Evaluation of 2-Bromocyclohexenone Acetals as Vehicles for the Introduction of C-7 Oxygen Preliminary to the Synthesis of Taxane Diterpenes

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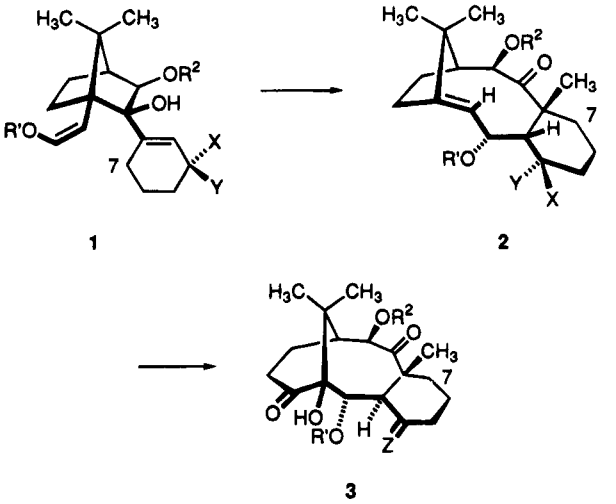
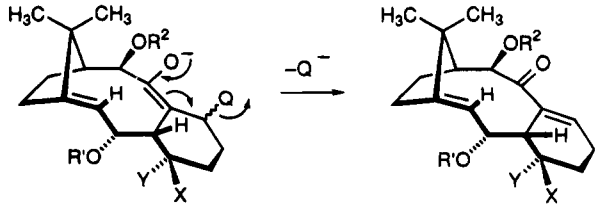
The coupling of an optically pure, camphor-derived, β,γ-unsaturated, bicyclic ketone with a suitable vinyl organometallic is recognized to result in 1,2-addition from the endo face. Anionic oxy-Cope rearrangement of these carbinols proceeds via an "endo-chair" transition state to deliver a strained and reactive enolate that is formed regioselectively and is amenable to α-methylation from the top face. These steps, which are preliminary to a broad-based approach to the taxane diterpenes, had not yet accommodated suitable introduction of a C-7 oxygen substituent as required of taxol. Typically, an ether substituent at this site experiences β-elimination once the enolate anion intermediate is accessed. Herein it is demonstrated that the parent 2-bromocyclohexenone acetal is well suited to resolving this complication. Halogen–metal exchange proceeds well to provide a suitably nucleophilic building block. Direct charge-accelerated sigmatropic rearrangement of the carbinol products does proceed with β-elimination, but under the present circumstances the second C–O bond remains in the form of a vinylogous ester. Alternatively, the carbinols are amenable to chemoselective hydrolysis of the acetal, thereby unmasking a conjugated cyclohexenone part structure. These intermediates have been found to rearrange along completely analogous reaction trajectories to provide enolates of a β-diketone subunit. The extent to which these anions undergo C- versus O-methylation under various conditions has been examined. When O-methylation does occur, it is the C-7 oxygen (and not the one at C-9) that is engaged in reaction.

Our laboratory has been involved in the development of a practical synthetic route to taxol at several levels.[1] One goal has been to produce alcohols such as **1** in a highly convergent coupling reaction,[2] to effect stereochemically well defined anionic oxy-Cope rearrangement of **1** to **2**,[3] and to bring about bridge migration to **3** through application of the α-ketol rearrangement.[4] Although this scheme has proven successful to various degrees and may augur well for accessing the powerfully cytotoxic 7-deoxytaxol,[5] proper incorporation of the C-7 oxygen substituent present in taxol has persisted as an issue requiring suitable resolution.

The complication to be circumvented resides in the fact that implementation of the charge-accelerated [3,3] sigmatropic transposition[6] generates an enolate anion of type **4**. The formation of this reactive intermediate under conditions where charge separation is maximized through the addition of 18-crown-6 is ideally suited to facile alkylative introduction of the angular methyl group from the top face. However, the presence in **4** of a β substituent defined as Q would in the great majority of circumstances result in elimination with formation of **5**. Indeed, ether substituents are rapidly lost under these circum-





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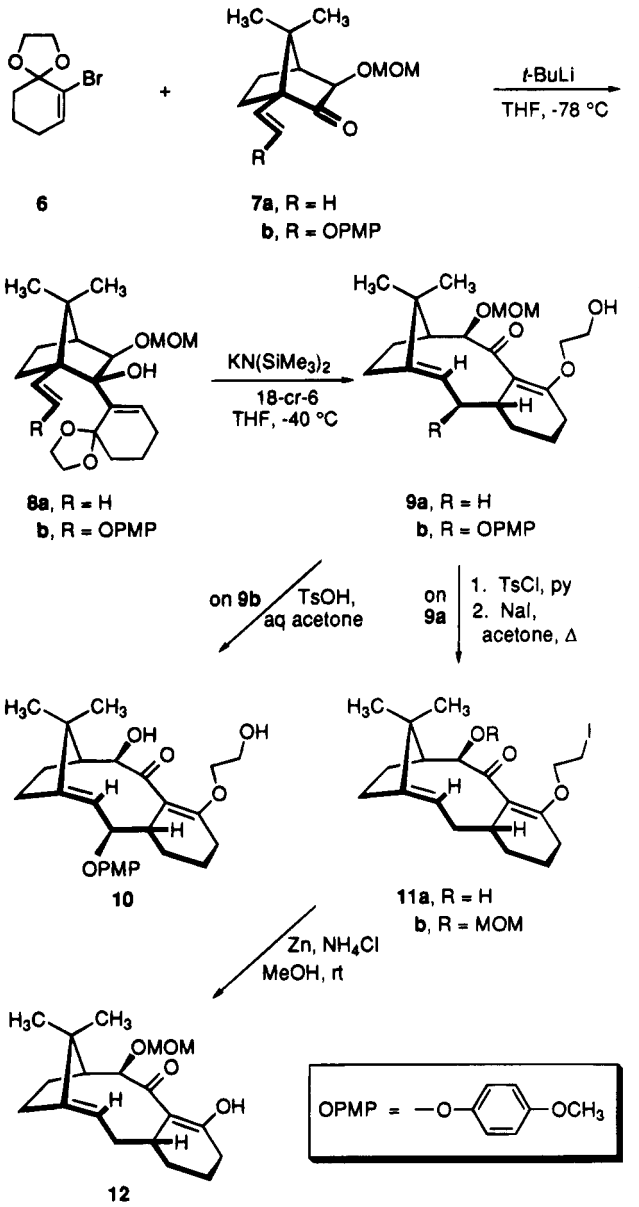
stances.[7] Silyl groups might prove resistant to being ejected in this manner;[8] studies of this type have yet to be undertaken. Instead, the use of 2-halocyclohexenone acetals has been pursued since these building blocks were expected to serve us well in two respects. One possibility is not to control the β-elimination and to allow fragmentation of the acetal to occur. Under these circumstances, the second C–O bond is maintained in proper position for future chemical manipulation. Alternatively, the ketal subunit might be hydrolyzed in advance of anionic oxy-Cope rearrangement. Although precedent for sigmatropic isomerization in compounds containing this array of functional groups was not found, the advantage of this scheme resides in the generation of a stabilized β-diketone enolate, again with preservation of the crucial C-7 oxygen substitution pattern. The outcome of such experiments is detailed in this paper.

Results and Discussion

The mechanistic considerations advanced above contemplate ready access to 2-bromocyclohexenone acetals. Although this class of compounds has been little exploited in synthesis, they are readily prepared from the parent enone[9] and are conveniently susceptible to halogen–metal exchange.[10] In a first series of experiments, bromo acetal **6** was treated sequentially with *tert*-butyllithium (2 equiv) and the β,γ-unsaturated ketone **7a**[2c] in THF solution at −78 °C (Scheme 1). Addition occurred from the endo surface to provide carbinol **8a** (88%), which rearranged rapidly in THF solution containing potassium hexamethyldisilazide and 18-crown-6 at −40 °C. After 1 h, ketone **9a** was isolated in an unoptimized 80% yield. Several spectroscopic features of **9a** serve as markers to indicate that the acetal had experienced ring opening. In addition to an intense infrared hydroxyl absorption centered at 3467 cm^{-1}, the ^{13}C NMR spectrum displayed four sp^2-hybridized olefinic carbons beyond that associated with the carbonyl group. We have previously recognized that introduction of a double bond into this sector of the C ring causes the structure to become conformationally quite inflexible.[2b] Moreover, the carbonyl π-bond is projected downward in a fashion that disrupts effective conjugation with the adjacent double bond. This state of affairs is not expected to be appreciably altered in **9a**. Indeed, although **9a** is a vinylogous ester, its carbonyl absorption (1656 cm^{-1}) differs little from that of simpler enone congeners (1650 cm^{-1}).

When the reaction of the more highly substituted ketone **7b**[2c] with the lithiated acetal was performed under comparable conditions, **8b** was obtained after quenching. Brief treatment of this carbinol with potassium hexamethyldisilazide and 18-crown-6 effected its smooth, stereocontrolled conversion to **9b** (69%) as a consequence of continued adherence to an "endo-chair" transition state topography.[3a] The strategic implications are that an *E* enol ether gives rise ultimately to a β-oriented C-2 substituent, while the proper taxol α-configuration mandates use of a *Z* enol ether.[3b] Particularly helpful in assigning C-2 stereochemistry to **9b** was the considerable similarity of its 300 MHz ^1H NMR spectrum to those of analogous compounds for which X-ray crystallographic determinations are available.

Scheme 1



Some measure of the relative hydrolytic stability of the several oxygenated substituents in **9b** was gained by stirring the compound in acetone solution containing a catalytic quantity of *p*-toluenesulfonic acid at rt for 16 h. These mild conditions resulted in removal of the MOM group exclusively with formation of **10**. A companion observation was made when the tosylate of **9a** was heated with a large excess of sodium iodide in acetone. Workup of this reaction gave rise to **11a** indicating that removal of the MOM protecting group occurs more rapidly than degradation of the 2-iodoethoxy side chain.[11]

Briefer treatment of the tosylate with a lesser amount of NaI made possible the acquisition of **11b**. This success

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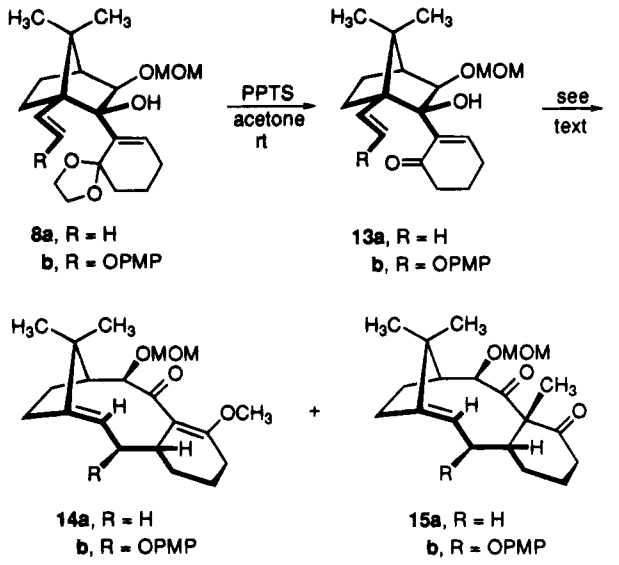
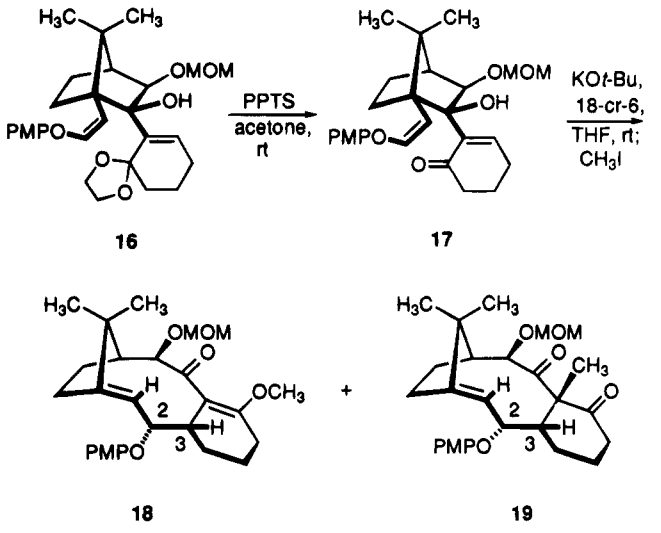
Scheme 2



Scheme 3



was believed to represent a target of opportunity for unmasking the C-7 carbonyl group. Indeed, the reduction of **11b** with zinc and ammonium chloride in methanol[12] led reliably to a single product whose assignment as **12** is supported by its high-field ^{1}H NMR spectrum. However, this substance proved unpredictably to be prone to decomposition when stored neat or in $CDCl_3$ or C_6D_6 solution. When several alternative attempts to rectify this matter went unrewarded, our attention turned to establishing the feasibility of performing the acetal hydrolysis in advance of the oxy-Cope rearrangement.

When either **8a** or **8b** was subjected to the action of pyridinium *p*-toluenesulfonate in wet acetone solution at rt, the acetal group was cleaved chemoselectively in quantitative yield (Scheme 2). These conditions are obviously of insufficient harshness to effect concomitant hydrolysis of the vinyl ether in **8b**. Upon exposure of **13a** to potassium *tert*-butoxide and 18-crown-6 in DMSO at rt for 40 min with subsequent introduction of excess methyl iodide, a 1:3.5 mixture of **14a** and **15a** was formed in 83% yield. Use of dimethyl sulfate as the electrophile resulted expectedly[13] in sole formation of **14a**.

It is important to recognize the role of solvent effects in these rearrangements. When **13b** was similarly treated with potassium *tert*-butoxide and 18-crown-6 in DMSO, only efficient cleavage to norbornanone **7b** was observed.[14] A commensurate change to anhydrous THF, but with preservation of the proportions of potassium *tert*-butoxide and 18-crown-6, led at rt to **14b** (26%) and to the norbornanone **7b** in 44% yield. When 18-crown-6 was omitted, only rather efficient fragmentation to **7b** (67%) was observed.

Notwithstanding, we see that the anionic oxy-Cope rearrangement of hydroxy enones such as **13** represents a seemingly reliable means for the construction of intermediates potentially suited to the elaboration of taxanes. Since this sigmatropic process follows a geometrically well defined three-dimensional arrangement and is not disrupted by the presence of a ketone carbonyl group, an enolate anion is generated regioselectively and provides for face-selective methylation at C-8. It now becomes possible to introduce a C-7 oxygen substituent into frameworks typified by **15** as desired.

In order to expand on the breadth of this strategy, the *Z* isomer of **7b**[2c] was converted to **19** (Scheme 3). Despite the change in configuration about the vinyl ether double bond, no complications were encountered in producing **17** (96%). Beyond this point, the isomerization of this intermediate was performed at rt in THF solution containing potassium *tert*-butoxide and 18-crown-6. These conditions were conducive to the formation of a somewhat greater amount of **18** relative to **19** (ratio 1.6:1, 54%) alongside 27% of norbornanone **iii** as a consequence of competing retro-aldol cleavage.[14]

The spectroscopic features of these tricyclic products are quite distinctive and revealing of overall stereochemical detail. Most diagnostic are the coupling constants between H-2 and H-3 (J = 4.65 and 4.5 Hz, respectively), which correspond to an axial−equatorial interrelationship between these vicinal protons. When these two protons are positoned trans and diaxial to each other as they are in **14b** and **15b**, the level of spin-spin coupling is significantly larger (9.0 Hz). Thus, **17** also undergoes oxy-Cope rearrangement via an endo-chair transition state.

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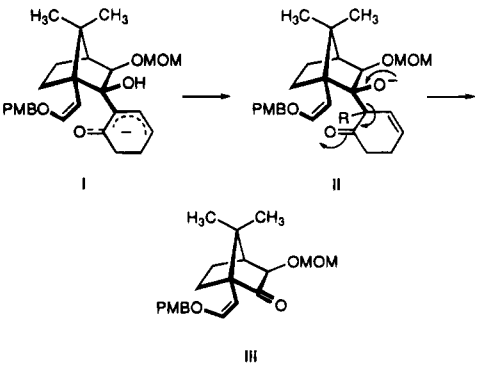
(13) Paquette, L. A.; Broadhurst, M. J. *J. Org. Chem.* **1973**, *38*, 1886.

(14) One possible mechanistic scenario involves the conversion of **17** to a β,γ-unsaturated ketone such as **ii**. Although proton transfer is required to reach **ii** (R = H), it is equally possible that enolate anion **i** persists until the methyl iodide is introduced, at which point **ii** (R = CH_3) would result. The cleavage of **ii** under strongly basic conditions can be expected to occur rapidly.



The results described above point to the common adoption of a [3,3] sigmatropic pathway that enables the complete control of C-2 stereochemistry. When acetals are involved, β-elimination operates readily to deliver 7-oxygenated products such as **9**–**11**. Chemoselective hydrolysis of the acetal in advance of the oxy-Cope rearrangement makes possible the direct conversion to tricyclic β-dicarbonyl anions which undergo C- or O-methylation depending upon reaction conditions. The regioselectivity of O-methylation is such that only the C-7 oxygen and not the C-9 oxygen acts as the nucleophilic center. This phenomenon, which is very likely linked to the level of steric strain that necessarily develops in the competing transition states is particularly well suited to the established goals.

Further application of the key elements of the protocol developed herein, together with allied aspects of this construction scheme, are planned and will be reported when achieved.

Experimental Section[15]

(1*S*,2*R*,3*R*,4*S*)-2-(1,4-Dioxaspiro[4.5]dec-6-en-6-yl)-3-(methoxymethoxy)-7,7-dimethyl-1-vinyl-2-norbornanol (8a). A solution of **6** (78 mg, 0.35 mmol) in cold (-78 °C) THF (2 mL) was treated with 2 equiv of *tert*-butyllithium under N_2 and stirred for 30 min. A solution of **7a** (88 mg, 0.40 mmol) in THF (1 mL) was introduced via syringe as rapidly as possible and stirring at this temperature was maintained for 3 h, at which point saturated NH_4Cl solution was added as quench. The product was extracted into ethyl acetate, the combined organic layers were dried and concentrated, and the residue was purified by chromatography on silica gel (elution with 6% ethyl acetate and 1% triethylamine in hexanes) to give 112 mg (88%) of **8a** as a colorless oil: IR (neat, cm^{-1}) 3518, 1626, 1477, 1374, 1277, 1113, 1067, 1041, 944, 908; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, J = 3.8 Hz, 1 H), 6.38–6.31 (m, 1 H), 5.22 (q, J = 2.1, 11.1 Hz, 1 H), 4.97 (q, J = 2.1, 17.9 Hz, 1 H), 4.74 (d, J = 1.4 Hz, 2 H), 4.17 (s, 1 H), 4.09–3.96 (m, 4 H), 3.95 (s, 1 H), 3.41 (s, 3 H), 2.15–2.08 (m, 2 H), 1.94 (d, J = 4.7 Hz, 1 H), 1.82–1.60 (m, 5 H),1.58 (s, 1 H), 1.45 (m, 1 H), 1.28 (s, 3 H), 1.13 (m, 1 H), 0.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.0, 137.6, 135.7, 114.3, 108.7, 97.1, 85.3, 84.8, 62.7 (2 C), 60.2, 55.8, 50.6, 50.1, 32.7, 25.7, 25.2, 23.7, 22.7, 22.5, 19.4; MS m/z (M^+) calcd 364.2250, obsd 364.2256; $[\alpha]^{22}_D$ +53.5° (c 1.85, $CHCl_3$). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.86; H, 8.85.

(1*S*,2*R*,3*R*,4*S*)-2-(1,4-Dioxaspiro[4.5]dec-6-en-6-yl)-3-(methoxymethoxy)-1-[(*E*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanol (8b). *tert*-Butyllithium (2.26 mL of 1.7 M in pentane, 3.84 mmol) was added dropwise to a solution of **6** (800 mg, 3.65 mmol) in THF (10 mL) at −78 °C. The reaction mixture was stirred for 30 min, treated with a solution of **7b** (634 mg, 1.83 mmol) in THF (4 mL), and continuously stirred at −78 °C for 1 h prior to being quenched with saturated NH_4Cl solution and warmed to rt. The product was extracted into CH_2Cl_2, the combined organic layers were dried and concentrated, and the residue was chromatographed on silica gel (elution with 20–25% ethyl acetate in hexanes). There was isolated 567 mg (64%) of **8b** as a colorless oil: IR (neat, cm^{-1}) 3401, 1627, 1269, 1110, 1038; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 9.2 Hz, 2 H), 6.84 (d, J = 9.2 Hz, 2 H), 6.50 (t, J = 4.0 Hz, 1 H), 6.26 (d, J = 12.6 Hz, 1 H), 5.78 (d, J = 12.6 Hz, 1 H), 4.75 (d, J = 6.5 Hz, 1 H), 4.70 (d, J = 6.5 Hz, 1 H), 4.21 (s, 1 H), 4.02 (m, 4 H), 3.77 (s, 3 H), 3.41 (s, 3 H), 2.46 (m, 1 H), 2.18 (m, 1 H), 1.95 (m, 1 H), 1.70 (m, 7 H), 1.30 (s, 3 H), 1.20 (m, 1 H), 0.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 155.0, 151.8, 143.5, 138.2, 136.1, 117.5, 114.7, 111.7, 108.7, 97.8, 96.8, 84.8, 84.3, 62.9, 62.6, 57.6, 55.7, 50.7, 49.8, 32.8, 25.9, 23.9, 23.0, 22.7, 22.4, 19.5; MS m/z (M^+) calcd 486.2589, obsd 486.2612; $[\alpha]^{20}_D$ +40.7° (c 1.50, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 69.48; H, 7.84.

(6*R*,7*S*,10*E*,12a*R*)-2,3,6,7,8,9,12,12a-Octahydro-4-(2-hydroxyethoxy)-6-(methoxymethoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (9a). To a solution of **8a** (53 mg, 0.146 mmol) and 18-crown-6 (46 mg, 0.175 mmol) in THF (2 mL) was added 1.2 equiv of potassium hexamethyldisilazide at −50 °C under N_2. The reaction mixture was stirred at −40 °C for 1 h, quenched with saturated NH_4Cl solution. The product was extracted into ether, the combined organic layers were dried and concentrated, and the residue was chromatographed on silica gel (elution with 10–15% ethyl acetate in hexane) to give **9a** as a colorless crystalline solid: mp 107–108.5 °C (42 mg, 80%); IR (film, cm^{-1}) 3478, 1656, 1627, 1461, 1363, 1231, 1144, 1100, 1036; ^1H NMR (300 MHz, C_6D_6) δ 5.45 (d, J = 2.6 Hz, 1 H), 5.29 (m, 1 H), 4.70 (d, J = 7.2 Hz, 1 H), 4.44 (d, J = 7.2 Hz, 1 H), 4.04 (t, J = 7.1 Hz, 1 H), 3.56–3.46 (m, 3 H), 3.33 (t, J = 4.1 Hz, 2 H), 3.13 (s, 3 H), 2.50–2.90 (series of m, 6 H), 1.85–1.60 (m, 3 H), 1.57 (s, 3 H), 1.50–1.25 (m, 4 H), 1.07 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 203.0, 156.8, 146.5, 122.5, 119.6, 94.9, 85.7, 69.3, 61.3, 55.4, 55.2, 45.7, 37.1, 33.6, 27.7, 26.8, 25.9, 24.9, 24.2, 21.2, 18.7; MS m/z (M^+) calcd 364.2250, obsd 364.2246; $[\alpha]^{22}_D$ −301° (c 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.24; H, 8.85.

(6*R*,7*S*,10*E*,12*S*,12a*S*)-2,3,6,7,8,9,12,12a-Octahydro-4-(2-hydroxyethoxy)-6-(methoxymethoxy)-12-(*p*-methoxyphenoxy)-13,13-dimethyl-7,10-methanobenzo-cyclodecen-5(1*H*)-one (9b). A solution of **8b** (36 mg, 0.075 mmol) and dry 18-crown-6 (40 mg, 0.150 mmol) in THF (5 mL) was cooled to −50 °C, treated dropwise with potassium hexamethyldisilazide (300 μL of 0.5 M in toluene, 0.150 mmol), stirred at −50 °C for 30 min, quenched with saturated NH_4Cl solution, and worked up in the predescribed manner. Purification by silica gel chromatography (elution with 3:1 then 1:1 hexanes/ethyl acetate) gave **9b** as a colorless oil (25 mg, 69%): IR (neat, cm^{-1}) 3451, 1658, 1626, 1505, 1228, 1147; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (m, 4 H), 5.35 (d, J = 2.5 Hz, 1 H), 5.00 (d, J = 8.7 Hz, 1 H), 4.64 (m, 3 H), 4.12 (br s, 1H), 3.91 (m, 2 H), 3.78 (m, 5 H), 3.51 (m, 1 H), 3.42 (s, 3 H), 2.44 (m, 2 H), 2.19 (m, 5 H), 1.77 (m, 3 H), 1.50 (m, 1 H), 1.19 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.0, 157.5, 153.7, 153.2, 147.0, 124.4, 118.7, 116.3, 114.6, 95.5, 86.4, 78.3, 64.3, 62.9, 55.7, 55.4, 54.6, 45.6, 42.3, 26.3, 25.9, 24.7, 23.7, 23.2, 20.9, 18.4; MS m/z (M^+) calcd 486.2589, obsd 486.2608; $[\alpha]^{20}_D$ −164° (c 1.81, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 69.18; H, 7.88.

(6*R*,7*S*,10*E*,12*S*,12a*S*)-2,3,6,7,8,9,12,12a-Octahydro-6-hydroxy-4-(2-hydroxyethoxy)-12-(*p*-methoxyphenoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (10). A solution of **9b** (20 mg, 0.041 mmol) in acetone (1 mL) and water (100 μL) was treated with *p*-toluenesulfonic acid (1 mg), stirred at rt for 16 h, and refluxed for 6 h. The cooled reaction mixture was freed of solvent in vacuo to leave a residue which was purified by chromatography on silica gel (elution with 1:2 hexanes/ethyl acetate) to give **10** (14 mg, 77%) as a colorless oil: IR (neat, cm^{-1}) 3385, 1626, 1506, 1228, 1158; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 4 H), 4.98 (m, 2 H), 4.66 (t, J = 9.2 Hz, 1 H), 3.99 (m, 1 H), 3.90 (m, 1 H), 3.78 (s, 2 H), 3.75 (s, 3 H), 3.50 (m, 1 H), 2.90 (br s, 2 H), 2.44 (m, 4 H), 2.41 (m, 3 H), 1.78 (m, 3 H), 1.50 (m, 1 H), 1.08 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.6, 157.6, 153.7, 153.2, 147.0, 124.3, 118.6, 116.2, 114.6, 86.3, 78.1, 64.3, 62.8, 55.8, 55.5, 45.6, 42.3, 26.1, 25.9, 24.6, 23.8, 23.2, 21.0, 18.2; MS m/z (M^+) calcd 442.2355, obsd 442.2361; $[\alpha]^{20}_D$ −78.2° (c 0.80, $CHCl_3$).

(6*R*,7*S*,10*E*,12a*R*)-2,3,6,7,8,9,12,12a-Octahydro-6-hydroxy-4-(2-iodoethoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (11a). *p*-Toluenesulfonyl chloride (190 mg, 1.0 mmol) was added to a magnetically stirred solution of **9a** (63 mg, 0.172 mmol) in pyridine (3 mL) at 0 °C. The reaction mixture was allowed to warm to rt, stirred overnight, poured into ice–water, and extracted with ether. The combined organic extracts were washed with saturated $CuSO_4$ solution and concentrated. The crude product was purified by chromatography on silica gel (elution with 25%

(15) For general details, consult ref 2c.

ethyl acetate in hexanes) to furnish 85 mg (95%) of the tosylate as a colorless syrup: IR (neat, cm^{-1}) 1660, 1634, 1459, 1362, 1177, 1146, 1100, 1043, 919; ^1H NMR (300 MHz, C_6D_6) δ 7.77 (d, J = 8.2 Hz, 2 H), 6.75 (d, J = 8.5 Hz, 2 H), 5.30–5.24 (m, 1 H), 5.13 (d, J = 2.8 Hz, 1 H), 4.60 (d, J = 6.9 Hz, 1 H), 4.56 (d, J = 6.8 Hz, 1 H), 4.18–3.90 (series of m, 2 H), 3.51–3.40 (m, 1 H), 3.20 (s, 3 H), 3.20–3.10 (m, 1 H), 2.40–1.95 (series of m, 6 H), 1.85 (s, 3 H), 1.84–1.65 (m, 2 H), 1.56 (s, 3 H), 1.55–1.20 (m, 6 H), 1.06 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.4, 155.5, 146.8, 144.4, 134.2, 129.9, 128.1, 122.7, 122.2, 95.6, 86.5, 68.2, 65.2, 55.4, 55.3, 45.7, 37.1, 33.3, 27.6, 26.8, 25.9, 24.2 (2 C), 21.3, 21.1, 18.5; MS m/z (M^+) calcd 518.2338, obsd 518.2318; $[\alpha]^{20}_D$ −214° (c 1.4, $CHCl_3$).

A 40 mg (0.077 mmol) sample of the above tosylate dissolved in acetone (5 mL) was treated with sodium iodide (500 mg, 3.3 mmol), refluxed for 3.5 h, cooled to rt, poured into sodium thiosulfate solution, and extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) gave **11a** as a colorless solid: mp 152–154 °C (28 mg, 85%); IR (film, cm^{-1}) 3455, 1628, 1458, 1362, 1233, 1144, 1062; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10–5.00 (m, 1 H), 4.94 (J = 3.5 Hz, 1 H), 4.15–3.44 (series of m, 2 H), 3.35–3.15 (m, 4 H), 2.40–2.15 (series of m, 5 H), 2.10–1.45 (series of m, 2 H), 1.92–1.72 (m, 4 H), 1.65–1.55 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.6, 156.2, 147.5, 121.0, 120.1, 82.6, 67.9, 55.6, 45.2, 37.7, 32.9, 27.3, 26.5, 26.3, 23.9, 22.1, 20.8, 18.1, 1.0; MS m/z (M^+) calcd 430.1005, obsd 430.1007; $[\alpha]^{20}_D$ −312° (c 4.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{27}IO_3$: C, 53.03; H, 6.32. Found: C, 52.52; H, 6.28.

(6*R*,7*S*,10*E*,12a*R*)-2,3,6,7,8,9,12,12a-Octahydro-4-(2-iodoethoxy)-6-(methoxymethoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (11b). Heating the above tosylate (40 mg, 0.077 mmol) dissolved in acetone (10 mL) containing sodium iodide (150 mg, 1 mmol) at reflux for 2.5 h and workup as described above (silica gel chromatography, elution with 10% ethyl acetate in hexanes) afforded 37 mg (82%) of **11b** as a colorless syrup: IR (neat, cm^{-1}) 1655, 1631, 1459, 1364, 1228, 1144, 1102, 1039, 917, 893, 866; ^1H NMR (300 MHz, C_6D_6) δ 5.35–5.25 (m, 1 H), 5.25 (d, J = 2.8 Hz, 1 H), 4.72 (d, J = 6.9 Hz, 1 H), 4.62 (d, J = 6.9 Hz, 1 H), 3.55–3.38 (m, 2 H), 3.24 (s, 3 H), 3.23–3.03 (m, 3 H), 2.90–2.80 (m, 1 H), 2.50–1.90 (series of m, 7 H), 1.80–1.70 (m, 1 H), 1.59 (s, 3 H), 1.55–1.25 (m, 4 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.3, 155.1, 146.9, 122.6, 122.1, 95.5, 86.3, 68.1, 55.5, 55.4, 54.8, 37.0, 33.5, 27.7, 26.9, 26.0, 24.3, 24.2, 21.4, 18.5, 1.8; MS m/z (M^+) calcd 474.1267, obsd 474.1267; $[\alpha]^{20}_D$ −333° (c 0.6, $CHCl_3$).

(6*R*,7*S*,10*E*,12a*R*)-2,3,6,7,8,9,12,12a-Octahydro-4-hydroxy-6-(methoxymethoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (12). A 500 mg sample of zinc powder was activated by means of $Cu(OAc)_2$.[12a] To this mixture of zinc and methanol (4 mL) was added at 5 °C a solution of **11a** (22 mg, 0.05 mmol) followed by solid NH_4Cl (20 mg). After being stirred at rt for 2 h, the heterogeneous mixture was freed of methanol on a rotary evaporator, diluted with 20% ethyl acetate in hexanes, filtered, and concentrated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded **12** as a colorless oil which decomposed rapidly when dissolved in $CDCl_3$ or C_6D_6: ^1H NMR (200 MHz, $CDCl_3$) δ 5.27 (d, J = 2.8 Hz, 1 H), 5.17–5.05 (m, 1 H), 4.88 (d, J = 6.5 Hz, 1 H), 4.22 (d, J = 6.5 Hz, 1 H), 3.48 (s, 3 H), 3.35–3.20 (m, 1 H), 2.40–2.05 (m, 5 H), 2.00–1.70 (m, 4 H), 1.67–1.55 (m, 3 H), 1.34–1.15 (m, 2 H), 1.22 (s, 3 H), 1.05 (s, 3 H).

2-[(1*S*,2*R*,3*R*,4*S*)-2-Hydroxy-3-(methoxymethoxy)-7,7-dimethyl-1-vinyl-2-norbornyl]-2-cyclohexen-1-one (13a). A solution of **8a** (100 mg, 0.275 mmol) in acetone was treated with pyridinium p-toluenesulfonate (2 mg), allowed to stir at rt for 1.5 h, and poured into saturated $NaHCO_3$ solution. The product was extracted into ether, dried, concentrated, and chromatographed on silica gel (elution with 1:10 ether–hexanes). There was obtained 88 mg (100%) of **13a** as a colorless oil: IR (neat, cm^{-1}) 3501, 1668, 1145, 1109, 1074, 1038, 947, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 4.3 Hz, 1 H), 6.25 (dd, J = 11.0, 17.9 Hz, 1 H), 5.20 (dd, J = 2.0, 11.1 Hz, 1 H), 4.94 (dd, J = 2.1, 17.8 Hz, 1 H), 4.78 (d, J = 6.6 Hz, 1 H), 4.73 (d, J = 6.6 Hz, 1 H), 4.36 (br s, 1 H), 4.15 (s, 1 H), 3.37 (s, 3 H), 2.40–2.25 (m, 4 H), 2.00–1.80 (m, 3 H), 1.80–1.60 (m, 2 H), 1.28 (s, 3 H), 1.25–1.15 (m, 2 H), 0.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.8, 148.6, 141.1, 136.9, 115.6, 97.9, 86.0, 83.3, 59.3, 55.6, 51.0, 50.7, 39.9, 26.1, 25.3, 23.6, 22.4 (2 C), 22.2; MS m/z (M^+) calcd 320.1988, obsd 320.1995; $[\alpha]^{22}_D$ +78.2° (c 1.47, $CHCl_3$).

2-[(1*S*,2*R*,3*R*,4*S*)-2-Hydroxy-3-(methoxymethoxy)-1-[(*E*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornyl]-2-cyclohexen-1-one (13b). Pyridinium p-toluenesulfonate (37 mg, 164 mmol) was added to a magnetically stirred solution of **8b** (356 mg, 0.731 mmol) in wet acetone (7 mL) at rt. After 30 min, the reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated to leave a residue, which was purified by flash chromatography on silica gel (elution with 25–30% ethyl acetate in hexanes) to provide 307 mg (95%) of **13b** as a colorless oil: IR (neat, cm^{-1}) 3498, 1666, 1504, 1224, 1147, 1116, 1069, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J = 4.3 Hz, 1 H), 6.87 (m, 4 H), 6.23 (d, J = 12.6 Hz, 1 H), 5.67 (d, J = 12.6 Hz, 1 H), 4.77 (d, J = 6.5 Hz, 1 H), 4.72 (d, J = 6.5 Hz, 1 H), 4.41 (s, 1 H), 4.34 (s, 1 H), 3.77 (s, 3 H), 3.38 (s, 3 H), 2.49–2.41 (m, 4 H), 1.98–1.93 (m, 3 H), 1.76–1.56 (m, 2 H), 1.32 (s, 3 H), 1.27–1.15 (m, 2 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.9, 155.2, 151.9, 149.3, 144.4, 140.9, 117.7, 114.7, 110.3, 97.8, 85.1, 83.6, 56.8, 55.7, 55.6, 50.9, 50.3, 40.1, 26.6, 26.4, 23.9, 22.7, 22.5, 22.2; MS m/z (M^+) calcd 442.2355, obsd 442.2352; $[\alpha]^{25}_D$ +87.3° (c 1, $CHCl_3$). Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.19; H, 7.81.

Oxy-Cope Rearrangement of 13a. A. Methyl Iodide as Electrophile. To a solution of potassium *tert*-butoxide (7.7 mg, 0.049 mmol) in anhydrous DMSO (1 mL) was added **13a** (15.6 mg, 0.049 mmol) dissolved in the same solvent (1 mL). The reaction mixture was stirred at rt under N_2 for 40 min, treated with methyl iodide (40 μL), and 1.5 h later poured into saturated $NaHCO_3$ solution. The product was extracted into ether (5×), and the combined organic phases were dried and evaporated. Removal of solvent and chromatography of the residue on silica gel (elution with 8% ethyl acetate in hexanes) afforded 3.1 mg (18%) of **14a** and 11 mg (65%) of **15a**, both as colorless solids.

For **14a**: mp 121–122.5 °C; IR (film, cm^{-1}) 1653, 1624, 1466, 1368, 1243, 1193, 1142, 1099, 1038, 919; ^1H NMR (300 MHz, C_6D_6) δ 5.40–5.25 (m, 1 H), 5.26 (d, J = 2.8 Hz, 1 H), 4.74 (d, J = 6.8 Hz, 1 H), 4.69 (d, J = 6.8 Hz, 1 H), 3.60–3.45 (m, 1 H), 3.27 (s, 3 H), 2.99 (s, 3 H), 2.50–1.90 (m, 6 H), 1.90–1.50 (m, 5 H), 1.60 (s, 3 H), 1.45–1.15 (m, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.3, 156.8, 146.4, 121.9, 121.6, 95.7, 86.6, 55.1 (2 C), 54.3, 45.5, 36.7, 33.2, 27.5, 26.7, 25.1, 24.0, 23.9, 21.1, 18.3; MS m/z (M^+) calcd 434.2144, obsd 434.2142; $[\alpha]^{22}_D$ −281° (c 1.8, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.13; H, 9.27.

For **15a**: mp 66–67 °C; IR (neat, cm^{-1}) 1701, 1450, 1145, 1102, 1045, 1004; ^1H NMR (300 MHz, C_6D_6) δ 5.60 (d, J = 1.7 Hz, 1 H), 5.00 (dd, J = 4.7, 11.7 Hz, 1 H), 4.54 (d, J = 6.9 Hz, 1 H), 4.47 (d, J = 6.9 Hz, 1 H), 3.16 (s, 3 H), 2.72 (br s, 1 H), 2.40–1.80 (series of m, 10 H), 1.80–1.70 (m, 1 H), 1.66 (s, 3 H), 1.62–1.40 (m, 2 H), 1.10 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.9, 209.2, 146.1, 125.1, 95.9, 86.1, 62.4, 57.1, 55.4, 46.7, 46.6, 36.9, 32.0, 29.1, 26.5, 24.5, 24.1, 23.5, 20.4, 18.9; MS m/z (M^+) calcd 434.2144, obsd 434.2145; $[\alpha]^{22}_D$ −155° (c 1.2, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.60; H, 9.18.

B. Dimethyl Sulfate as Electrophile. A solution of potassium *tert*-butoxide (32 mg, 0.285 mmol) and **13a** (78 mg, 0.244 mmol) in anhydrous DMSO (2.5 mL) was stirred under N_2 at rt for 40 min and then treated with dimethyl sulfate (28 μL, 0.29 mmol). The reaction mixture was stirred for an additional 1 h, treated with 2 N NaOH solution, and extracted with ether (5x). Workup in the predescribed manner gave 57 mg (70%) of **14a**.

Oxy-Cope Rearrangement of 13b. Potassium *tert*-butoxide (92 mg, 0.82 mmol) was introduced portionwise into a

magnetically stirred solution of **13b** (91 mg, 0.205 mmol) and 18-crown-6 (216 mg, 0.818 mmol) in anhydrous THF (4 mL) at rt under N_2. After 30 min, methyl iodide (300 μL) was added followed 30 min later with saturated NH_4Cl solution. The reaction mixture was extracted with CH_2Cl_2, the combined extracts were dried and concentrated, and the residue was purified by flash chromatography (silca gel, elution with 20–30% ethyl acetate in hexanes) to afford 31 mg (44%) of **7b** and 24 mg (26%) of **14b**.

For **14b**: colorless oil; IR (neat, cm^{-1}) 1660, 1629, 1505, 1465, 1226, 1190, 1146, 1104, 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81–6.75 (m, 4 H), 5.08 (d, J = 2.4 Hz, 1 H), 4.98 (d, J = 9.0 Hz, 1 H), 4.67 (d, J = 6.6 Hz, 1 H), 4.64 (t, J = 9.0 Hz, 1 H), 4.49 (d, J = 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.61 (s, 3 H), 3.53–3.50 (m, 1 H), 3.37 (s, 3 H), 2.51–2.12 (m, 7 H), 1.87–1.64 (m, 3 H), 1.55–1.46 (m, 1 H), 1.16 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.1, 159.2, 153.9, 153.2, 147.0, 124.4, 118.6, 116.3, 114.5, 95.6, 85.8, 78.4, 55.7, 55.5, 54.8, 54.5, 45.5, 42.3, 26.4, 25.4, 24.7, 23.8, 23.3, 20.7, 18.3; MS m/z (M^+) calcd 456.2512, obsd 456.2492; $[\alpha]^{25}_D$ −67.9° (c 2.11, $CHCl_3$). Anal. Calcd for $C_{27}H_{36}O_6$: C, 71.03; H, 7.95. Found: C, 70.68; H, 8.11.

(1*S*,2*R*,3*R*,4*S*)-2-(1,4-Dioxaspiro[4.5]dec-6-en-6-yl)-3-(methoxymethoxy)-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanol (16). *tert*-Butyllithium (400 μL of 1.7 M in pentane, 0.679 mmol) was added dropwise to a magnetically stirred solution of **6** (141 mg, 0.647 mmol) in THF (3 mL) at −78 °C under N_2. After 15 min, (1*S*,3*R*,4*S*)-3-(methoxymethoxy)-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanone[3c] (112 mg, 0.323 mmol) dissolved in THF (2 mL) was introduced via cannula. The reaction mixture was stirred at −78 °C for 1 h, quenched with saturated NH_4Cl solution (10 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated to leave a residue which was chromatographed on silica gel (elution with 25–30% ethyl acetate in hexanes). There was isolated 82 mg (72% based on recovered starting material) of **16** as a colorless oil and 20% of unreacted ketone.

For **16**: IR (neat, cm^{-1}) 3519, 1663, 1505, 1219, 1118, 1069, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91–6.79 (m, 4 H), 6.60 (t, J = 4.0 Hz, 1 H), 6.38 (d, J = 7.1 Hz, 1 H), 5.09 (d, J = 7.1 Hz, 1 H), 4.13–4.09 (m, 2 H), 4.07–4.05 (m, 1 H), 4.04–3.91 (m, 4 H), 3.88–3.85 (m, 1 H), 3.75 (s, 3 H), 3.41 (s, 3 H), 2.41–2.30 (m, 2 H), 2.10–2.06 (m, 2 H), 1.93–1.79 (m, 3 H), 1.70–1.57 (m, 3 H), 1.14–1.05 (m, 1 H), 1.33 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 154.9, 151.6, 141.5, 137.7, 135.4, 117.1, 114.6, 109.7, 108.8, 97.3, 86.0, 85.0, 62.7, 62.6, 58.4, 55.7, 55.6, 51.4, 48.9, 32.6, 27.2, 25.8, 24.2, 23.4, 22.5, 19.3; MS m/z (M^+) calcd 486.2618, obsd 486.2641; $[\alpha]^{25}_D$ +28.6° (c 1.05, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 69.17; H, 7.93.

2-[(1*S*,2*R*,3*R*,4*S*)-2-Hydroxy-3-(methoxymethoxy)-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornyl]-2-cyclohexen-1-one (17). Pyridinium *p*-toluenesulfonate (10 mg) was added to a magnetically stirred solution of **16** (113 mg, 0.232 mmol) in wet acetone at rt. After 15 min, the reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried, filtered, and evaporated to leave a residue, purification of which by flash chromatography on silica gel (elution with 25–30% ethyl acetate in hexanes) afforded 99 mg (96%) of **17** as a colorless oil: IR (neat, cm^1) 3504, 1667, 1505, 1219, 1041; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, J = 4.3 Hz, 1 H), 6.83 (m, 4 H), 6.36 (d, J = 7.0 Hz, 1 H), 4.94 (d, J = 7.0 Hz, 1 H), 4.77 (d, J = 6.6 Hz, 1 H), 4.75 (s, 1 H), 4.73 (d, J = 6.6 Hz, 1 H), 4.12 (s, 1 H), 3.75 (s, 3 H), 3.38 (s, 3 H), 2.40–2.33 (m, 4 H), 2.17–2.08 (m, 1 H), 1.91–1.83 (m, 3 H), 1.75–1.65 (m, 2 H), 1.37 (s, 3 H), 1.13–1.05 (m, 1 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.3, 155.1, 151.4, 147.7, 142.7, 140.7, 117.1, 114.6, 108.4, 97.6, 85.8, 84.5, 57.3, 55.6, 55.5, 51.8, 49.4, 39.9, 27.6, 26.3, 24.3, 23.1, 22.2 (2 C); MS m/z (M^+) calcd 442.2355, obsd 442.2361; $[\alpha]^{25}_D$ +40.5° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.39; H, 7.84.

Oxy-Cope Rearrangement of 17. Potassium *tert*-butoxide (116 mg, 1.03 mmol) was added portionwise to a magnetically stirred solution of **17** (84 mg, 0.190 mmol) and 18-crown-6 (301 mg, 1.14 mmol) in THF (4 mL) at rt under N_2. After 20 min, methyl iodide (300 μL) was introduced, followed 20 min later with saturated NH_4Cl solution (5 mL). The products were extracted into CH_2Cl_2, and the combined organic extracts were dried, filtered, and evaporated. Chromatography of the residue on silica gel (elution with 25–30% ethyl acetate in hexanes) resulted in the isolation of 29 mg (33%) of **18**, 18 mg (21%) of **19**, and 18 mg (27%) of norbornanone **iii**.

For **18**: colorless oil; IR (neat, cm^{-1}) 1659, 1633, 1505, 1228, 1192, 1145, 1102, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 4 H), 5.16–5.14 (m, 1 H), 5.11 (d, J = 2.3 Hz, 1 H), 4.67 (d, J = 6.5 Hz, 1 H), 4.65 (t, J = 4.8 Hz, 1 H), 4.49 (d, J = 6.5 Hz, 1 H), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.37 (s, 3 H), 3.11–2.97 (m, 1 H), 2.62–2.38 (m, 2 H), 2.29–2.03 (m, 4 H), 1.96–1.80 (m, 3 H), 1.76–1.55 (m, 2 H), 1.18 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 205.0, 159.1, 153.5, 152.0, 150.2, 122.0, 118.1, 115.8, 114.4, 95.5, 87.4, 80.5, 55.7, 55.5, 54.6, 54.4, 46.0, 40.0, 26.7, 25.8, 25.4, 24.7, 24.5, 21.0, 20.0; MS m/z (M^+) calcd 456.2512, obsd 456.2504; $[\alpha]^{25}_D$ −276° (c 1.48, $CHCl_3$).

For **19**: colorless oil; IR (neat, cm^{-1}) 1698, 1506, 1226, 1104, 1041; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (m, 4 H), 5.35 (d, J = 1.5 Hz, 1 H), 4.93 (d, J = 4.5 Hz, 1 H), 4.77 (t, J = 4.5 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 1 H), 4.39 (d, J = 6.8 Hz, 1 H), 3.75 (s, 3 H), 3.43–3.35 (m, 1 H), 3.32 (s, 3 H), 3.26–3.22 (m, 1 H), 2.57–2.44 (m, 2 H), 2.42–2.11 (m, 3 H), 2.03–1.74 (series of m, 5 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.4, 210.4, 153.9, 151.6, 148.4, 124.1, 115.6, 114.5, 95.7, 85.7, 80.7, 60.8, 56.3, 55.7, 55.6, 49.1, 46.9, 38.1, 29.3, 26.4, 24.6, 24.3, 20.3, 19.8, 18.7; MS m/z (M^+) calcd 456.2512, obsd 456.2511; $[\alpha]^{25}_D$ −119° (c 0.625, $CHCl_3$).

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Supplementary Material Available: 300 MHz ^1H NMR and 75 MHz ^{13}C NMR spectra of those compounds lacking combustion data (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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