Evaluation of D-Ribose as an Enantiopure Building Block for Construction of the C-Ring of Taxol and Its Congeners

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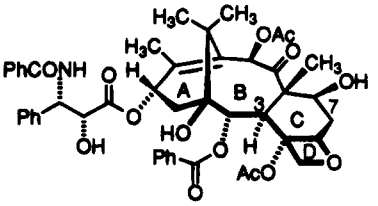
The enantiomerically pure *Z* vinyl iodide **20** is shown to be readily available from D-ribose via a sequence involving zinc-promoted reductive unmasking of an aldehyde and homologation with (iodomethylene)triphenylphosphorane. The vinyl anion produced by halogen–metal exchange adds from the endo direction to an enantiopure ketone prepared from D-camphor. The resulting carbinol undergoes anionic oxy-Cope rearrangement and C-methylation with complete stereocontrol to set the appropriate C-3 stereochemistry of taxol. Dihydroxylation of this intermediate brings about facile transannular hemiketalization. DIBAL-H reduction of this intermediate does not affect the hemiketal, but does reduce the acetonide regiospecifically. An unusual transannular hydride shift occurs during subsequent heating with dibutyltin oxide, as confirmed by X-ray crystallography. When transannular hemiketalization is skirted, hydroboration–oxidation of the side chain leads to an acetaldehyde which is notably prone to β-elimination. Treatment with potassium carbonate in methanol does eventuate in ring closure via an aldol addition reaction, but only after methanol has been added in Michael fashion to the α,β-unsaturated aldehyde.

The diterpene known as taxol[1] or paclitaxel (**1**) has rapidly established itself to be an almost indispensable chemotherapeutic agent against refractory ovarian cancer. The remarkable antitumor activity of **1** is believed to arise from its capability to deter cell replication by preventing microtubules from depolymerizing.[2] The exciting inhibitory properties of this drug likewise cause it to be effective against breast, lung, and skin carcinomas.[3] This wide-ranging activity has attracted the attention of many synthetic organic chemists,[4] and two research groups have successfully accomplished the step-by-step assembly of this structurally complex target.[5,6] Despite these notable achievements, both undertakings involve a very large number of synthetic manipulations and the development of significantly shorter approaches is an important and viable objective.



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Our strategy for the *de novo* acquisition of **1** and related taxanes calls for the initial convergent elaboration of an *exo*-2-norbornanol, e.g., **5**, anionic oxy-Cope rearrangement of which with direct *in situ* methylation delivers a product ketone (**4**) containing functionality adequate to complete the synthesis (Scheme 1).[7] The allowances for structural diversity are obvious and need only be designed to withstand the α-ketol rearrangement associated with the isomerization of **3** to **2**. The developmental phases of this research endeavor have demonstrated the remarkable efficiency with which the absolute configuration of the ultimate precursor to **6**, D-(+)-camphor, can be adapted to elaboration of the entire western and central sectors of **1**.[8] The exceptional fidelity with which the oxy-Cope rearrangement transfers stereogenicity via an "endo-chair" transition state[9] when proceeding from **5** to **4** has played a central role in these developments.

More recently, our attention has turned to the strategic selection of a suitable C/D ring precursor. Early on, recourse to 3-oxygenated cyclohexenyl bromides revealed a direct relationship between the stereodisposition of the

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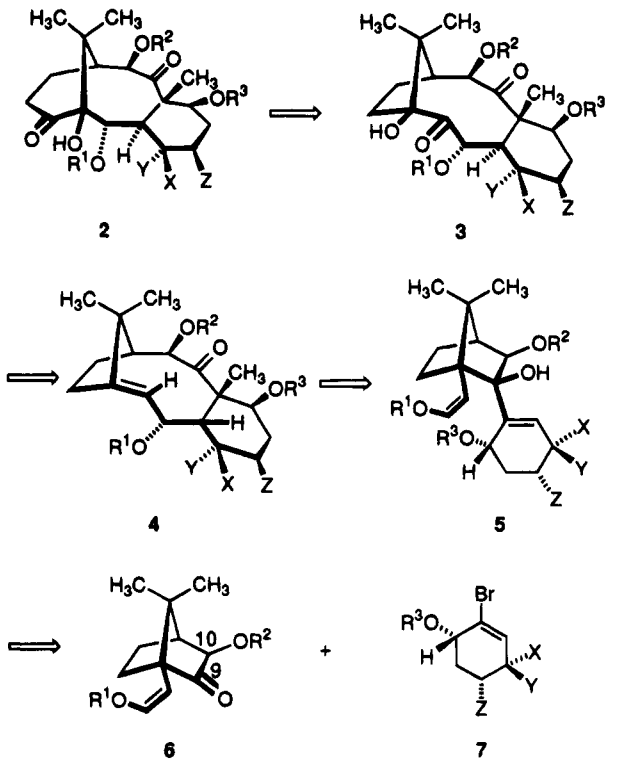
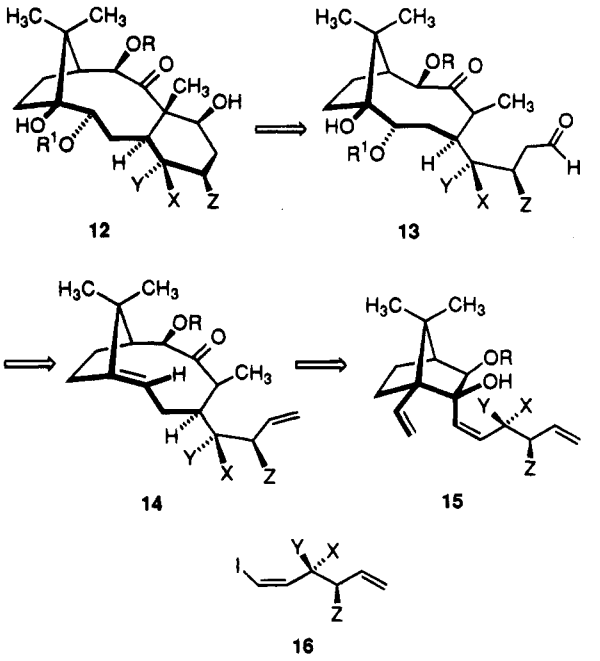
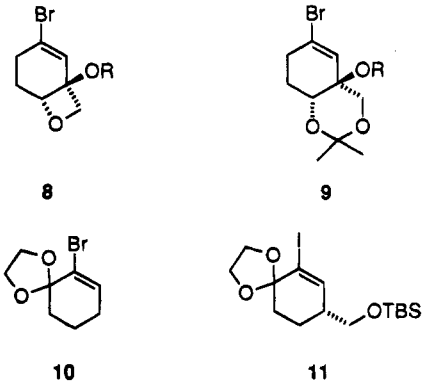
Scheme 1



Scheme 2



X/Y substituents (most often RO and H) and the atropselectivity with which **4** is formed.[10] Preincorporation of the entire oxetane subunit as in **8** was next considered.[11] However, cleavage of the heterocyclic ring occurs under the strongly alkaline conditions of the oxy-Cope rearrangement, which operates at or near room temperature. This complication does not persist with **9**.[11] However, neither **8** nor **9** allow for the proper incorporation of the requisite C-7 oxygen in **1**. Although 2-halocyclohexenone acetals such as **10** serve us well in this regard,[12]



the more highly functionalized enantiopure variant **11** readily available from D-(−)-quinic acid,[13] has proven to be too sterically congested for effective coupling to **6**.

In the above examples, the cyclohexene is perceived to be the source of ring C. However, utilization of these synthons brings with it the need to effect cis/trans postequilibration as in **4** → **3**. This need for stereochemical inversion at C-3 (taxol numbering) requires functional group manipulation, e.g., the conversion of X and Y into a ketone carbonyl, and therefore necessitates the implementation of additional unwanted steps.

For the above reasons, we have now sought to effect the coupling of suitably functionalized *acyclic* cis vinyl halides to camphor-derived ketones related to **6**. Exploitation of this strategy was expected to be an exceptionally convenient route to carbinols of general formula **15** (Scheme 2). The obvious challenge posed by this approach is the need to establish the feasibility of intramolecular aldol cyclization, viz. **13** → **12**, subsequent to the sigmatropic event giving rise to **14**.

The experiments that constitute a first test of this more streamlined approach are described herein. The feasibility of utilizing inexpensive D-ribose as a precursor to **16** in a proposed highly convergent route to **12** forms the basis of this study. In the companion paper,[14] a complementary route starting with D-glyceraldehyde acetonide is detailed and shown to circumvent the pitfalls experienced in this inaugural undertaking.

Results and Discussion

An array of functionality conducive to the projected end game is found in **20**. To arrive at this intermediate, the readily available iodoribose derivative **18**[15,16] was first cleaved reductively with zinc in hot methanol according to Gallos and co-workers[16,17] (Scheme 3). In our hands, an approximate 1:1 mixture of aldehyde **19** and its methyl hemiacetal was formed under these conditions. Following filtration through Florisil to remove zinc iodide and distillation in a Kugelrohr apparatus, pure **19** was isolated in 82% yield. Since **19** obtained in this manner remained enantiomerically and diastereomerically ho-

(10) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 1335.
(11) Paquette, L. A.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 4952.
(12) Paquette, L. A.; Su, Z.; Bailey, S.; Montgomery, F. J. *J. Org. Chem.* **1995**, *60*, 897.
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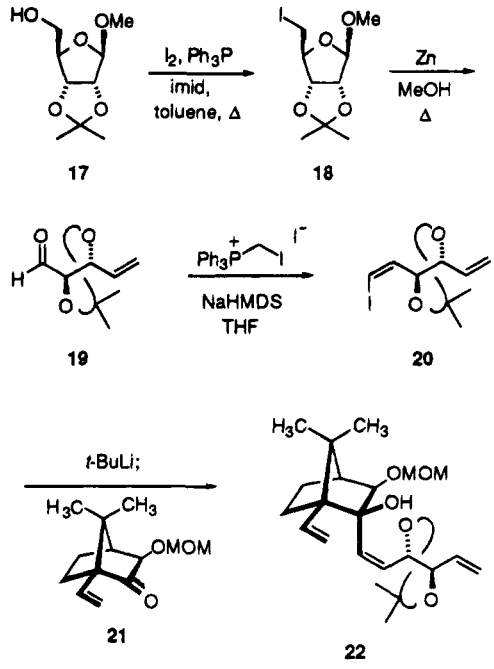
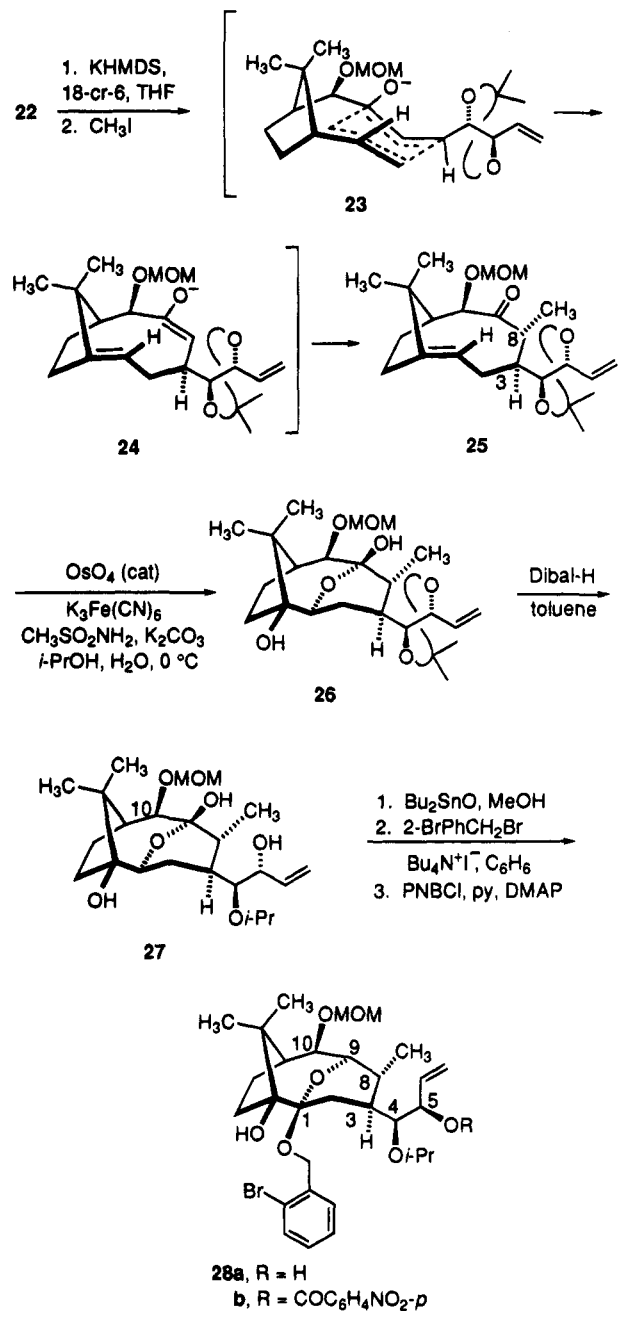
(17) Gallos, J. K.; Koftis, T. V.; Koumbis A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 613.

Scheme 3



Scheme 4



mogeneous, no racemization obviously occurred during the heating process.

Exposure of **19** to the ylide prepared from (iodomethyl)-triphenylphosphonium iodide[18] and sodium hexamethyldisilazide gave rise stereoselectively[19] to the homologated (*Z*)-1-iodo alkene **20** (50%). Chromatographic separation of **20** from its *E* isomer (17%) was not at all problematical. The stereochemical integrity of **20** is fully preserved during halogen–metal interconversion with *tert*-butyllithium and condensation with **21**. This important conclusion was corroborated by independent coupling of the *E* vinyl iodide to the same bicyclic ketone, which resulted in formation of a diastereomeric carbinol. Nucleophilic attack from the endo direction is reinforced in both instances by the exo orientation of the OMOM substituent.[8f]

The bicyclic alcohol **22** produced in this manner embraces three significant design features. Should the anionic oxy-Cope rearrangement planned for this intermediate continue to adhere to the topological features so strictly adopted in cyclohexenyl examples, the *Z* geometry of the double bond internal to the side chain will be transformed with total stereoinduction via **23** to the enantiomerically homogeneous enolate anion **24** (Scheme 4). Direct in situ methylation of this species should lend itself to electrophilic capture from the less sterically congested α-face and deliver **25**. Thirdly, the terminal vinyl group in **25** was expected to be amenable to conversion into an acetaldehyde derivative in advance of aldol cyclization.

The tandem process associated with the projected conversion of **22** to **25** has proven to operate very effectively, leading to the isolation of **25** in 73% yield. One direct consequence of the adoption of **23** as the low-energy transition state is the formation of a *trans*-cyclononene double bond having the vinylic proton syn to the *gem*-dimethyl array. This stereochemical arrangement can be readily confirmed by appropriate NOE measurements. The configurations at C-3 and C-8 in **25** were not as amenable to unequivocal spectroscopic corroboration. Definitive confirmation does rest, however, on an X-ray crystallographic analysis of **28b** to be described below.

Of the two sites of unsaturation present in **25**, that associated with the bridgehead double bond is the more strained. As a consequence, dihydroxylation of this bicyclic ketone with catalytic osmium tetraoxide and potassium ferricyanide as reoxidant[20] was expected to proceed with high regioselectivity. The reactivity difference is indeed sufficiently disparate that attack does materialize exclusively in the desired direction, as indicated by the fact that the transannular hemiketal **26** is

(18) Seyferth, D.; Heeren, J. K.; Singh, G.; Grun, S. O.; Hughes, W. R. *J. Organomet. Chem.* **1966**, *5*, 267.
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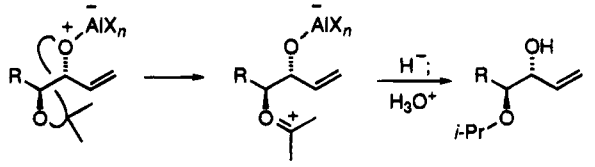
Scheme 5



29 30 31

formed exclusively (74%). Internal 1,2-carbonyl additions of this type have been observed previously; furthermore, such hemiketals are recognized to be rather resistant to chemical change.[8e] Consequently, it came as no surprise that treatment of **26** with DIBAL-H in toluene at 25 °C had no effect on this functionality. However, its acetonide subunit underwent smooth reductive cleavage to afford **27** (83%). The unilateral regioselectivity of this process indicates that chelation to the aluminum reagent occurs preferentially as shown in **29** for steric reasons (Scheme 5). As the acetal begins to open, oxonium ion **30** develops and experiences controlled reduction to give the allylic alcohol **31**.[21,22] Hydrolysis then provides the observed product with complete stereochemical retention at both C–O bonds.

At this stage, the hemiketal functionality present in **27** was regarded as a target of opportunity for regioselective manipulation of the vicinal hydroxyl substituents introduced during osmylation. The extent to which dibutylstannylenes, formed by reaction of a diol with dibutyltin oxide, lend themselves to indirect, site-controlled acylation, alkylation, and oxidation is widely appreciated.[23] For such chemistry to be applicable in the present context, the hemiketal would be required to equilibrate with its hydroxy ketone tautomer at a level sufficient to allow conversion to the *O*-stannylene acetal. In the event, reaction of **27** with an equivalent of dibutyltin oxide in hot methanol for 5 h afforded a product which was heated in benzene with equimolar amounts of 2-bromobenzyl bromide and tetrabutylammonium iodide. Quite unexpectedly, the product proved to be **28a** (76% overall), as confirmed by X-ray crystallographic analysis of its *p*-nitrobenzoate ester **28b** (Figure 1).

Evidence for the structural assignments to **26** and **28** is found in the multiplicity of H-10 in each compound. For **26**, this proton appears as a doublet (δ 3.81, J = 1 Hz) as a consequence of its coupling to H-11. In the case of **28**, H-10 is further split (δ 4.10, J = 11, 2 Hz) due to its spin interaction with both H-9 and H-11. The spectrum of **27** mirrors that recorded for **26** in that H-10 is seen again to be only a doublet (J = 2 Hz).

The ensemble of information realized from this crystal structure study is rather extensive. The first feature to be rigorously established is the reversal in level of oxidation that has transpired at C-1 and C-9. A possible rationalization of this site exchange, illustrated in Scheme 6, involves transannular hydride transfer within **32**.

No information is available on precisely how this migration takes place, although it is clear that the 1,6-shift occurs syn to the *gem*-dimethyl bridge and that dibutyltin oxide promotes the reaction since heating **27**

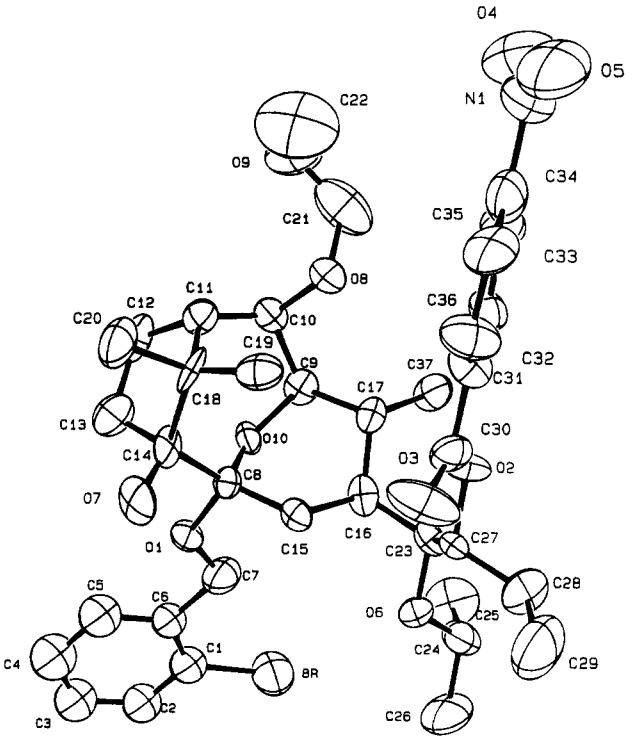
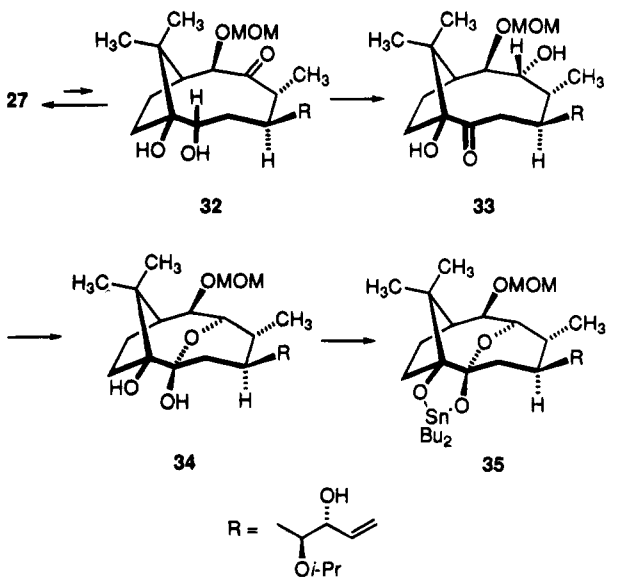


Figure 1. ORTEP plot of the final X-ray model of **28a**. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius.

Scheme 6



alone in methanol has no effect. Once **33** is formed, ketalization materializes in the reverse sense. With arrival at **34**, generation of stannylene acetal **35** is made possible, thereby setting the stage for regioselective benzylation of the hemiketal hydroxyl.

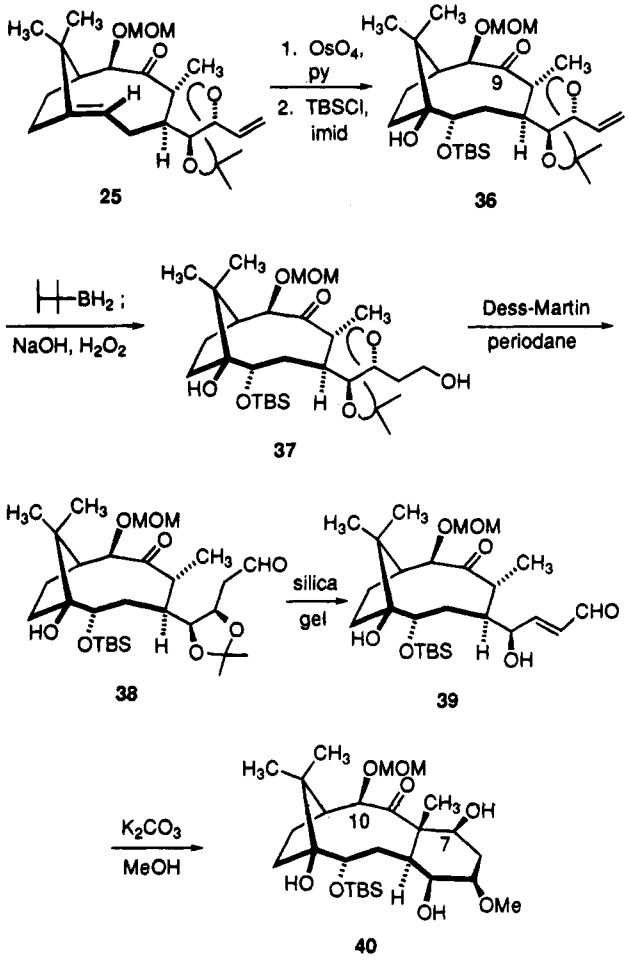
The stereochemical relationships revealed for C-3 and C-8 conform accurately to those expectations based on the mechanistic detail presented earlier. Also clearly apparent is the substitution plan on the oxygen atoms at C-4 and C-5, which is supportive of the arguments summarized in Scheme 5. The conformation adopted by ring B in **28b** is also of interest. The bridging oxygen divides the original nine-membered ring into pyran and oxepane sectors. The smaller heterocyclic subunit adopts

(21) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904.

(22) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

(23) Review: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

Scheme 7



a conventional chair conformation with the C-3 and C-8 substituents both projected equatorially. The strain resident in the oxepane substructure appears to be equally low since the constituent carbon bridge is disposed anti to the oxygen.

The provocative transannular aspects of the dihydroxylation of **25** could be skirted to a reasonable degree by reaction with a stoichiometric quantity of osmium tetraoxide and direct reaction of the freshly liberated diol with *tert*-butyldimethylsilyl chloride. By proceeding along these lines, it was possible to isolate **36** in 32% yield, alongside 26% of hemiacetal **26** (Scheme 7). The steric screening experienced by the C-9 carbonyl group in **36** is sufficiently elevated that reaction with thexylborane proceeds chemoselectively at the terminal double bond to deliver the primary carbinol **37**, oxidation of which with the Dess–Martin periodinane reagent[24] provided aldehyde **38**. During attempts to purify **38** by chromatographic means, β-elimination with the loss of acetone occurred to some extent to form the trans α,β-unsaturated aldehyde **39**. The relevant geometric features of the newly generated double bond are apparent from the J value of 16 Hz. As a consequence of this facile retro-Michael reaction, one can expect that treatment of **38** with potassium carbonate in methanol will initially lead as well to **39**. Under these conditions, it appears that methanol is capable of 1,4-addition to the unsaturated aldehyde as a prelude to aldol cyclization since **40** is formed in 40% yield.

(24) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

The ^{1}H NMR spectrum of **40**, assigned with the aid of a 2D-COSY analysis, showed H-5 to experience diaxial coupling (J = 12 Hz) to H-6$_{ax}$ and a pair of axial–equatorial spin interactions (J = 3–5 Hz) to H-4 and H-6$_{eq}$. Furthermore, in an NOE experiment, irradiation of H-10 gave rise to 11% enhancement of the integral associated with H-7. Molecular models convincingly reveal that this level of proximity can be achieved only when the C-7/C-8 stereochemistry is as shown.

The limitations associated with the deployment of vinyl iodide **20** as a building block for the C ring of taxol have now been defined. Although the Z geometry of this intermediate is fully accommodated during the anionic oxy-Cope rearrangement of its adduct **22** and delivers only the targeted ketone **25**, the further elaboration of this intermediate is disadvantaged. Transannular hemiketalization in the dihydroxylated derivative is difficult to inhibit and to reverse. Once accomplished, however, conversion of the terminal double bond in the side chain to an acetaldehyde is accompanied by a heightened sensitivity to β-elimination.

The enlightenment provided by these observations has facilitated the design of the modified, highly controlled approach detailed in the ensuing paper[14] where these complications are bypassed and advanced construction of the taxol framework is made possible.

Experimental Section

General Considerations. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230–400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^{1}H (300 MHz) and ^{13}C NMR (75 MHz). The high-resoution and fast-atom-bombardment mass spectra were obtained at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(4*R*,2*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carboxaldehyde (19).[16,17] Concentrated hydrochloric acid (3.5 mL) was added to a suspension of D-ribose (35 g, 0.233 mmol) in acetone (140 mL) and methanol (140 mL) at rt. The mixture was refluxed for 1 h, cooled to rt, neutralized with pyridine, and partitioned between water (350 mL) and ether (100 mL). The separated aqueous phase was extracted with ether (2 × 100 mL) and ethyl acetate (3 × 100 mL), and the combined organic phases were washed with saturated copper sulfate solution, water, and brine prior to drying and solvent evaporation. The residue was distilled to give 37.1 g (78%) of **17** as a 5:1 mixture of anomers: This colorless oil[15] was directly carried into the next step.

A solution of these epimers (26.1 g, 128 mmol), imidazole (13.1 g, 192 mmol), and triphenylphosphine (40.5 g, 154 mmol) in toluene (500 mL) and acetonitrile (100 mL) was treated portionwise with iodine (39.0 g, 154 mmol), refluxed for 5 min, and cooled to rt. Additional iodine was introduced in approximately 100 mg portions until the reaction mixture remained dark-brown in color. After dilution with ether and repeated washing of the organic extracts with 10% sodium thiosulfate solution, water, and brine, the solution was dried and concentrated in vacuo to leave a residue which was filtered through a short plug of silica gel (elution with 95:5 hexanes–ethyl acetate) to give **18** (39.7 g, 99%) as a colorless, oily, 5:1 mixture of anomers.[16]

Powdered zinc (15.6 g, 239 mmol) was added to the above iodides (15.0 g, 47.8 mmol) in methanol (100 mL), and the mixture was refluxed for 1 h, cooled, and filtered. The filtrate was concentrated in vacuo at 10 °C, and the residue was triturated with 4:1 hexanes–ethyl acetate prior to filtration through a short plug of Florisil (elution with the same solvent mixture). The filtrate was evaporated and the residue was

subjected to bulb-to-bulb distillation at 5 Torr (oven temp: 70–100 °C) to afford 6.14 g (82%) of **19** as a homogeneous colorless oil: IR (film, cm^{-1}) 1736, 1375, 1216, 1067; ^1H NMR (300 MHz, C_6D_6) δ 9.36 (d, J = 3 Hz, 1 H), 5.56 (m, 1 H), 5.21 (dd, J = 17, 1 Hz, 1 H), 4.97 (dd, J = 10, 1 Hz, 1 H), 4.44 (t, J = 7 Hz, 1 H), 4.01 (dd, J = 7, 3 Hz, 1 H), 1.44 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 199.8, 132.0, 118.4, 111.1, 82.4, 79.0, 27.4, 25.3; $[\alpha]^{20}_D$ −3.1 (*c* 1.9, $CHCl_3$).

(4*S*,5*R*)-4-[(*Z*)-2-Iodovinyl]-2,2-dimethyl-5-vinyl-1,3-dioxolane (20). Sodium hexamethyldisilazide (56.1 mL of 1 M in THF, 56.2 mmol) was added dropwise to a suspension of (iodomethyl)triphenylphosphonium iodide[18] (29.8 g, 56.2 mmol) in THF (130 mL) at 0 °C for 5 min, cooled to −78 °C, and treated dropwise with a solution of **19** (5.84 g, 37.4 mmol) in THF (60 mL). The mixture was maintained at −78 °C for 1 h, quenched with methanol (10 mL) and saturated NH_4Cl solution (100 mL), warmed to rt, diluted with ether (300 mL), and filtered. The separated aqueous phase was extracted with ether, and the combined organic phases were washed with brine, evaporated, and concentrated. Chromatography of the residue on silica gel (elution with 1 → 2% ether in hexanes) provided **20** (5.24 g, 50%) as a colorless oil. Also isolated was its more polar *E* isomer (1.76 g, 17%).

For **20**: IR (film, cm^{-1}) 1611, 1380, 1245, 1210, 1052; ^1H NMR (300 MHz, C_6D_6) δ 6.11 (t, J = 7 Hz, 1 H), 5.95 (m, 1 H), 5.64 (m, 1 H), 5.25 (m, 1 H), 5.01 (m, 1 H), 4.89 (t, J = 7 Hz, 1 H), 4.55 (t, J = 7 Hz, 1 H), 1.45 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 138.7, 134.0, 117.4, 109.4, 84.1, 81.3, 79.0, 28.1, 25.5; MS m/z (M^+ − 1) calcd 278.9841, obsd 278.9865; $[\alpha]^{20}_D$ +112.5 (*c* 2.1, $CHCl_3$).

For the *E* isomer: IR (film, cm^{-1}) 1599, 1373, 1216, 1049; ^1H NMR (300 MHz, C_6D_6) δ 6.40 (ddd, J = 15, 7, 1 Hz, 1 H), 6.18 (d, J = 15 Hz, 1 H), 5.58 (m, 1 H), 5.16 (d, J = 15 Hz, 1 H), 5.00 (br d, J = 10 Hz, 1 H), 4.81 (m, 1 H), 4.17 (m, 1 H), 1.43 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 143.0, 138.7, 134.3, 117.8, 109.1, 80.8, 79.3, 28.0, 25.5; $[\alpha]^{20}_D$ −32.1 (*c* 1.9, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-2-[(*Z*)-2-[(4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]vinyl]-3-(methoxymethoxy)-7,7-dimethyl-1-vinyl-2-norbornanol (22). *tert*-Butyllithium (20.2 mL of 1.7 M in pentane, 34.4 mmol) was added dropwise to a solution of ketone **21**[8f] (3.85 g, 17.2 mmol) and iodide **20** (5.16 g, 17.2 mmol) in THF (45 mL) at −78 °C. The reaction mixture was stirred for 1 h at this temperature, quenched with saturated $NaHCO_3$ solution, and allowed to warm to rt. The separated aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 4:1 hexanes/ethyl acetate) gave **22** (3.76 g, 55%) as a colorless oil: IR (film, cm^{-1}) 3463, 1380, 1253, 1038; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (dd, J = 18, 11 Hz, 1 H), 5.64 (m, 1 H), 5.47 (m, 2 H), 5.25 (dd, J = 12, 9 Hz, 1 H), 5.12 (m, 2 H), 5.02 (m, 1 H), 4.81 (dd, J = 18, 4 Hz, 1 H), 4.58 (s, 2 H), 4.38 (t, J = 6 Hz, 1 H), 3.46 (s, 1 H), 3.27 (s, 3 H), 3.21 (s, 1 H), 1.85 (d, J = 5 Hz, 1 H), 1.65 (m, 1 H), 1.52 (m , 1 H), 1.38 (s, 3 H), 1.28 (s, 3 H), 1.21 (m, 1 H), 1.18 (s, 3 H), 0.98 (m, 1 H), 0.65 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.4, 135.3, 135.0, 128.3, 117.3, 116.9, 108.2, 97.5, 91.8, 83.6, 80.1, 73.9, 60.3, 55.7, 50.9, 50.4, 28.2, 25.7, 25.4, 24.1, 22.0, 21.9; MS m/z (M^+ − C_3H_6O) calcd 320.1987, obsd 320.1980; $[\alpha]^{20}_D$ −7.7 (*c* 2.2, $CHCl_3$). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.87; H, 9.07.

(1*S*,2*S*,4*R*,5*S*,7*E*)-5-[(4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]-2-(methoxymethoxy)-4,11,11-trimethylbicyclo[6.2.1]undec-7-en-3-one (25). To a solution of **22** (905 mg, 2.39 mmol) and 18-crown-6 (915 mg, 2.63 mmol) in dry THF (50 mL) cooled to −78 °C was added a toluene solution of potassium hexamethyldisilazide (7.2 mL of 0.5 M, 3.6 mmol). After 45 min at −78 °C, methyl iodide (750 μL, 12.0 mmol) was introduced, the mixture was warmed to 0 °C during 1 h, and saturated $NaHCO_3$ solution was added. The separated aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 8:1 hexanes/ethyl acetate) to provide **25** (683 mg, 73%) as a colorless oil: IR (film, cm^{-1}) 1690, 1252, 1150, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17, 10, 8 Hz, 1 H), 5.26 (m, 3 H), 4.71 (d, J = 7 Hz, 1 H), 4.55 (m, 2 H), 4.29 (dd, J = 10, 6 Hz, 1 H), 3.84 (d, J = 5 Hz, 1 H), 3.39 (s, 3 H), 3.17 (m, 1 H), 2.25 (m, 2 H), 2.12 (t, J = 11 Hz, 1 H), 1.87 (m, 4 H), 1.65 (br d, J = 13 Hz, 1 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.14 (d, J = 7 Hz, 3 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.6, 147.9, 135.2, 120.5, 118.6, 108.7, 96.0, 87.6, 81.2, 80.9, 56.0, 53.4, 45.8, 44.5, 42.0, 28.4, 26.2, 26.1, 25.7, 23.5, 23.1, 21.9, 19.4; MS m/z (M^+) calcd 392.2564, obsd 392.2589; $[\alpha]^{20}_D$ −36.9 (*c* 1.21, $CHCl_3$). Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.11; H, 9.37.

(1*S*,2*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-9-[(4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]-6-(methoxymethoxy)-8,12,12-trimethyl-11-oxatricyclo[5.3.1.1^{2,5}]dodecane-2,7-diol (26). A solution of **25** (70 mg, 0.179 mmol), potassium ferricyanide (118 mg, 0.357 mmol), methanesulfonamide (51 mg, 0.536 mmol), and K_2CO_3 (74 mg, 0.536 mmol) in isopropyl alcohol (450 μL) and water (450 μL) cooled to 0 °C was treated with a small crystal of osmium tetraoxide, stirred at 0 °C for 2.5 h, and quenched with Na_2SO_3 solution. Following extraction with ethyl acetate, the organic phase was washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 2:1 hexanes/ethyl acetate) gave **26** (56 mg, 74%) as a colorless oil, trituration of which with hexanes afforded a colorless solid: mp 113–114 °C; IR (film, cm^{-1}) 3442, 1379, 1108, 1048; ^1H NMR (300 MHz, C_6D_6) δ 6.17 (m, 1 H), 5.24 (m, 2 H), 4.81 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H), 4.39 (dd, J = 10, 7 Hz, 1 H), 4.10 (m, 3 H), 3.36 (s, 3 H), 3.01 (m, 1 H), 2.22 (m, 4 H), 2.00 (m, 4 H), 1.74 (m, 2 H), 1.67 (s, 3 H), 1.48 (s, 3 H), 1.44 (s, 6 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 135.8, 118.4, 108.2, 102.4, 100.0, 97.6, 92.9, 82.8, 81.4, 80.6, 79.1, 55.4, 50.6, 47.1, 40.3, 38.8, 34.3, 30.0, 28.9, 26.1, 25.4, 25.3, 23.3; MS m/z (M^+ − CH_3) calcd 411.2384, obsd 411.2379; $[\alpha]^{20}_D$ +29.0 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{23}H_{38}O_7$: C, 64.76; H, 8.98. Found: C, 64.34; H, 8.83.

(1*S*,2*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-9-[(1*S*,2*R*)-2-Hydroxy-1-isopropoxy-3-butenyl]-6-(methoxymethoxy)-8,12,12-trimethyl-11-oxatricyclo[5.3.1.1^{2,5}]dodecane-2,7-diol (27). Diisobutylaluminum hydride in toluene (5.63 mL of 1.0 M, 5.63 mmol) was added dropwise to a solution of **26** (240 mg, 0.563 mmol) in dry toluene (5.6 mL) at 0 °C. The reaction mixture was stirred at rt for 3.5 h, returned to 0 °C, and quenched with methanol (2.5 mL). Saturated NH_4Cl solution (1 mL) was introduced, and the mixture was stirred for 1 h at rt prior to addition of Celite and $MgSO_4$ and filtration through a pad of Celite. The solids were rinsed extensively with ethyl acetate, and the combined filtrates were concentrated. Chromatography of the residue on silica gel (elution with 2:1 hexanes/ethyl acetate) furnished **27** (201 mg, 83%) as a white solid, mp 122–123 °C (from chloroform-hexanes); IR (film, cm^{-1}) 3448, 1368, 1098, 1037; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (m, 1 H), 5.22 (m, 2 H), 4.66 (s, 2 H), 4.12 (m, 2 H), 3.77 (d, J = 2 Hz, 1 H), 3.66 (pent, J = 7 Hz, 1 H), 3.59 (m, 1 H), 3.39 (s, 3 H), 2.90 (m, 1 H), 2.49 (br s, 1 H), 1.95 (m, 9 H), 1.60 (m, 1 H), 1.34 (s, 3 H), 1.11 (m, 6 H), 1.04 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.2, 116.1, 102.4, 97.1, 92.8, 83.1, 79.6, 78.9, 73.4, 70.6, 55.6, 50.4, 46.7, 38.2, 36.8, 35.5, 29.9, 25.3, 23.2, 22.8, 22.3, 22.2, 14.4; MS m/z (M^+) calcd 428.2774, obsd 428.2770; $[\alpha]^{20}_D$ +20.1 (*c* 0.8, $CHCl_3$).

(α*R*,β*S*,1*S*,2*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-1-[(*o*-Bromobenzyl)oxy]-2-hydroxy-β-isopropoxy-6-(methoxymethoxy)-8,12,12-trimethyl-α-vinyl-11-oxatricyclo[5.3.1.1^{2,5}]dodecane-9-ethanol (28a). A solution of **27** (33 mg, 0.077 mmol) and dibutyltin oxide (19 mg, 0.077 mmol) in methanol (1.9 mL) was refluxed for 5 h, cooled to rt, and concentrated under reduced pressure. The residue was dissolved in benzene (800 μL), tetrabutylammonium iodide (29 mg, 0.077 mmol) together with 2-bromobenzyl bromide (39 mg, 0.15 mmol) were added, and the mixture was refluxed for 4 h, cooled, diluted with chloroform, and washed with Na_2SO_3 solution. The organic phase was dried and concentrated in vacuo to leave a residue which was chromatographed on silica gel. Elution with 6:1 hexanes/ethyl acetate gave **28a** (35 mg, 76%) as a white solid: mp 108–109 °C; IR (film, cm^{-1}) 3448, 1368, 1098, 1037; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2 H), 7.30 (m, 1 H), 7.13

(m, 1 H), 6.13 (m, 1 H), 5.25 (m, 2 H), 4.77 (d, J = 12 Hz, 1 H), 4.70 (d, J = 7 Hz, 1 H), 4.64 (d, J = 12 Hz, 1 H), 4.59 (d, J = 7 Hz, 1 H), 4.21 (m, 2 H), 4.11 (m, 1 H), 3.78 (pent, J = 7 Hz, 1 H), 3.69 (m, 1 H), 3.40 (s, 3 H), 2.55 (m, 4 H), 2.06 (m, 3 H), 1.83 (br s, 2 H), 1.52 (m, 2 H), 1.38 (s, 3 H), 1.19 (m, 9 H), 1.09 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.7, 138.2, 132.4, 128.8, 128.6, 127.3, 122.6, 116.4, 103.4, 99.7, 96.7, 87.1, 83.1, 79.1, 78.3, 73.3, 70.7, 61.8, 55.8, 50.3, 45.2, 39.3, 32.4, 30.4, 28.7, 26.7, 23.8, 23.1, 22.3, 21.8; MS m/z (M^+) calcd 596.2348, obsd 596.2342; $[\alpha]^{20}_D$ −11.2 (c 1.5, $CHCl_3$). Anal. Calcd for $C_{30}H_{45}BrO_7$: C, 60.30; H, 7.59. Found: C, 60.10; H, 7.65.

p-Nitrobenzoate **28b**, prepared in the usual way from **27a** (40 mg, 0.067 mmol), triethylamine (47 μL, 0.335 mmol), DMAP (1 mg), and *p*-nitrobenzoyl chloride (19 mg, 0.100 mmol) in CH_2Cl_2 (700 μL, rt, 16 h) was obtained as colorless crystals (45 mg, 90%): mp 140.5−141 °C (from hexanes); IR (film, cm^{-1}) 3480, 1732, 1528, 1268, 1101, 1037; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9 Hz, 2 H), 8.20 (d, J = 9 Hz, 2 H), 7.53 (m, 1 H), 7.45 (m, 1 H), 7.30 (m, 1 H), 7.14 (m, 1 H), 6.16 (m, 1 H), 5.64 (t, J = 6 Hz, 1 H), 5.38 (m, 2 H), 4.74 (d, J = 12 Hz, 1 H), 4.64 (d, J = 12 Hz, 1 H), 4.56 (d, J = 7 Hz, 1 H), 4.45 (d, J = 7 Hz, 1 H), 4.20 (dd, J = 9, 7 Hz, 1 H), 4.06 (m, 1 H), 3.94 (m, 1 H), 3.82 (pent, J = 7 Hz, 1 H), 3.29 (s, 3 H), 2.55 (m, 2 H), 2.33 (m, 2 H), 2.04 (m, 3 H), 1.57 (m, 1 H), 1.41 (m, 1 H), 1.24 (d, J = 7 Hz, 3 H), 1.21 (s, 3 H), 1.18 (d, J = 7 Hz, 6 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 163.3, 150.5, 137.9, 135.8, 133.7, 132.4, 130.7, 129.1, 128.9, 128.3, 127.4, 123.5, 122.8, 119.7, 103.4, 96.7, 86.9, 83.1, 78.9, 76.4, 71.7, 61.9, 55.7, 50.2, 45.2, 40.2, 32.3, 30.2, 29.0, 26.8, 26.0, 23.9, 22.8, 22.4, 21.5; MS m/z (M^+) calcd 745.2461, obsd 745.2474; $[\alpha]^{20}_D$ +41.6 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{37}H_{48}BrNO_{10}$: C, 59.53; H, 6.48. Found: C, 59.93; H, 6.45.

(1*S*,2*R*,4*R*,5*S*,7*S*,8*S*)-7-(*tert*-Butyldimethylsiloxy)-5-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]-8-hydroxy-2-(methoxymethoxy)-4,11,11-trimethylbicyclo[6.2.1]-undecane (36). Osmium tetraoxide (449 mg, 1.77 mmol) was added to a solution of **25** (660 mg, 1.68 mmol) in pyridine (15 mL) at 0 °C. The black solution was stirred in the cold for 35 min, quenched with 10% sodium dithionite solution (20 mL), warmed to rt, stirred vigorously for 16 h, and partitioned between brine (75 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic phases were dried and concentrated. The residual yellow foam was directly dissolved in DMF (1.5 mL) containing imidazole (572 mg, 8.42 mmol), treated with *tert*-butyldimethylsilyl chloride (760 mg, 5.05 mmol), stirred at rt for 24 h, and partitioned between ether and water. The aqueous layer was extracted with ether, and the combined organic phases were dried and concentrated in vacuo. Chromatography of the residue on silica gel (elution with 9:1 hexanes/ethyl acetate) gave **36** (292 mg, 32%) as a colorless oil. Continued elution with 1:1 → 1:2 hexanes/ethyl acetate afforded hemiacetal **26** (190 mg, 26%).

For **36**: IR (film, cm^{-1}) 3465, 1701, 1380, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (m, 1 H), 5.40 (m, 2 H), 4.55 (d, J = 7 Hz, 1 H), 4.45 (d, J = 10, 5 Hz, 1 H), 4.36 (d, J = 7 Hz, 1 H), 4.18 (s, 1 H), 4.06 (s, 1 H), 3.92 (dd, J = 10, 5 Hz, 1 H), 3.74 (dd, J = 10, 2 Hz, 1 H), 3.31 (s, 3 H), 2.91 (m, 1 H), 2.45 (m, 3 H), 2.19 (m, 1 H), 1.69 (m, 2 H), 1.49 (s, 3 H), 1.45 (m, 1 H), 1.35 (s, 3 H), 1.25 (m, 1 H), 1.15 (d, J = 7 Hz, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.88 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.3, 133.7, 121.1, 107.9, 95.1, 87.4, 81.8, 80.0, 79.9, 70.0, 55.8, 55.1, 50.3, 48.2, 33.7, 32.3, 31.1, 30.1, 28.6, 27.4, 25.7, 25.6, 18.0, 16.9, 8.3, −3.3, −4.7; MS m/z (M^+) calcd 540.3482, obsd 5409.3497; $[\alpha]^{20}_D$ +42.5 (c 1.7, $CHCl_3$). Anal. Calcd for $C_{29}H_{52}O_7Si$: C, 64.41; H, 9.69. Found: C, 64.03; H, 9.70.

(1*S*,2*R*,4*R*,5*S*,7*S*,8*S*)-7-(*tert*-Butyldimethylsiloxy)-8-hydroxy-5-[(4*S*,5*R*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(methoxymethoxy)-4,11,11-trimethylbicyclo[6.2.1]undecan-3-one (37). Borane·THF (1.02 mL of 1 M in THF, 1.02 mmol) was added to a solution of 2,3-dimethyl-2-butene (1.02 mL of 1 M in THF, 1.02 mmol) at 0 °C. The resultant mixture was warmed to rt, stirred for 1 h, and recooled to 0 °C. A solution of **36** (110 mg, 0.204 mmol) in THF (800 μL) was introduced, and the mixture was stirred for 2 h at rt, returned to 0 °C, and quenched with 2 N NaOH (2.5 mL, 5.1 mmol) and 30% hydrogen peroxide solutions (1.2 mL, 10.2 mmol). Oxidation was allowed to proceed at 0 °C for 1 h, 10% Na_2SO_3 solution was introduced, and the mixture was extracted with ethyl acetate. The combined organic phases were dried and concentrated. The residue was chromatographed on silica gel (elution with 3:2 hexanes/ethyl acetate) to provide **37** (53 mg, 47%) as a colorless oil: IR (film, cm^{-1}) 3467, 1701, 1380, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (d, J = 7 Hz, 1 H), 4.37 (d, J = 7 Hz, 1 H), 4.33 (m, 1 H), 4.19 (s, 1 H), 4.11 (br s, 1 H), 3.89 (m, 3 H), 3.79 (dd, J = 10, 3 Hz, 1 H), 3.30 (s, 3 H), 2.91 (m, 1 H), 2.51 (m, 3 H), 2.24 (m, 1 H), 2.02 (m, 2 H), 1.80 (m, 3 H), 1.55 (m, 2 H), 1.49 (s, 3 H), 1.35 (s, 3 H), 1.25 (s, 1 H), 1.14 (d, J = 7 Hz, 3 H), 1.08 (s, 3 H), 1.00 (s, 3 H), 0.85 (s, 9 H), 0.16 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 212.3, 107.7, 95.1, 87.3, 81.9, 79.6, 76.4, 69.8, 60.4, 55.8, 55.0, 50.2, 48.3, 34.3, 32.8, 31.6, 30.9, 30.1, 28.5, 27.5, 25.8, 25.7, 18.0, 16.8, 8.3, −3.3, -4.7; MS m/z (M^+) calcd 558.3588, obsd 558.3571; $[\alpha]^{20}_D$ +48.7 (c 1.0, $CHCl_3$).

(4*S*,5*R*)-5-[(1*S*,2*S*,4*R*,5*R*,7*R*,8*S*)-2-(*tert*-Butyldimethylsiloxy)-1-hydroxy-7-(methoxymethoxy)-5,11,11-trimethyl-6-oxobicyclo[6.2.1]undec-4-yl]-2,2-dimethyl-1,3-dioxolane-4-acetaldehyde (38) and (1*S*,2′*E*,2*S*,3′*S*,4*S*,5*R*,7*R*,8*S*)-2-(*tert*-Butyldimethylsiloxy)-4-(3-formyl-1-hydroxy-2-propenyl)-1-hydroxy-7-(methoxymethoxy)-5,11,11-trimethyloxobicyclo[6.2.1]undecan-6-one (39). Dess−Martin periodinane reagent (74 mg, 0.175 mmol) was added to a solution of **37** (65 mg, 0.117 mmol) and pyridine (47 μL, 0.585 mmol) in CH_2Cl_2 (1.2 mL) at rt. The reaction mixture was stirred for 1 h, quenched with saturated $NaHCO_3$ and 10% sodium thiosulfate solutions, and stirred vigorously for 30 min prior to extraction with CH_2Cl_2. The combined organic phases were concentrated, and the residue was purified by chromatography on silica gel (elution with 4:1 hexanes/ethyl acetate). Aldehyde **38** was obtained as a colorless glass (22 mg, 34%). Further elution with 2:1 hexanes/ethyl acetate gave **39** (26 mg, 45%), also a colorless glass. TLC analysis of the reaction mixture before and after workup indicated that the β-elimination was occurring during the chromatographic process.

For **38**: IR (film, cm^{-1}) 3450, 1727, 1698, 1220, 1040; ^{1}H NMR (300 MHz, C_6D_6) δ 9.51 (d, J = 4 Hz, 1 H), 4.38 (s, 2 H), 4.25 (m, 2 H), 4.10 (m, 2 H), 3.77 (dd, J = 10, 4 Hz, 1 H), 3.10 (s, 3 H), 3.04 (m, 1 H), 2.56 (m, 2 H), 2.44 (m, 1 H), 2.13 (m, 3 H), 1.84 (m, 1 H), 1.48 (m, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.25 (d, J = 7 Hz, 3 H), 1.13 (s, 3 H), 0.92 (s, 9 H), 0.20 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.6, 198.0, 108.2, 95.4, 87.7, 82.1, 79.6, 72.6, 70.0, 55.4, 55.3, 50.5, 47.9, 44.2, 34.7, 33.2, 31.0, 30.5, 28.0, 17.4, 25.6, 25.5, 17.9, 17.3, 8.5, −3.5, −4.8; MS m/z (M^+) calcd 556.3431, obsd 556.3440; $[\alpha]^{20}_D$ +45.4 (c 1.3, $CHCl_3$).

For **39**: IR (film, cm^{-1}) 3450, 1693, 1255, 1093, 1039; ^{1}H NMR (300 MHz, C_6D_6) δ 9.23 (d, J = 7.5 Hz, 1 H), 6.34 (dd, J = 16, 6 Hz, 1 H), 6.15 (ddd, J = 16, 7.5, 1 Hz, 1 H), 4.40 (m, 3 H), 4.09 (m, 2 H), 4.00 (dd, J = 11, 3 Hz, 1 H), 3.62 (dd, J = 7, 6 Hz, 1 H), 3.08 (m, 5 H), 2.58 (m, 1 H), 2.33 (m, 1 H), 2.04 (m, 1 H), 1.60 (m, 3 H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.10 (d, J = 7 Hz, 1 H), 0.86 (s, 9 H), 0.15 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.4, 191.8, 155.5, 132.6, 95.3, 87.4, 83.0, 72.5, 71.0, 56.3, 55.3, 50.2, 46.1, 37.0, 34.3, 33.6, 30.7, 28.1, 25.6, 17.9, 17.7, 9.7, −3.5, −4.9; MS m/z (M^+) calcd 498.3013, obsd 498.2997; $[\alpha]^{20}_D$ +45.6 (c 1.0, $CHCl_3$).

(1*S*,2*R*,4*S*,4a*S*,6*R*,7*S*,10*S*,11*S*,12a*S*)-11-(*tert*-Butyldimethylsiloxy)-dodecahydro-1,4,10-trihydroxy-2-methoxy-6-(methoxymethoxy)-4a,13,13-trimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (40). A solution of **38** (10 mg, 0.018 mmol) in methanol (360 μL) was treated with one drop of saturated K_2CO_3 solution, stirred at rt for 2 h, and partitioned between ether and brine. The organic phase was dried and concentrated, and the residue was purified by chromatography on silica gel (elution with 1:1 hexanes/ethyl acetate). There was obtained 4 mg (40%) of **40** as a colorless film: IR (film, cm^{-1}) 3449, 1700, 1254, 1038; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (d, J = 7 Hz, 1 H), 4.52 (d, J = 7 Hz, 1 H), 4.41 (s, 1 H), 4.13 (s, 1 H), 4.00 (m, 2 H), 3.81 (dd, J = 10, 3 Hz, 1 H), 3.42 (s, 3H), 3.35 (s, 3 H), 3.28 (m, 1H), 3.15 (br s, 1

H), 1.55 (m, 3 H), 2.20 (m, 1 H), 2.10 (m, 1 H), 1.97 (m, 2 H), 1.80 (m, 2 H), 1.57 (m, 2 H), 1.37 (s, 3 H), 1.11 (s, 3 H), 1.04 (s, 3 H), 0.90 (s, 9 H), 0.23 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.1, 96.1, 83.9, 82.5, 79.0, 73.4, 70.2, 70.0, 58.3, 56.8, 56.2, 56.1, 49.7, 35.6, 34.2, 32.7, 30.2, 29.9, 28.1, 25.8, 18.0, 17.1, 11.0, −3.3, −4.7; MS m/z (M^+) calcd 530.3275, obsd 530.3273; $[\alpha]^{20}_D$ −18.8 (c 0.8, $CHCl_3$).

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of those compounds for which analytical data are not provided (14 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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(25) Atomic coordinates for the structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.