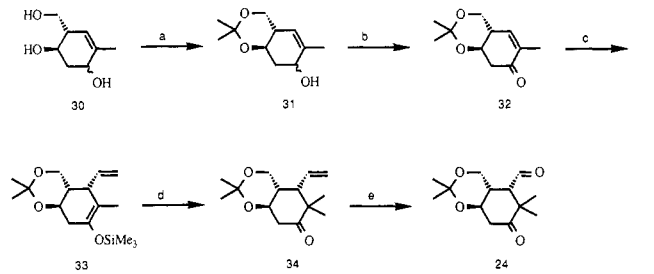
A convergent synthesis of taxol (**5**), which joins the A and C/D ring precursors **1** and **2**, must correctly situate the chiral centers at C1 and C8. Our strategy is to relate C8 to C11 in an aldol reaction (**1** + **2** → **3**; X = OH, Y = H), and C1 to C11 in annulating the B ring (**3** → **4**; X, Y = bond). Having C10 axial to ring A would maximize the possibility of this annulation. These requirements are met in **24** (Scheme IV), whose rigidity derives from a trans-fused dioxadecalin and whose relative stereochemistry results from the axial conjugate addition of a vinyl Normant reagent[25,26] to an enone.

Scheme V[a]



[a] Reagents and conditions: (a) NaOEt, EtOH; (b) HCl; (c) EtOH, TsOH; (d) Me_3SiCl, Et_3N, $ZnCl_2$, petroleum ether; (e) Na^0, Et_2O; (f) acetyl chloride, Et_2O; (g) hydroquinone, 180 °C; (h) LAH, THF.

Scheme VI[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, TsOH, DMF; (b) MnO_2, CH_2Cl_2; (c) Me_2S–CuBr, vinylmagnesium bromide (2 equiv), HMPA, Me_3SiCl, THF; (d) $PhCh_2NMe_3{}^+F^-$, MeI, THF, 4-Å molecular sieves; (e) ozone, methanol, Me_2S.

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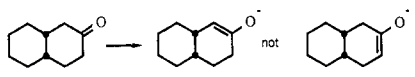
(20) (a) Cis-fused decahydronaphthalene-2-one prefers to lose a proton from C1 rather than C3 during enolization. This is usually attributed to the reflex



effect. In the cis-fused octahydronaphthalene, the double bond from C2 to C3 causes the fully saturated 6-membered ring to pucker while the double bond from C1 to C2 causes the fully saturated 6-membered ring to flatten. Since the puckering distortion is more energetically costly than the flattening distortion, the double bond from C1 to C2 is preferred when the octahydronaphthalene is cis-fused.[20b] (b) Akhrem, A. A.; Titov, Yu. A. *Total Steroid Synthesis*; Hazzard, B. J., Translater; Plenum: New York, 1970; pp 45–50.
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The Diels–Alder reaction of 1-ethoxy-3-[(trimethylsilyl)oxy]-2-methyl-1,3-butadiene with ethyl (*E*)-2-acetoxyacrylate afforded the A ring skeleton. Formylation of 2-butanone[27] and treatment of the α-formyl ketone with ethanol and *p*-toluenesulfonic acid (Scheme V) produced the desired vinylogous ester **25** (52%),[28] and silylation using the method of Danishefsky gave the desired 1-ethoxy-3-[(trimethylsilyl)oxy]-2-methyl-1,3-butadiene (**26**) (68%).[29] A similar diene has been made and used by Ibuka et al.[30] and also Danishefsky et al.[29]

The known dienophile[31] ethyl (*E*)-2-acetoxyacrylate (**28**)[32] was produced by the formylation of ethyl acetate and acetylation of the sodium salt of the α-formyl ester **27** using acetyl chloride. On occasion, the distilled ethyl acetoxyacrylate was an *E*/*Z* mixture, and isomerization using traces of acetic acid and hydroquinone at 150 °C afforded the pure *E* isomer.

Heating excess neat diene **26** with neat dienophile **28** at 180 °C and removing the excess, volatile diene under vacuum at 80 °C gives the Diels–Alder adduct **29** in 85% yield as a 1:1 mixture of endo and exo adducts. Surprisingly, this reaction proceeds more rapidly than the elimination of acetic acid. Reduction using excess lithium aluminum hydride, following the procedure of Fraser-Reid,[33] gives the triol **30** (56%).

The stereochemical ambiguity introduced in the Diels–Alder reaction has now been removed, and the rigidity of the ring can be established by the creation of a trans-fused dioxadecalin. To this end, the triol **30** was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in *N*,*N*-dimethylformamide to give the acetonide **31** (80%). The stage for 1,4-addition was set by oxidizing the remaining allylic alcohol with manganese dioxide[34] to the enone **32** (89%; Scheme VI).

Copper-catalyzed addition of vinylmagnesium bromide[35] followed by the addition of hexamethylphosphoric triamide and methyl iodide[36,37] gave the desired 1,4-addition and methylation. The stereochemistry of the addition, 2:1 equatorial/axial, was tentatively attributed to reversible addition. The product mixture would then reflect the thermodynamic stabilities of the intermediate enolates rather than the activation energies of the transition states, and so the equatorial isomer would be preferred. The requirement of in situ methylation following the conjugate addition of a vinyl Normant reagent demands that the intermediate enolate be stable, since the methylation is slow. However, Ley and co-workers[26a] reported the sequential axial conjugate addition of a vinyl Normant reagent and the trapping of the resulting enolate using monomeric formaldehyde, which should be a reactive trapping agent. Therefore, the addition and methylation steps were isolated so that a more rapid trapping protocol could be used.

The copper-catalyzed 1,4-addition of vinylmagnesium bromide was followed by trapping the enolated with chlorotrimethylsilane in the presence of hexamethylphosphoric triamide. Analysis of the stereochemistry at this point proved impractical since no analytical method for separating the stereoisomers, either chromatographically or spectroscopically, was found. However, methylation of the silyl ether with methyl iodide and benzyltrimethylammonium fluoride by the method of Kuwajima and Nakamura[38] gave rigid products, and the two stereoisomers were clearly distinguishable by ^{1}H NMR at 60 MHz. Product mixtures were typically 1:1 equatorial/axial. However, after much experimentation it was discovered that adding vinylmagnesium bromide (4 equiv) in tetrahydrofuran to a solution of copper(I) bromide–dimethyl sulfide complex (2 equiv) in tetrahydrofuran, stirring 20 min at −78 °C, and adding chlorotrimethylsilane (5 equiv) and hexamethylphosphoric triamide (2 equiv) gave a reagent[25,26,37] that added axially to the enone **32** (1 equiv). The crude weight recovery (in this case 93%) is typically very good; isolated yields following methylation are in the 50–60% range for the two steps. Although the true cause for the stereochemical outcome remains unproven because the fate of the remaining product is unknown, this is a respectable method for placing a quaternary center in the pentasubstituted cyclohexane ring. The resulting silyl enol ether was methylated by the methodology of Nakamura and Kuwajima[38] (53%, or 49% overall for the two steps) and ozonolysis completed the synthesis of the desired A ring precursor.

In summary, the stereochemical problem was solved by the axial conjugate addition of a vinyl Normant reagent[25,26] after removal of the stereochemical relationship introduced in the Diels–Alder reaction. The aldehyde was reliably produced by ozonolysis.

Experimental Section

General Procedures. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from the blue benzophenone radical anion under nitrogen. Methylene chloride (CH_2Cl_2), acetonitrile (CH_3CN), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (Me_2SO), dimethyl sulfide (Me_2S), benzene, xylenes, pentane, hexanes, triethylamine, diisopropylamine, diisopropylethylamine, and pyridine were distilled from calcium hydride and stored over 3-Å molecular sieves under nitrogen. Methanol was distilled from magnesium methoxide, acetone from anhydrous potassium carbonate, and methanesulfonyl chloride from calcium hydride. Chlorotrimethylsilane (distilled from calcium hydride) and methyl iodide were freshly distilled just prior to use. Hexamethylphosphoric triamide (HMPA) was distilled under reduced pressure from sodium and stored over activated

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3-Å molecular sieves. Tetra-*n*-butylammonium fluoride in tetrahydrofuran (Aldrich) was dried over activated 4-Å molecular sieves for 12 h before use. Benzyltrimethylammonium fluoride was prepared according to the procedure of Kuwajima and Nakamura[38] and stored under nitrogen in a Schlenck tube. When prepared in large quantities, it takes several days to thoroughly dry the salt at 50 °C (0.025 mmHg) with a liquid nitrogen cooled trap. Stirring the viscous residue at 12–14-h intervals facilitates the drying process, perhaps by breaking up a surface film. E. Merck silica gel 60 of 0.040–0.063-mm mesh size was used for column chromatography. The ^{1}H NMR spectra were recorded on a Varian EM-360 or a JEOL FX-90Q NMR spectrometer. The $CHCl_3$ contaminant in $CDCl_3$ or tetramethylsilane was used as an internal standard. The ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer at 22.5 MHz. Chemical shifts for both ^{1}H and ^{13}C NMR spectra are expressed in parts per million downfield from tetramethylsilane (δ). The infrared spectra were recorded on a Beckman Model IR-10 or a Perkin-Elmer Model 599 spectrophotometer and were calibrated with a polystyrene standard.

6-Hydroxy-3-methyl-2-cyclohexen-1-one (9). Following the procedure of Rubottom[9] to a solution of diisopropylamine (1.35 mL, 9.6 mmol, 1.1 equiv) in THF (20 mL) under nitrogen at −24 °C was added *n*-butyllithium (7.3 mL of a 1.35 M solution in hexane, 9.9 mmol, 1.1 equiv). After 10 min, enone **7** (1.0 mL, 8.8 mmol, 1.0 equiv) was added dropwise, and the reaction mixture was allowed to stir for 10 min. Then chlorotrimethylsilane (2.35 mL, 18.5 mmol, 2.1 equiv) was quickly added. After it was stirred for 2.5 h at 25 °C, the solution was diluted with pentane (30 mL) and was washed with a cold, saturated aqueous solution of sodium bicarbonate (10 mL). The organic layer was dried over anhydrous sodium sulfate. Filtration and removal of the solvents in vacuo afforded the crude enol silyl ether. To a prestirred (20 min at 25 °C, then cooled to −25 °C) solution of *m*-chloroperoxybenzoic acid (1.85 g of 90% MCPBA, 9.7 mmol, 1.1 equiv) in hexanes (100 mL) at −25 °C was added the entire crude enol silyl ether in hexanes (5 mL) over 8 min. After it was stirred for 1 h at 25 °C, the reaction mixture was filtered, the volatile materials were removed in vacuo, and the residue was triturated with pentane. The resulting solution was concentrated under reduced pressure, and methylene chloride (137 mL) and tetra-*n*-butylammonium fluoride (11 mL of a 1.0 M solution in THF, 11.0 mmol, 1.2 equiv) were added at 0 °C. After 2 h of stirring at 25 °C, the reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate (25 mL), a 5% aqueous solution of hydrochloric acid (25 mL), and a saturated aqueous solution of sodium bicarbonate (25 mL). The resulting organic phase was dried, filtered, and concentrated in vacuo, and the residue was purified by column chromatography (5:1, v/v, hexanes/EtOAc) using silica gel (20 g) to yield **9**: 0.81 g, 73%; IR (neat) 3480, 2950, 1660, 1630, 1100, 880, 860, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.73 (s, 1 H), 3.93 (dd, J = 5.6, 13.2 Hz, 1 H), 3.68 (s, 1 H), 2.49–1.53 (m, 7 H including s at 1.82); ^{13}C NMR ($CDCl_3$) δ 199.39, 163.95, 123.30, 71.67, 30.63, 30.24, 23.81; mass spectrum, m/e (relative intensity) 27 (33.8), 38 (23.8), 53 (8.1), 54 (30.6), 82 (100, $M^+ - CH_2{=}CHOH$), 83 (8.8), 126 (13.1, M^+).

3-Methyl-6-[(*tert*-butyldimethylsilyl)oxy]-2-cyclohexen-1-one (10). To a solution of **7** (717 mg, 5.7 mmol, 1.0 equiv) and imidazole (1.18 g, 17.3 mmol, 3.0 equiv) in DMF (19 mL) at 0 °C was added *tert*-butyldimethylchlorosilane (1.12 g, 7.4 mmol, 1.3 equiv). After it was stirred overnight at 25 °C, the reaction mixture was diluted with pentane (30 mL) and water (10 mL), and after separation of the layers, the aqueous layer was extracted with pentane (30 mL). The combined organic layers were dried and concentrated in vacuo. Chromatography of the residue (30:1, v/v, hexanes/EtOAc) on silica gel (20 g) yielded **10**: 1.36 g 100%; IR (neat) 2950, 1690, 1280, 1160, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.81 (s, 1 H), 4.09 (dd, J = 5.9, 9.8 Hz, 1 H), 2.53–1.76 (m, 7 H including s at 1.94), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.02, 161.48, 125.06, 73.16, 31.94, 29.98, 25.69, 23.87, 18.34, −4.55, −5.52.

3-Methyl-1-methylene-6-[(*tert*-butyldimethylsilyl)oxy]-2-cyclohexene (13). Into a solution of **10** (1.4 g, 5.8 mmol, 1.0 equiv) in THF (36 mL) under nitrogen was added [(trimethylsilyl)methyl]magnesium chloride (36 mL of a 1.0 M solution in ether, 36.0 mmol, 6.2 equiv) over 11 min. After it was stirred for 12 h at ambient temperature, the reaction mixture was quenched with a cold, saturated aqueous solution of ammonium chloride (25 mL) and washed with three 40-mL portions of ether. The combined organic layers were dried, filtered, and concentrated under reduced pressure to yield the crude diastereomeric tertiary alcohols (2.2 g). A portion (428 mg, 1.3 mmol, 1.0 equiv) was dissolved in anhydrous methanol (5 mL), and a catalytic amount of oxalic acid was added to the solution at 0 °C. After 50 min of stirring at 25 °C, a saturated aqueous solution of sodium bicarbonate was added at 0 °C until the solution was basic. The volatile material was removed in vacuo, and the residue was diluted with ether (30 mL) and washed with one 5-mL portion of a saturated aqueous solution of sodium bicarbonate. The aqueous phase was washed with two 20-mL portions of ether, and the organic layers were combined, dried, filtered, and concentrated under reduced pressure. Chromatography of the residual oil on silica gel (12 g) using hexanes afforded pure **13**: 0.19 g; IR (neat) 2960, 2950, 2940, 1650, 1260, 1120, 1080, 950, 940, 900, 890, 860, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.89 (s, 1 H), 4.98 (s, 1 H), 4.75 (s, 1 H), 4.38–4.11 (m, 1 H), 2.29–1.56 (m, 7 H including s at 1.76), 0.95 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.65, 137.54, 124.02, 107.63, 70.37, 32.52, 29.33, 25.95, 23.29, 18.34, −4.68.

Osmylation of 13. Into a solution of *N*-methylmorpholine *N*-oxide monohydrate (246 mg, 1.8 mmol, 1.0 equiv) and osmium tetroxide (4.5 mL of a 0.02 M solution in *tert*-butyl alcohol, 0.09 mmol, 0.05 equiv) in water (2 mL) and acetone (12 mL) at 0 °C was added a solution of **13** (432 mg, 1.8 mmol, 1.0 equiv) in acetone (5 mL) over 3 min. After 5 h of stirring and warming to 25 °C, a slurry of sodium thiosulfate (319 mg) and florisil (1.2 g) in water was added. After 30 min, the mixture was filtered, the volatile material was removed under reduced pressure, and the residue was diluted with brine (15 mL) and extracted with three 20-mL portions of ethyl acetate. The combined organic layers were dried, filtered, and concentrated under reduced pressure, and chromatography of the residue on silica gel (15 g) using hexane/ethyl acetate (5:1, v/v) yielded the less polar **15** and the more polar **16**. **15**: 215 mg, 44%; IR (neat) 3430, 2925, 1680, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.23 and 5.04 (both s, 1 H), 4.17–3.66 (m, 2 H), 3.44–2.72 (m, 3 H), 2.12–1.40 (m, 7 H including s at 1.60), 0.84 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 139.56, 138.52, 123.37, 122.65, 76.80, 72.32, 71.60, 69.72, 67.05, 66.53, 28.62, 28.42, 27.97, 27.06, 25.69, 23.22, 22.90, 17.82, −4.29, −4.81, −5.07. **16**: 94 mg, 19%; IR ($CHCl_3$) 3560, 2925, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.04 (s, 1 H), 4.98 (s, 1 H), 4.44–4.27 (m, 1 H), 4.09 (s, 1 H), 2.64 (br s, 2 H), 1.88–1.46 (m, 4 H), 1.23 (s, 3 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 149.90, 109.32, 76.80, 73.16, 71.67, 32.52, 31.61, 25.69, 25.17, 18.08, −4.94, −5.07; mass spectrum, m/e (relative intensity) 73 (11.2), 75 (53.0), 81 (10.4), 95 (31.3), 97 (9.7), 105 (41.8), 122 (10.4), 123 (22.4), 140 (25.4), 157 (8.2, $M^+ - t$-BuSiMe$_2$), 179 (39.6), 180 (6.7), 197 (100.0), 198 (16.4), 201 (9.7), 215 (8.2, $M^+ - C(CH_3)_3$), 240 (2.5), 254 (3.2, $M^+ - H_2O$), 272 (0.15, M^+).

Mesylation of 15. Into a solution of **15** (249 mg, 0.92 mmol, 1.0 equiv) in pyridine (9 mL) at 0 °C was added slowly methanesulfonyl chloride (0.09 mL, 1.2 mmol, 1.3 equiv), and the resulting solution was allowed to stand for 48 h at 0 °C. The reaction mixture was diluted with methylene chloride (30 mL) and washed successively with three 10-mL portions of a 10% aqueous solution of hydrochloric acid, one 10-mL portion of a saturated aqueous solution of sodium bicarbonate, and one 10-mL portion of brine. The organic phase was dried, filtered, and concentrated under reduced pressure to give crude **17**: 305 mg, 95%; IR (neat) 3350, 2920, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.38 and 5.19 (s, 1 H), 4.32 and 4.16 (AB quartet, J = 10.2 Hz, 2 H), 4.03 (s, 1 H), 3.89–3.64 (m, 1 H), 3.02 and 3.01 (both s, 3 H), 2.09–1.49 (m, 7 H including s at 1.68), 0.88 and 0.85 (both s, 9 H), 0.11, 0.08, and 0.07 (3 s, 6 H); ^{13}C NMR ($CDCl_3$) δ 140.41, 121.29, 120.12, 74.20, 72.38, 71.80, 69.26, 37.40, 28.55, 27.06, 26.67, 25.69, 23.29, 17.89, −4.22, −4.55, −5.07.

Protection of 17. Into a solution of crude **17** (305 mg, 0.87 mmol, 1.0 equiv) in diisopropylethylamine (1.2 mL, 6.9 mmol, 7.9 equiv) at 0 °C was added chloromethyl methyl ether (0.33 mL, 4.3 mmol, 5.0 equiv). After being stirred at room temperature for 14 h, the reaction mixture was diluted with ether (30 mL) and washed successively with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL). Drying, filtering, and concentrating in vacuo afforded crude **18**: 322 mg, 94%; IR (neat) 2920, 1660,

1420, 1340, 1240, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.35 and 5.16 (both s, 1 H), 4.84 and 4.65 (one AB quartet, J = 7.1 Hz) and 4.77 and 4.56 (second AB quartet, J = 7.1 Hz, combined 2 H), 4.31–4.12 (m, 2 H), 3.97–3.73 (m, 1 H), 3.34 and 3.33 (both s, 3 H), 3.01 and 2.99 (both s, 3 H), 2.18–1.47 (m, 7 H including s at 1.73), 0.88 and 0.85 (both s, 9 H), 0.09, 0.08, 0.07 (3 s, 6 H); ^{13}C NMR ($CDCl_3$) δ 143.33, 119.40, 116.93, 92.61, 91.83, 77.52, 76.35, 72.64, 71.80, 70.30, 69.91, 55.54, 55.15, 37.40, 29.14, 26.99, 26.47, 25.76, 23.55, 20.49, 18.02, –4.35, –5.07; mass spectrum, m/e (relative intensity) 46 (25.0), 73 (14.5), 75 (17.8), 81 (85.5), 89 (28.9), 91 (65.8), 93 (17.8), 95 (14.5), 101 (9.2), 105 (64.5), 106 (13.2), 107 (12.5), 109 (10.5), 119 (11.8), 123 (23.7), 127 (47.4), 129 (43.4), 153 (21.7), 179 (13.8), 197 (100.0, 254 – $C(CH_3)_3$), 198 (15.8), 209 (21.1), 211 (11.8), 237 (9.9), 254 (9.2, 285 – OCH_3), 285 (8.4, M^+ – CH_2OMs), 333 (1.4, M^+ – OCH_2OCH_3), 335 (2.2), 394 (0.05 M^+).

Desilylation of 18 under Reflux. To a solution of **18** (322 mg, 0.82 mmol, 1.0 equiv) in THF (14 mL) was added tetra-*n*-butylammonium fluoride (3.2 mL of a 1.0 M solution in tetrahydrofuran, 3.2 mmol, 3.9 equiv). After being stirred for 15 min, the reaction mixture was heated under reflux for 15 min, diluted with ether (60 mL), and washed with saturated aqueous sodium bicarbonate (10 mL). Thin-layer chromatographic analysis of the residue following drying, filtering, and concentration in vacuo revealed two products. After column chromatography (hexanes; then 10:90, v/v, ethyl acetate/hexanes; then 50:50, v/v, ethyl acetate/hexanes) using silica gel (15 g) the polar compound (61.6 mg, 27%) was found to be **19**β and the less polar compound the desired oxetane **8**. **19**β: ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 1 H), 4.78 and 4.51 (AB quartet, J = 7.1 Hz, 2 H), 4.36–3.97 (m, 3 H), 3.70–3.40 (m, 1 H), 3.27 (s, 3 H), 2.93 (s, 3 H), 2.20–1.39 (m, 7 H including s at 1.67); ^{13}C NMR ($CDCl_3$) δ 145.41, 118.16, 91.96, 75.83, 71.15, 68.61, 55.48, 36.94, 29.53, 26.21, 23.35; mass spectrum, m/e (relative intensity) 43 (14.2), 45 (83.8), 79 (11.8), 81 (32.4), 93 (16.9), 95 (18.9), 109 (45.9), 123 (18.2), 127 (12.6), 139 (100.0), 140 (10.3), 141 (10.4), 171 (17.6, M^+ – CH_2OMs), 219 (1.4, M^+ – OCH_2OCH_3), 279 (1.4), 280 (0.3, M^+). **8**: 90 mg, 60%; IR (neat) 2930, 1260, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.42 (s, 1 H), 5.01 (s, 1 H), 4.77 and 4.49 (AB quartet, J = 6.8 Hz, 2 H), 4.65 and 4.10 (AB quartet, J = 5.4 Hz, 2 H), 3.40 (s, 3 H), 2.20–1.70 (m, 7 H including s at 1.84); ^{13}C NMR ($CDCl_3$) δ 140.86, 120.51, 92.28, 86.17, 81.49, 73.03, 55.34, 24.65, 24.20, 23.35; mass spectrum, m/e (relative intensity) 45 (100.0, CH_2OCH_3), 81 (15.3), 95 (16.6), 105 (10.3), 109 (9.4), 123 (50.0, M^+ – OCH_2OCH_3), 125 (11.2), 137 (13.2), 154 (32.6, M^+ – CH_2O), 155 (20.1).

Reaction of 6-[(*tert*-Butyldimethylsilyl)oxy]-1-methylcyclohex-1-ene with Dichloroketene. A solution of 6-[(*tert*-butyldimethylsilyl)oxy]-1-methylcyclohex-1-ene[39] (502 mg, 2.2 mmol, 1.0 equiv; prepared by $NaBH_4/CeCl_3$ reduction[40] of the 2-methyl-2-cyclohexen-1-one[41] and then silylation[10]) in ether (2 mL) was added via syringe to a suspension of zinc–copper couple[22] (221 mg, 3.4 mmol, 1.5 equiv) in ether (4.4 mL) and 1,2-dimethoxyethane (1.1 mL). Then freshly distilled trichloroacetyl chloride[22] (0.35 mL, 3.1 mmol, 1.4 equiv) was added. The mixture was heated under reflux for 48 h and then cooled to room temperature. Dilution with pentane (30 mL) afforded an organic phase that was washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The resulting organic phase was dried, filtered, and concentrated in vacuo, and the residue was subjected to column chromatography on silica gel (15 g) to give recovered starting material (51 mg, 9.3%) and a clear, colorless oil (221 mg, 29.5%) that solidified on standing to give a white crystalline solid: IR (neat) 2950, 2870, 1810, 1460, 1260, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92–3.51 (m, 2 H), 2.10–1.20 (m, 9 H including s at 1.50), 0.90 (s, 9 H), 0.08 (s, 6 H).

4β,6α-Dihydroxy-3α-(hydroxymethyl)-1-methylcyclohex-1-ene and 4β,6β-Dihydroxy-3α-(hydroxymethyl)-1-methylcyclohex-1-ene (30). A mixture of 1-ethoxy-3-[(trimethylsilyl)oxy]-2-methyl-1,3-butadiene[27,28,29,30] (10.1 g, 50.5 mmol, 1.6 equiv), ethyl (*E*)-3-acetoxyacrylate[31,32] (5.0 g, 31.6 mmol, 1.0 equiv), and hydroquinone (35 mg, 0.32 mmol, 0.01 equiv) was placed under nitrogen. The pale yellow solution was heated at 180–185 °C for 1.5 h, at which time ^{1}H NMR spectroscopy showed the complete disappearance of ethyl (*E*)-3-acetoxyacrylate. The volatile materials were removed in vacuo (0.025 mm) at 70 °C. The residue (9.6 g, 85%) was 2-methyl-3α-ethoxy-4α-carbethoxy-5β-acetoxy-1-[(trimethylsilyl)oxy]-1-cyclohexene and 2-methyl-3β-ethoxy-4α-carbethoxy-5β-acetoxy-1-[(trimethylsilyl)oxy]-1-cyclohexene (**29**), as indicated by spectral data: IR (neat) 2990, 2921, 2900, 1730, 1678, 1638, 1454, 1386, 1330, 1267, 1223, 1105, 1063, 889, 800, 780 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.63–4.63 (m, 1 H), 4.43–3.80 (m, 3 H including a quartet at 4.13), 3.77–3.13 (m, 2 H), 3.07–1.83 (m, 6 H including s at 1.93), 1.73–0.87 (m, 9 H including br s at 1.52 and t at 1.20), 0.10 (s, 9 H). The entire crude residue (9.6 g, 26.8 mmol, 1.0 equiv) in tetrahydrofuran (9 mL) was added dropwise to a solution of lithium aluminum hydride (8.2 g, 215.8 mmol, 8 equiv) in tetrahydrofuran (80 mL) at 0 °C,[19] protected by a calcium chloride guard tube. After 30 min at 0 °C, the reaction was stirred at room temperature for 18 h. The reaction was cooled to 0 °C, and ethyl acetate (60 mL) was added slowly, followed by water (41 mL). The slurry was stirred at room temperature for 30 min and then filtered through a sintered glass funnel, and the filtrate was concentrated under reduced pressure. Chromatography of the crude residue on silica gel (25 g) with 1% methanol in ethyl acetate and then 5% methanol in ethyl acetate gave 2.4 g (56%) of a mixture of 1-methyl-3α-(hydroxymethyl)-4β,6α-dihydroxy-1-cyclohexene and 1-methyl-3α-(hydroxymethyl)-4β,6β-dihydroxy-1-cyclohexene (**30**): IR (neat) 3300, 2920, 1450, 1380, 1300, 1085, 1045, 910 cm^{-1}; ^{1}H NMR (60 MHz, pyridine-d_5) δ 6.53–5.03 (m, 5 H), 4.83–3.77 (m, 4 H), 3.20–1.77 (m, 5 H including br s at 2.10).

7α-Hydroxy-2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin and 7β-Hydroxy-2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin (31). To a mixture of 1-methyl-3α-(hydroxymethyl)-4β,6α-dihydroxy-1-cyclohexene and 1-methyl-3α-(hydroxymethyl)-4β,6β-dihydroxy-1-cyclohexene (**30**, 2.4 g, 15.2 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (30 mL) and 2,2-dimethoxypropane (18 mL, 146.6 mmol, 9.6 equiv) was added *p*-toluenesulfonic acid (57 mg, 0.30 mmol, 0.02 equiv). The reaction mixture was stirred at room temperature for 1 h, diluted with methylene chloride (150 mL), and washed with two 30-mL portions of a saturated aqueous solution of sodium bicarbonate and then one 30-mL portion of brine. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo, first at 15 mm and then at 0.025 mm. The crude residue was subjected to chromatography on silica gel (25 g) with 25% ethyl acetate in hexanes and then 40% ethyl acetate in hexanes to give 2.4 g (80%) of a mixture of 7α-hydroxy-2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin and 7β-hydroxy-2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin (**31**): IR (neat) 3385, 3010, 2965, 2890, 1457, 1398, 1387, 1291, 1264, 1220, 1184, 1092, 1042, 995, 975, 945, 921, 895, 858, 818, 794 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.02 (br s, 1 H), 4.53–3.20 (m, 4 H), 2.60–1.60 (m, 7 H including br s at 1.73), 1.45 (s, 3 H), 1.40 (s, 3 H).

2,2,6-Trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin-7-one (32). A solution of a mixture of 7α-hydroxy-2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin and 7β-hydroxy-2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin (**31**; 1.7 g, 8.6 mmol, 1.0 equiv) and activated manganese dioxide[34] (8.5 g, 9.8 mmol, 11.4 equiv) in methylene chloride (43 mL) was stirred at room temperature for 9 h. The black slurry was filtered through Celite and concentrated in vacuo to give 1.5 g (89%) of 2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin-7-one (**32**): mp 97–99 °C; IR ($CHCl_3$) 3010, 2895, 1670, 1399, 1372, 1294, 1270, 1220, 1190, 1155, 1115, 1067, 982, 922, 895 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.24 (br s, 1 H), 4.24–3.52 (m, 3 H), 3.00–2.24 [m, 3 H including 2.76 (dd, J = 5.1, 16.3 Hz) and 2.39 (dd, J = 12.4, 16.3 Hz)], 1.75 (br s, 3 H), 1.45 (s, 3 H), 1.40 (s, 3 H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.95; H, 8.07. Following careful chromatography, a small amount of the cis-fused enone 2,2,6-trimethyl-4aβ,7,8,8aβ-tetrahydro-4*H*-1,3-benzodioxin-7-one could be isolated and characterized: IR ($CHCl_3$) 3005, 2900, 1670, 1399, 1385, 1295, 1245, 1218, 1180, 1160, 1105, 1041, 1005, 992, 948, 925, 870 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.42 (br s, 1 H), 4.50 (m, 1 H), 4.20 (dd, J =

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3.4, 12.0 Hz, 1 H), 3.83 (dd, J = 1.7, 12.0 Hz, 1 H), 2.74–2.18 (m, 3 H), 1.79 (br s, 3 H), 1.42 (s, 3 H), 1.25 (s, 3 H).

2,2,6,6-Tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one and 2,2,6,6-Tetramethyl-5β-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one. To purified cuprous iodide (1.6 g, 8.4 mmol, 1.1 equiv) in ether (39 mL) at −50 °C under nitrogen was added dropwise vinylmagnesium bromide (12.6 mL of a 1.35 M solution in tetrahydrofuran, 17 mmol, 2.2 equiv).[25,26] The slurry was warmed to −30 °C over 20 min and then stirred at −30 °C for 15 min. The light brown slurry was cooled to −50 °C and 2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin-7-one (**32**; 1.5 g, 7.7 mmol, 1.0 equiv) in ether (20 mL) was added dropwise. The reaction was stirred at −50 °C for 30 min. Then chlorotrimethylsilane (2 mL, 15.8 mmol, 2.0 equiv) was added, followed by hexamethylphosphoric triamide (1.3 mL, 7.5 mmol, 1 equiv).[37] The bath was allowed to warm slowly to room temperature over 12 h. The reaction mixture was diluted with hexanes (120 mL), stirred at room temperature for 10 min, and then filtered through Celite. The filtrate was concentrated in vacuo, the residue was triturated with hexanes, and the supernatant was dried with anhydrous sodium sulfate. Concentration in vacuo gave 2.0 g (88%) of crude 2,2,6-trimethyl-7-[(trimethylsilyl)oxy]-5-vinyl-4aβ,5,8,8aα-tetrahydro-4*H*-1,3-benzodioxin: ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.08–4.75 (m, 3 H), 4.42–3.28 (m, 3 H), 2.82–1.12 (m, 13 H including 2 s at 1.47 and 1.40), 0.18 (s, 9 H). The compound was immediately methylated.

Following the procedure of Kuwajima and Nakamura,[38] a suspension of benzyltrimethylammonium fluoride (1.7 g, 10.2 mmol, 1.5 equiv) and activated 4-Å molecular sieves (8.9 g) in tetrahydrofuran (14 mL) was stirred at room temperature under nitrogen for 18 h. To this was added methyl iodide (4.3 mL, 69 mmol, 10 equiv) followed by 2,2,6-trimethyl-7-[(trimethylsilyl)-oxy]-5-vinyl-4aβ,5,8,8aα-tetrahydro-4*H*-1,3-benzodioxin (2.0 g, 6.8 mmol, 1.0 equiv) in tetrahydrofuran (10 mL). The slurry was stirred at room temperature for 24 h and then filtered through Celite and evaporated in vacuo. The residue was immediately subjected to chromatography on silica gel (40 g) with 5% ethyl acetate in hexanes and 10% ethyl acetate in hexanes to give 1.08 g (59%) of 2,2,6,6-tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one and 2,2,6,6-tetramethyl-5β-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one as a 1:1 mixture of diastereomers, not separable by chromatography: ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.07–4.70 (m, 3 H), 4.33–3.23 (m, 3 H), 3.07–1.57 (m, 4 H), 1.41 (s, 6 H), 1.33 (s) and 1.10 (s) and 0.99 (s) and 0.94 (s, combined 6 H).

5α-Formyl-2,2,6,6-tetramethyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one and 5β-Formyl-2,2,6,6-tetramethyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one. Ozone was passed into a solution of 2,2,6,6-tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one and 2,2,6,6-tetramethyl-5β-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (874 mg, 3.67 mmol, 1.0 equiv) in dry methanol (92 mL) at −78 °C for 25 min. The excess ozone was dispersed by bubbling oxygen through the solution until the blue color had disappeared. Then at −78 °C dimethyl sulfide (5 mL) was added. The reaction was stirred at room temperature for 7 h. The volatile material was removed in vacuo, and the residue was chromatographed on silica gel (45 g) with 15% ethyl acetate in hexanes and then 20% ethyl acetate in hexanes. From this was isolated 73 mg (8%) of recovered 2,2,6,6-tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (**34**) and 260 mg (30%) of 5β-formyl-2,2,6,6-tetramethyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one: IR ($CHCl_3$) 3015, 2965, 2895, 1715, 1480, 1403, 1295, 1223, 1195, 1156, 1117, 1065, 985, 901, 890, 767, 717 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 9.18 (d, J = 3.6 Hz, 1 H), 4.10–3.27 (m, 3 H), 3.03–2.23 (m, 3 H), 2.06 (dd, J = 3.7, 12.0 Hz, 1 H), 1.43 (s, 6 H), 1.24 (s, 3 H), 1.21 (s, 3 H); ^{1}H NMR (60 MHz, benzene-d_6) δ 9.15 (d, J = 3.6 Hz, 1 H), 3.97–2.90 (m, 3 H), 2.67–1.77 (m, 3 H), 1.47 (s) and 1.43 (dd, J = 3.6, 12.0 Hz,* combined 4 H), 1.18 (s, 3 H), 1.04 (s, 3 H), 0.68 (s, 3 H). Also isolated was 270 mg (31%) of 5α-formyl-2,2,6,6-tetramethyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (**24**): mp 112–113.5 °C; IR ($CHCl_3$) 3010, 2960, 2895, 1710, 1470, 1400, 1296, 1270, 1215, 1190, 1150, 1108, 1065, 1032, 981, 895, 850, 792, 732 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 9.88 (d, J = 4 Hz, 1 H), 4.67–3.05 (m, 3 H), 3.00–2.27 (m, 4 H), 1.42 (s, 6 H), 1.37 (s, 3 H), 1.10 (s, 3 H); ^{1}H NMR (60 MHz, benzene-d_6) δ 9.13 (d, J = 4 Hz, 1 H), 4.40–3.20 (m, 3 H), 2.90–2.00 (m, 3 H), 1.88 (t, J = 4 Hz,* 1 H), 1.43 (s, 3 H), 1.17 (s, 3 H), 0.90 (s, 3 H), 0.73 (s, 3 H). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.64; H, 8.48. Irradiating the aldehyde hydrogen atom and observing the starred resonance resulted in a collapse to a doublet with J = 12 Hz for the equatorial isomer and a doublet with J = 4 Hz for the axial isomer.

Axial 1,4-Addition of Vinyl. 2,2,6,6-Tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (34). To dimethyl sulfide–copper bromide complex (2.09 g, 10.2 mmol, 2.0 equiv) in THF (26 mL) at −75 °C under nitrogen was added dropwise over a period of 20 min a solution of vinylmagnesium bromide [16 mL of a 1.25 M solution in THF, 20.4 mmol, 4.0 equiv, that had been diluted with THF (10 mL)].[25,26] The resulting heterogeneous brown-green solution was stirred at −75 °C for 20 min. Then a solution of chlorotrimethylsilane (3.2 mL, 25.5 mmol, 5.0 equiv) and HMPA (1.8 mL, 10.2 mmol, 2.0 equiv) in THF (10 mL) was added over a period of 4 min. This was immediately followed by a solution of 2,2,6-trimethyl-4aβ,7,8,8aα-tetrahydro-4*H*-1,3-benzodioxin-7-one (**32**; 1.0 g, 5.1 mmol, 1.0 equiv) in THF (10 mL). The reaction was stirred at −75 °C, and the bath was allowed to warm slowly to room temperature.[42] After being stirred for 18 h, the reaction mixture was diluted with hexanes (200 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure, the residue was triturated with hexanes, and the supernatant was dried over anhydrous sodium sulfate. Filtration and evaporation of the supernatant under reduced pressure gave 1.41 g (93%) of 2,2,6-trimethyl-7-[(trimethylsilyl)oxy]-5α-vinyl-4aβ,5,8,8aα-tetrahydro-4*H*-1,3-benzodioxin (**33**): ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.80–4.70 (m, 3 H), 4.37–3.47 (m, 3 H), 2.77–1.30 (m, 4 H), 1.50 (br s) and 1.43 (s) and 1.38 (s, combined 9 H), 0.18 (s, 9 H). Following the procedure of Kuwajima and Nakamura,[38] a suspension of benzyltrimethylammonium fluoride (1.17 g, 7.0 mmol, 1.6 equiv) and activated 4-Å molecular sieves (6.7 g) in THF (10 mL) was stirred under nitrogen at room temperature for 4 h. Then methyl iodide (2.7 mL, 42.9 mmol, 10 equiv) was added, followed by 2,2,6-trimethyl-7-[(trimethylsilyl)oxy]-5α-vinyl-4aβ,5,8,8aα-tetrahydro-4*H*-1,3-benzodioxin (**33**; 1.27 g, 4.29 mmol, 1.0 equiv) in THF (10 mL). The reaction mixture was stirred at room temperature for 15 h and then filtered through Celite and concentrated under reduced pressure. Chromatography of the residue on silica gel (40 g) with 2% ethyl acetate in hexanes, 5% ethyl acetate in hexanes, and finally 10% ethyl acetate in hexanes gave 538 mg (53%) of 2,2,6,6-tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (**34**): mp 90–92 °C; IR ($CHCl_3$) 3010, 2950, 2905, 1700, 1398, 1295, 1260, 1218, 1190, 1160, 1150, 1102, 1060, 1030, 960, 890, 875 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.68–4.80 (m, 3 H), 4.24–3.60 (m, 3 H), 2.96–1.96 (m, 4 H), 1.36 (s, 6 H), 1.29 (s, 3 H), 0.90 (s, 3 H). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.30. Found: C, 70.45; H, 9.38.

5α-Formyl-2,2,6,6-tetramethyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (24). A solution of 2,2,6,6-tetramethyl-5α-vinyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (**34**; 113.5 mg, 0.48 mmol) in dry methanol (10 mL) at −75 °C was treated with ozone for 15 min. The blue color was dispersed by a flow of oxygen, and dimethyl sulfide (1.0 mL) was added dropwise at −75 °C. The reaction was then stirred at room temperature for 7 h and then concentrated under reduced pressure. Chromatography on silica gel (15 g) with 15% ethyl acetate in hexanes and then 20% ethyl acetate in hexanes gave 61.6 mg (54%; 69% based on starting olefin not recovered) of pure 5α-formyl-2,2,6,6-tetramethyl-4aβ,5,6,7,8,8aα-hexahydro-4*H*-1,3-benzodioxin-7-one (**24**) whose spectral properties were identical with those of the sample reported above.

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(42) **Note Added in Proof.** In more recent studies, we observed that the length of time at which the final reaction mixture is kept at −78 °C is critical: shorter time leads to an increased equatorial/axial ratio.

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Registry No. 7, 1193-18-6; 8 (R = CH_3OCH_2), 108694-51-5; 9, 101514-23-2; 10, 108694-52-6; 12, 108694-53-7; 13, 108694-54-8; 15, 108694-55-9; 16, 108694-56-0; 17, 108710-75-4; 18, 108694-57-1; 19α, 108694-59-3; 19β, 108694-58-2; 20, 108694-60-6; 22, 72726-55-7; 23, 108694-61-7; 24 (isomer 1), 108741-17-9; 24 (isomer 2), 108694-70-8; 26, 108694-62-8; 28, 16544-46-0; 29 (isomer 1), 108694-63-9; 29 (isomer 2), 108741-18-0; 30 (isomer 1), 108694-64-0; 30 (isomer 2), 108694-69-5; 31 (isomer 1), 108694-65-1; 31 (isomer 2), 108741-16-8; *trans*-32, 108694-66-2; *cis*-32, 108694-71-9; 33, 108694-67-3; 34 (isomer 1), 108694-68-4; 34 (isomer 2), 108741-15-7; Me_3SiCH_2MgCl, 13170-43-9.

Chemical Synthesis of Rat Atrial Natriuretic Factor by Fragment Assembly on a Solid Support

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The chemical synthesis of a 26-residue atrial natriuretic peptide is reported where the assembly was carried out by using a solid-phase fragment based approach. This methodology allowed the production of the quantities necessary for safety assessment and clinical studies. A detailed description of the strategy, synthesis, purification, and associated problems is presented.

Introduction

Recently, a number of related peptides have been isolated from mammalian heart tissue which possess extremely potent vasorelaxant and diuretic properties.[1] These peptides are released from granules in the atrium in response to various stimuli, and they are thought to be a key factor in the control of water–electrolyte balance. Although the individual peptides have been given various names, they are generically known as atrial natriuretic factors(s) (ANF) or atrial natriuretic peptides(s). Despite the problems associated with isolation from tissue containing very small amounts of active material, several groups of investigators were able to characterize several peptides of varying length from rat tissue which all displayed complete sequence homology with a central "core" region, but with varying numbers of residues at the N- and C-termini.[1b-d] Almost all of the isolated peptides are active as natriuretic agents but display varying potencies. Most of these compounds also cause the relaxation of intestinal and vascular smooth muscle. We became interested in synthesizing larger amounts of one of the most potent of these peptides in order to fully determine its biological, chemical, and physical properties, as well as its possible use in a clinical setting. The 26-residue peptide 1 (rat ANF (8–33)) was chosen as our target, because it contained the minimum sequence necessary for full potency in the various tissues mentioned above.

Synthesis

Upon examination of 1 (numbering of the residues is based upon the longest ANF (33 amino acids) isolated at the Clinical Research Institute in 1983),[1b] approaches to its synthesis as well as problems that might be encountered are evident. The well-known synthetic problems[2] associated with arginine (Arg), aspartic acid (Asp), and tyrosine (Tyr) had to be considered for all possible syntheses and will be discussed in detail. The presence of several glycine (Gly) residues spaced throughout the sequence made a fragment condensation strategy worth consideration, since carboxyl activation of C-terminal Gly fragments could not lead to the problems of racemization frequently encountered in fragment couplings.[3] Fragment based syntheses rely on the assembly of several smaller peptides of high purity to provide the target peptide free of impurities that can arise in longer sequences made by the stepwise solid-phase method and that can be very difficult to remove.

Our first successful synthesis made use of minimally protected fragments that were coupled in solution by using the azide method.[4] However, in order to meet the ever increasing demand for material needed for safety evaluation and clinical testing, we required a more efficient route that was capable of yielding gram amounts of the peptide 1 in high purity. We then decided to evaluate an approach that involved the coupling of fully protected fragments onto a solid support to provide the full ANF sequence in the protected resin bound form 2 shown in Scheme I. In theory, this strategy could afford multigram amounts of resin bound peptide, which could then be processed to yield high purity material without extensive purification.

The route illustrated in Scheme I requires substantial amounts of the fragments 3, 4, and 5 in high purity, as well as the C-terminal resin-bound octapeptide 6. It seemed likely that the fragments could be synthesized by the

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