Stereoselective Construction of a Highly Functionalized Taxoid ABC-Ring System: the C2–C9 Oxa-Bridge Approach

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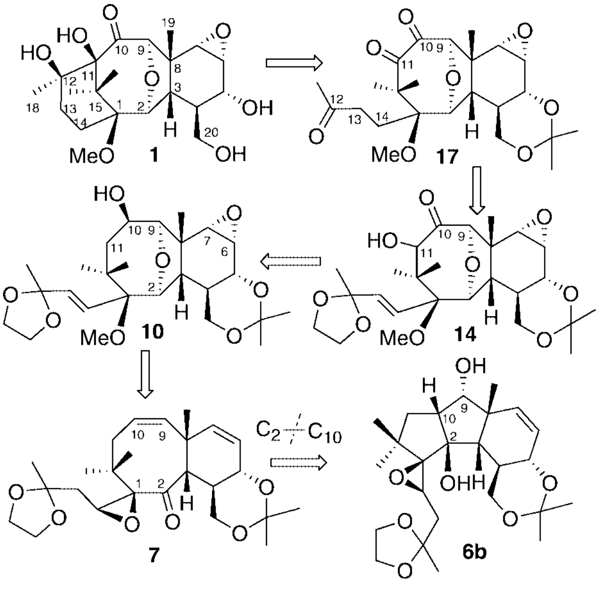
Keywords: Taxoids / Aldol reactions / Samarium iodide / Transannular reactions / Control elements

The goal of this investigation is to assemble the 20-carbon unit **1** of the taxoid diterpene skeleton with a high level of stereocontrol by means of a three-reaction sequence developed in this laboratory. The strategy involves seven C–C bond-forming operations together with eighteen functional group transformations, circumventing the stereoselectivity issue altogether. Furthermore, there is no isomer formation and hence no need for chromatographic separation. A temporary oxa-bridge (C2/C9) was used as a problem-solving approach. The key step in the planned sequence was based on achieving the last C–C bonding between C11 and C12, following a successful C11 functionalization. X-ray analyses of **8b**, **17**, **18**, **19**, **20**, and **21**, together with extensive use of 800 MHz ^1H (200 MHz ^{13}C) NMR spectra, support the suggested structures.

Introduction

Despite six existing total syntheses, the construction of the taxoid ABC ring system continues to enjoy development of new methods and strategies.[1] We have previously introduced a versatile synthetic strategy for accessing the BC subunit of the A-*seco* taxoid diterpene skeleton, based on a three-reaction sequence, which we dubbed the aldol-annulation-fragmentation methodology.[2] To avoid the problems associated with direct formation of the eight-membered ring, our strategy was based on a fragmentation sequence rather than a ring-closure operation. Our initial interest in this area was stimulated by the need to design a rapid and stereoselective route to a variety of heavily substituted eight-membered ring systems,[3] the precursors of several taxoid representatives.[4] From the foregoing results, it seemed desirable to generate a tricyclic intermediate that would incorporate all carbon atoms of the final taxoid skeleton and would allow indirect introduction of the central B-ring by fragmentation.[5] As the molecule shows a great tendency to undergo transannular processes, we decided to trigger and use them in the hope of avoiding potential difficulties inherent in an eight-membered ring system. To this end, a central intermediate **7** (prepared by the aldol-annulation-fragmentation sequence) that should allow stereoselective construction of the A-secotaxane framework **10** was identified (Scheme 1).



Scheme 1. Retrosynthetic analysis leading to oxa-bridged taxoid diterpene skeleton **1**.

The need for complete diastereocontrol, while placing emphasis on step efficiency, prompted us to devise a strategy based on sequential substrate-controlled diastereoselective reactions. We thus designed a synthetic plan based at the outset on one external control element, which in turn creates an additional internal control element after each C–C bonding operation. By removing all chiral centers on the aldol partners, **2** and **3**, we eliminated two out of three factors that govern the stereochemical outcome of an aldol reaction.[6] By choosing a cyclic enolate we forcibly imposed the (*E*)-enolate geometry,[7] leaving only one possible chair-

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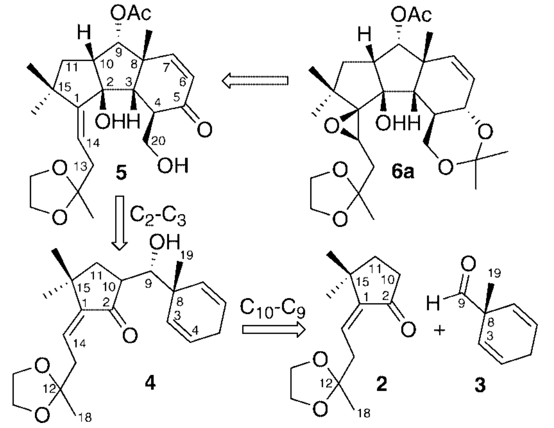
DOI: 10.1002/ejoc.200500347

like transition state[8] affording a single *threo*-aldol **4** (Scheme 2). At the outset, the *anti*-selective aldol reaction creates a new key control element for the subsequent transformation, the C2–C3 bonding, which in turn sets the stage for the C1 quaternary center construction in its desired configuration, by creating a further new control element at C2 for the hydroxy-directed Sharpless epoxidation. Note that, during the aldol-annulation sequence resulting in **5**, six out of seven C–C bonds are already formed, while six chiral centers are generated, starting from two achiral precursors **2** and **3**. Only one tricyclic intermediate out of 32 possible enantiomeric pairs of diastereoisomers is obtained, while efficient control is ensured (through C2β–OH) for the stereoselective construction of the C1 center. The full carbon backbone was completed in only six linear steps by an Yb(OTf)$_3$-catalyzed aldol reaction, which ensured the last carbon (C20). Although the resulting (±)-**5** was successfully transformed into the enantiomerically pure fragmentation precursor **6b**[2] by optical resolution, we chose for convenience to restrict these exploratory experiments to the conversion of **5** in the racemic series.



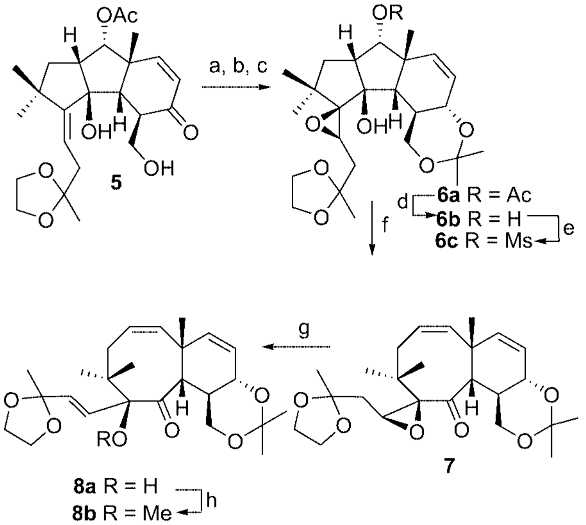
Scheme 2. Domino-type stereo planning for achieving single-isomer transformations used in our previous work.

The option presented in this paper involves temporary oxa-bridge formation through an in situ epoxide opening (**10**), a crucial C11 functionalization (**14**), and a subsequent three-step construction of triketone **17**. Successful intramolecular aldol reaction should then produce **18**, and hence **1**, which possesses functional groups suitable for use as a handle for the introduction of the C11–C12 *anti*-Bredt double bond[9] as well as for arranging the C3 stereochemistry and further C-ring functionalization. The proposed route to the target compound **1** is retrosynthetically outlined in Scheme 1.

Results and Discussion

Elaboration of the BC Subunit

The synthetic plan began with the construction of the fragmentation precursor **6b** as a key synthetic intermediate, synthesized from the previously accessed **5**[2] by a Luche reduction (CeCl$_3$·7H$_2$O, NaBH$_4$, CH$_2$Cl$_2$/EtOH, –78 °C, 98 %) and subsequent acetonide formation (acetone, 2,2-DMP, *p*TsOH cat., 0 °C, 88 %), followed by a hydroxy-directed epoxidation under Sharpless conditions [VO(acac)$_2$ cat., *t*BuOOH in decane, PhH, reflux, 92 %][10] as reported earlier.[2] Acetate hydrolysis at C-9 (6 N NaOH, MeOH, 98 %) afforded the targeted **6b**. Mesylation (MsCl, pyridine, DMAP cat., 0 °C) of **6b** set the stage for the crucial B-ring formation through a Grob-type fragmentation.[11] When the mesylate was simply heated in *t*BuOH in the presence of *t*BuOK, a bicyclo[6.4.0]-system **7**, which corresponds to the taxoid BC subunit, was obtained in 82 % yield over two steps (Scheme 3). The geometry of the C9–C10 double bond is *cis* (*Z*) and not *trans* (*E*) as mistakenly represented in our earlier publications (see ref.[21]). Opening of the C1–C14 epoxide was easily carried out at room temperature, thanks to the carbonyl activation at C-2. Upon treatment of **7** with LiEt$_2$N in THF in the presence of HMPA, epoxide at C1–C14 opened smoothly (rt., 20 min, 98 %), and subsequent protection as its methyl ether (KOH, DMSO, MeI, room temp., 30 min, 96 %) then ensured the required intermediate **8b** for further elaboration.



Scheme 3. a) CeCl$_3$·7H$_2$O, NaBH$_4$, CH$_2$Cl$_2$/EtOH, –78 °C. b) Acetone, 2,2-DMP, cat. *p*TsOH, 0 °C. c) VO(acac)$_2$, *t*BuOOH in decane, PhH, reflux. d) 6 N NaOH, MeOH. e) MsCl, pyridine, DMAP cat., 0 °C. f) *t*BuOK/*t*BuOH, THF, 70 °C. g) LiEt$_2$N, THF, HMPA, room temp. h) KOH, DMSO, MeI, room temp.

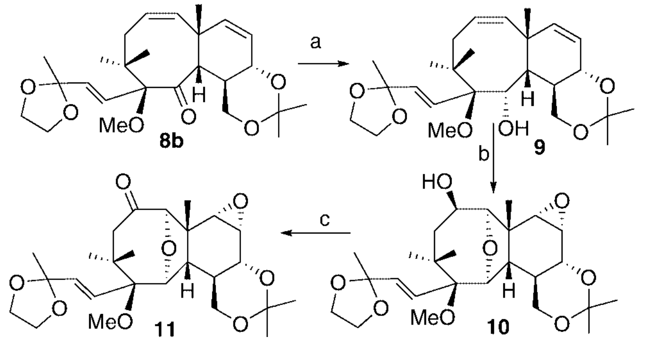
Key questions at this stage include the likelihood of achieving C11 functionalization and the nature of functional group transformations to be chosen en route to the targeted A-*seco* taxoid framework prior to final ring-closure (C11–C12). Introduction of the required functional group at C-11 proved difficult, since several possible routes to effect this transformation directly on the olefin remained unsuccessful. Complete recovery of starting material following allylic oxidation was routinely noted. Standard procedures reported by Corey (CrO$_3$/3,5-DMP, *t*BuOOH 70 % in H$_2$O, DCM),[12] Sharpless (SeO$_2$, *t*BuOOH, DCM, reflux),[13] Criegee [Pb(OAc)$_4$ in PhH],[14] Pearson [Cr(CO)$_6$, *t*BuOOH, MeCN, reflux],[15] and Kharash–Sosnovski

($PhCO_3tBu$, CuBr)[16] failed. Similarly, all attempts to induce migration of the double bond into the C10–C11 position under Barton's conditions ($RhCl_3$, EtOH, reflux)[17] proved ineffective. Various modifications of the approaches cited above, consisting mainly of temperature variations, solvent modifications, use of extra equivalents of the reagent, and extended reaction times, also met with failure. It should be pointed out, however, that the stability of **7** is noteworthy. Not only does it survive standard published conditions, but it can also be recovered intact after two days at reflux in the presence of the Sharpless system (SeO_2, *t*BuOOH).

Conformation in medium-sized rings strongly affects reactivity,[18] since the observed differences appear to arise primarily from conformational variations in ring substituents and the cyclooctenyl ring. Wender et al.,[1d] in their elegant synthesis of taxol, pointed out the crucial influence of the C1–C2 carbonate opening, which secured the correct alignment (C9–C=O/C8–H) for deprotonation and subsequent aldol cyclization. More recently, Paquette et al.[19] reported divergent regioselectivity in the base-promoted reactions of eight-membered α-ketols, recognizing the ability of a transannularly disposed double bond to provide conformational constraints and hence influence the reaction pathway.

Construction of the Oxa-Bridge

Since our attempts to functionalize the C11 position by direct allylic oxidation had not been rewarded with success, we opted for alteration of the central B-ring through the imposition of an oxa-bridge at C2–C9. Formation of this bridge involves transannular interaction between the C-2 hydroxy group and the C9–C10 epoxide formed by epoxidation of the corresponding olefin (Scheme 4). Paquette et al.[20] pointed out the ease with which transannular bonding occurs within medium-sized ring precursors of taxoid diterpene frameworks. In our previous studies we showed that transannular bonding arises with substantial facility within the eight-membered rings of A-*seco* taxoid frameworks synthesized by the aldol-annulation-fragmentation strategy.[21] Reduction of the C2-carbonyl ($LiAlH_4$, THF, reflux, 4 h, 68%) proceeded cleanly to yield **9** as a single diastereomer, albeit in modest yield. Furthermore, methyltrioxorhenium-catalyzed (MTO-catalyzed)[22] oxidation of **9**, by treatment with catalytic MTO and aqueous hydrogen peroxide as terminal oxidant in the presence of pyridine (the Sharpless modification[22e]) at room temperature for 12 h, took place to deliver **10** directly, through neighboring group participation by the α-hydroxy group at C2. Note that one cannot isolate the C9–C10 epoxide from **9**, since ring-closure to the fused tetrahydrofuran **10** is instantaneous and complete. The selection of MTO rather than standard *m*CPBA conditions (relatively acidic) was on the basis of the experimental ease of product recovery, the comparable cost, and the absence of byproducts. The alcohol **10**, resulting from transannular epoxide opening, was oxidized with Dess–Martin periodinane to give **11** (CH_2Cl_2, pyridine, room temp., 95%, Scheme 4).[23]



Scheme 4. a) LAH, THF, reflux. b) $MeReO_3$ cat., pyridine, H_2O_2, CH_2Cl_2. c) Dess–Martin periodinane, CH_2Cl_2, pyridine, room temp.

The C1, C8, and C15 configurations contribute thermodynamically to the preferred adoption of the ground state "carbonyl down" conformation by **8b**. This shows a pronounced tendency to minimize transannular nonbonded repulsions; as a consequence the *gem*-dimethyl group at C15 avoids proximity with the C8 angular methyl group. The X-ray structure (Figure 1) clearly shows that **8b** has a *cis* orientation between the C1–OMe and the C8 methyl group and a carbonyl down topology for the C2-carbonyl. Lithium aluminiumhydride reduction of this conformer, at reflux in THF, occurs from the more accessible convex face of the molecule, to afford **9**. The C-2β epimeric alcohol was not detected when the reduction was carried out in THF, even though its formation cannot be ruled out. Epoxide formation is assumed to take place on the sterically accessible convex face of the C9–C10 olefin, while insofar as the C6–C7 olefin is concerned, the C8 angular methyl group controls the facial selectivity, resulting in an α-epoxide. The low yield obtained after chromatography (64%) indicates that the unwanted diastereomer was degraded by a pathway unknown to us.

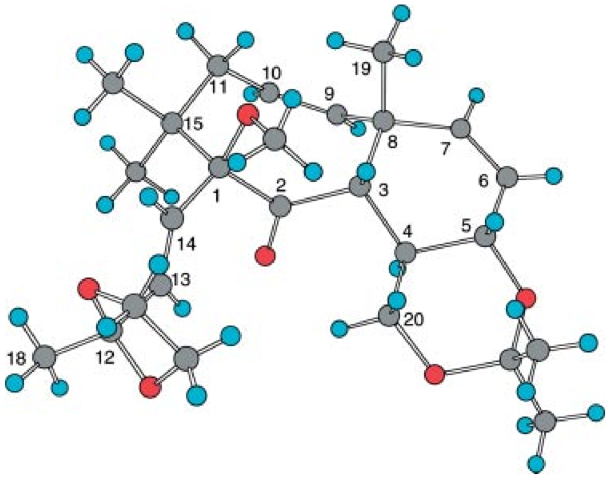
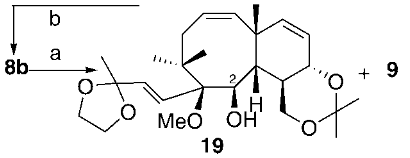


Figure 1. X-ray structure of **8b** (Chem. 3D output from X-ray coordinates).

The only transformation that failed to ensure total selectivity was the lithium aluminiumhydride reaction carried out in ether, in an attempt to increase the yield (Scheme 5, Figure 2), and this despite the very favorable disposition of the C2-carbonyl as pointed out above. Thus, lowering the reaction temperature by performing the reduction in a lower boiling solvent produced the only by-product **19** (21%), stereochemically speaking, of the entire synthetic scheme, along with a 65% yield of the desired **9**. Chromatographic separation was nevertheless avoided, simply by changing the solvent to THF. Presumably, the unwanted **19** was again formed, but was subsequently destroyed in the reaction medium, since its presence could not be detected.



Scheme 5. a) $LiAlH_4$, Et_2O, reflux. b) Dess–Martin periodinane, CH_2Cl_2, pyridine, room temp.

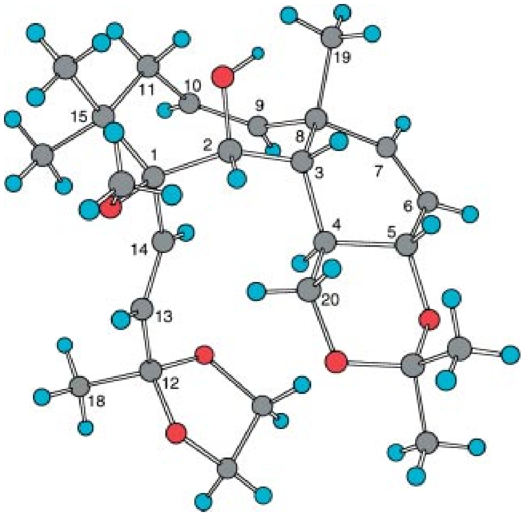
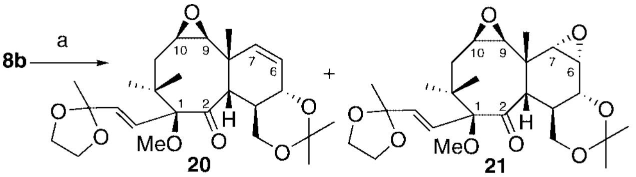


Figure 2. X-ray structure of **19** (Chem. 3D output from X-ray coordinates).

The same in situ epoxide opening could be observed when epoxidation was carried out before reduction of the C-2 carbonyl function. When **8b** was treated with catalytic amounts of methyltrioxorhenium ($MeReO_3$ cat., pyridine, H_2O_2, CH_2Cl_2, 8 h at 25 °C), the corresponding epoxide **20** was obtained as a single isomer in 67% isolated yield, together with the bis-epoxide **21** (16%), assigned as depicted in Scheme 6. MTO can be used either for single or for double epoxidation, depending on experimental conditions, longer reaction times resulting in the formation of bis-epoxide **21**. Unfortunately, **20** alone could not be synthesized, as **21** starts forming before the starting material is entirely converted into **20**. The rapid formation of **21** constitutes a drawback for the LAH-mediated in situ epoxide opening, as the C6–C7 epoxide is also reductively opened, albeit partially, thus complicating product recovery. The two diastereotopic faces of the C9–C10 olefin are significantly different and epoxidation proceeds exclusively from the less hindered convex face of the molecule. Total facial selectivity was observed for the epoxidation of the C6–C7 olefin as well, affording the α-epoxide exclusively.



Scheme 6. a) $MeReO_3$ cat., pyridine, H_2O_2, CH_2Cl_2.

In eight-membered and higher rings, sp^2 centers tend to be orientated perpendicular to the plane of the ring, through which important transannular nonbonded interactions are minimized.[18] This conformational arrangement, which favors transannular epoxide opening, may be seen on the X-ray structure of the derived epoxide. Thus, the carbonyl topology and the epoxide stereochemistry in **20** (Figure 3) and **21** (Figure 4) convincingly account for the observed ease of oxa-bridge formation.

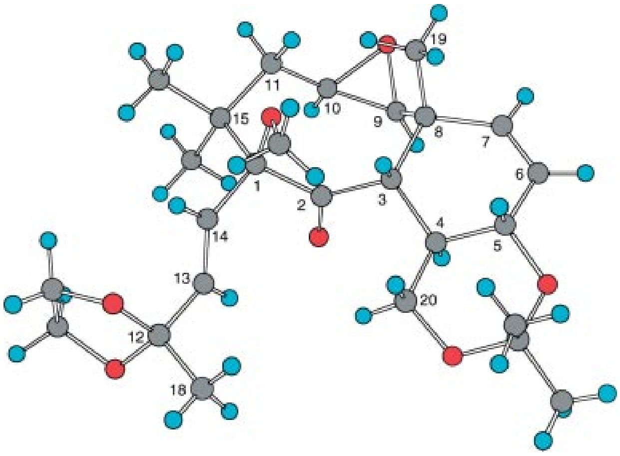


Figure 3. X-ray crystal structure of **20** (Chem. 3D output from X-ray coordinates).

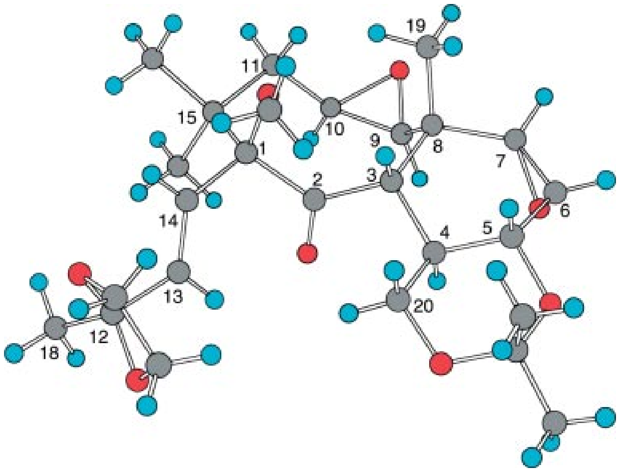


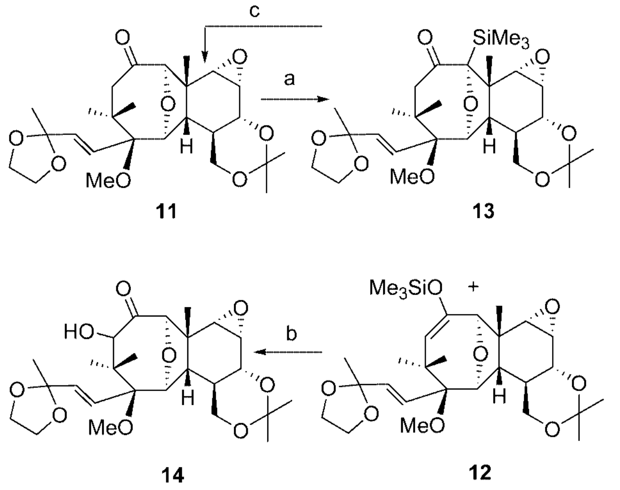
Figure 4. X-ray crystal structure of **21** (Chem. 3D output from X-ray coordinates).

The Final Functionalization and C–C Bond Construction

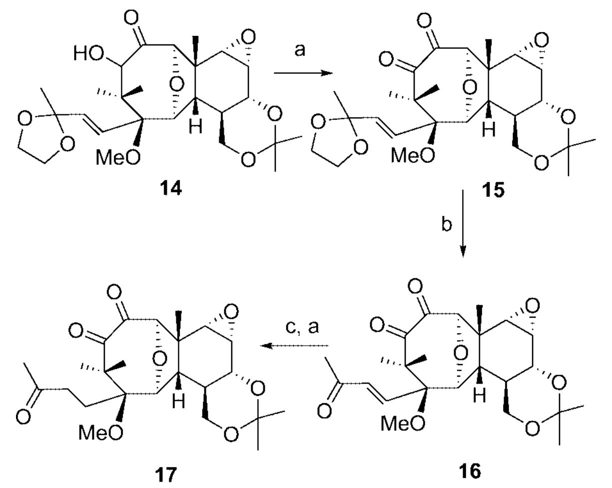
Having decided to reduce chromatographic separations to a minimum, we preferred to proceed as indicated in Scheme 4, by first reducing the C2 carbonyl and then performing the in situ oxa-bridge formation. With the pivotal intermediate **11** to hand, there remained the task of C11–C12 bonding en route to the intended target.

Two paths to the required ABC-intermediate **18** were considered: the TiCl$_4$-[24] or ZnCl$_2$-catalyzed[25] intramolecular Mukaiyama-type cross aldol reaction directly on the C13–C14 reduced analogue of **11** and a samarium(II) iodide-mediated aldol reaction through the more elaborated **17**. Efforts in the Mukaiyama aldol direction with use of the published procedures did not provide any useful advances. Attempts to force the reaction by varying experimental conditions met with no success. The unwillingness of the C13–C14 reduced analogue of **11** to undergo a Mukaiyama aldol reaction to provide the target compound forced us to try the second option for the ring-closure, which requires prior functionalization at the C11 carbon. Starting from **11**, the key substrate **14** was produced in two steps. Conditions typically employed for aldol reactions (LDA, TMSCl, THF, –70 °C) gave at best modest yields (69%) of the required silyl enol ether **12**, along with an equimolar amount of its C-silylated counterpart **13** (Scheme 7). With 28% of starting material recovered, the level of conversion was very high, the only problem being the recycling of the undesired C-silylation product. Such a C-silylation of a ketone enolate was originally reported by Winkler in his studies toward the total synthesis of taxane diterpenes and was attributed to the unusually congested environment at the central B-ring of the taxane nucleus.[26] The same author offered us the solution for efficient recycling of **13**. After some experimentation, it was found that this compound could be very efficiently recycled by use of a basic medium, hence considerably improving the yields. Thus, generation of a silyl enolether **12** by enolization at C10–C11 and a subsequent Rubottom hydroxylation (*m*CPBA, NaHCO$_3$, CH$_2$Cl$_2$, 0 °C, 20 min.), with recycling of undesired **13** (NaOH, THF, 0 °C, 100%), secured the α-hydroxy ketone **14** in 98% isolated yield, as shown in Scheme 7.

The final task in the construction of the ABC-taxoid diterpene **1** involves the appropriate functionalization of the C10–C11 segment to allow an aldol reaction, to provide the A-ring. A three-step procedure involving an oxidation (Dess–Martin periodinane, CH$_2$Cl$_2$, pyridine, room temp., 96%) to **15**, ketal deprotection (acetone, *p*TsOH cat., 3 h, then 4-Å molecular sieves, 96%)[27] and hydrogenation over Raney nickel (Ra-Ni, THF, 0 °C, 30 min) gave **17** contaminated with minor amounts of the overreduced starting material, which was recycled through Dess–Martin oxidation (69%, two steps, Scheme 8).



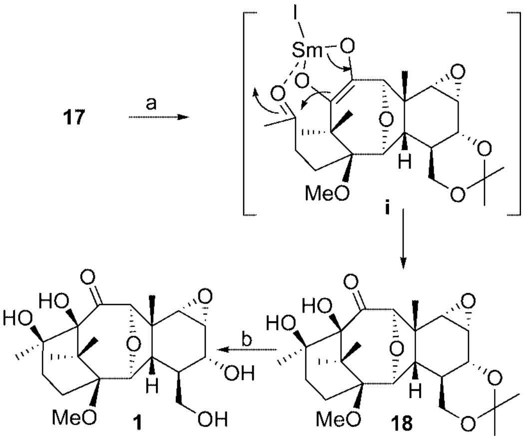
Scheme 7. a) LDA, TMSCl, THF, –70 °C. b) *m*CPBA, NaHCO$_3$, CH$_2$Cl$_2$, 0 °C, 20 min. c) 6% NaOH, THF, 0 °C, 1 h.



Scheme 8. a) Dess–Martin periodinane, CH$_2$Cl$_2$, pyridine, room temp. b) Acetone, *p*TsOH cat., 3 h, then 4-Å molecular sieves, 30 min. c) Raney-Ni, THF, 0 °C, 30 min.

Lastly, a samarium(II) iodide-mediated aldol reaction[28] successfully converted the A-secotaxane **17** into the target ABC tricyclic diterpene framework **1**. Some overreduced products were also formed, and the crude products were subjected to Dess–Martin oxidation to give the dihydroketone **18** in 74% overall yield along with recovery of **17** (7%). The intermediate in the reaction is considered to be the samarium enediolate **i** (Scheme 9), generated by a two-electron transfer from 2 equiv. of SmI$_2$ to triketone **17**.

The structures of **17** and **18** were initially assigned on the basis of a series of 1D NOEDIFF studies, the veracity of these assignments later being confirmed by single-crystal X-ray analysis of both (Figure 5 and Figure 6, respectively). The stereochemical outcome of the samarium iodide-mediated intramolecular aldol reaction can be mechanistically explained by assuming that the C11 configuration was set through the configuration of the β-methoxy group at C1. Exclusive cyclization from the α face of the A-*seco* taxoid system was observed. On the other hand, the relative configuration at C12 can be explained in terms of a chelated transient samarium enediolate **i** (Scheme 9). This could give rise to a *cis*-diol product with Me-18 occupying an equatorial position in the A-ring, thus avoiding 1,3-diaxial interactions with Me-17. Unusual $^5J_{\mathrm{H,C}}$ couplings, for which we



Scheme 9. a) SmI$_2$, THF, 0 °C, 30 min. b) 1 N HCl, *p*TsOH, THF, 1 h.

do not have any explanation, have been observed in **18** (between the Me-18 protons and quaternary carbon C1, as well as between the C1 methoxy protons and C11).

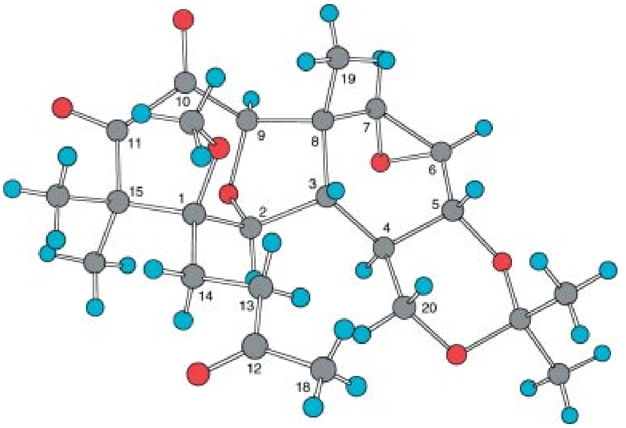


Figure 5. X-ray structure of **17** (Chem. 3D output from X-ray coordinates).

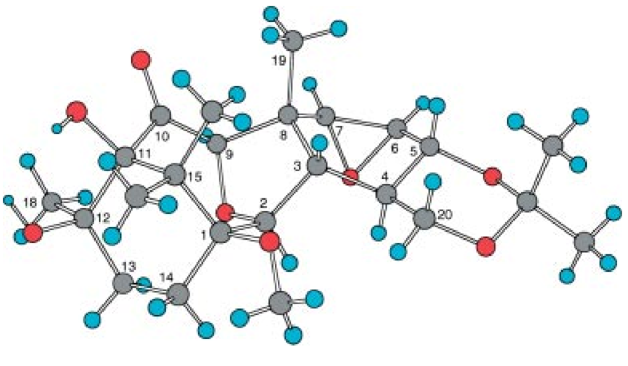


Figure 6. X-ray structure of **18** (Chem. 3D output from X-ray coordinates).

The expedient of leaving the C2–OH unprotected in **9** thus allowed the in situ transannular epoxide opening to give **10**, which in turn provided the desired C11 functionalization after oxidation, silyl-enol ether formation, and subsequent Rubottom hydroxylation. The highly elaborated polycyclic model **1** thus obtained, containing 11 stereogenic centers and capable of existing in 2048 stereomeric forms (1024 enantiomeric pairs of diastereomers), has been synthesized as a single isomer, from the readily available achiral aldol partners **2** and **3**. Within the limits of detection by high-field NMR spectroscopy, no stereoisomer was produced throughout this 25-step transformation. With the synthesis of **1**, a molecule possessing the carbon framework and the functionality suitable for the elaboration of the A-ring of the tricyclic taxoid diterpene skeleton we have reached an advanced step in taxoid construction. Among the tasks remaining are C3 epimerization and oxido-bridge opening.

Conclusion

In summary, the assembly of the taxoid ABC diterpene framework, oxa-bridged at C2–C9 and properly functionalized to serve as a possible precursor to taxanes, has been achieved in a highly stereoselective manner. Our synthetic strategy has been based on the simple diastereoselection offered by the enolate geometry and the feasibility of two efficient cyclizations, both mediated by SmI$_2$. The pivotal problem of the strategy was the C11 functionalization to secure formation of the A ring through the final C–C bonding operation.

The stereocontrolled synthesis of **1** once again demonstrates the importance of using appropriate stereocontrol elements in multi-step synthetic endeavors. The C2–C3 bond-forming operation offers spatial proximity of the reacting centers (C2β–OH and the adjacent olefin; compound **5**), but also imposes their strictly defined orientation (C2–C1O and C9α–OMs), thus ensuring success for the following steps. Readily synthesizable low-cost starting materials, and ease of product recovery, combined with high chemical yields and excellent stereocontrol, make this taxoid ABC-ring system potentially useful in the synthesis of taxoid analogs.

Experimental Section

General: Solvents and reagents used in this work were purified by standard literature techniques and stored under argon. Experiments requiring inert atmosphere were carried out under dry argon in a flame-dried glass system. Flash chromatography was run on silica gel (230–400 mesh) with the solvent mixture indicated. Thin layer chromatography was performed on commercial silica gel plates, developed by immersion in 5% phosphomolybdic acid in 95% ethanol. "Usual workup" means washing of the organic layer with brine, drying on anhydrous MgSO$_4$, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Melting points were uncorrected. IR spectra were recorded with an FT-IR instrument through NaCl cell windows. NMR spectra were run in CDCl$_3$ unless otherwise noted. Experimental evidence favoring the structures investigated came in the form of a comprehensive range of ^{1}H and ^{13}C NMR spectroscopic data (400–300–250 and 100–75–69.5 MHz, respectively, 1D and 2D experiments) and was corroborated by spatial proximity (n.O.e) studies, mainly by the 1D NOEDIFF technique.[29] ^{1}H (800 MHz) and ^{13}C NMR (200 MHz) experiments were carried out in a spectrometer equipped with triple resonance

H/C/N probeheads and a three-axis pulsed field gradient module. Gradients were used for the coherence transfer pathway selection in HMBC and HMQC experiments. In the latter, broadband decoupling was performed by use of adiabatic WURST-40 pulses. For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[30] ^{1}H chemical shifts are expressed in ppm downfield from TMS with use of the residual undeuterated solvent as internal standard ($CDCl_3$ ^{1}H, 7.27 ppm; C_6D_6 ^{1}H, 7.15). ^{13}C spectra were measured at 62.5 and 75 MHz and the chemical shifts are reported relative to the $CDCl_3$ or C_6D_6 triplets centered at $\delta = 77.0$ ppm and 128.0 ppm, respectively. Mass spectra acquired in the positive ion mode by electron spray ionization (ES^+) with a methanol mobile phase, are abbreviated as ESIMS (MeOH).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-229576–229579. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [Fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Sharpless Epoxidation. Preparation of Compound 6a: A mixture of the allylic alcohol (800 mg, 1.68 mmol) obtained in two steps from **5** as described earlier and $VO(acac)_2$ (6 mg, 0.023 mmol) in benzene (32 mL) was heated at reflux for 10 minutes under argon. Addition of *t*BuOOH in decane (5–6 M, 0.4 mL, 1.85 mmol) followed, and stirring was continued at this temperature for 15 min. After cooling, dilution with EtOAc, and washing with a saturated aqueous solution of $NaHCO_3$, workup as usual and chromatography on silica gel (heptane/EtOAc, 1:1) yielded **6a** (763 mg, 92%). m.p. 160 °C (heptane). ^{1}H NMR (300 MHz): $\delta = 0.88$ (s, 3 H), 1.16 (s, 3 H), 1.40 (s, 3 H), 1.43 (s, 4 H), 1.44 (s, 3 H), 1.50 (s, 3 H), 1.80 (m, 2 H), 2.04 (m, 1 H), 2.09 (s, 3 H), 2.10 (m, 2 H), 2.77 (m, 1 H), 3.14 (s, 1 H), 3.27 (dd, $J = 3.7$, 8.8 Hz, 1 H), 3.69 (t, $J = 11.0$ Hz, 1 H), 3.98 (m, 4 H), 4.10 (d, $J = 8.8$ Hz, 1 H), 4.16 (dd, $J = 3.6$, 11.1 Hz, 1 H), 5.09 (d, $J = 7.8$ Hz, 1 H), 5.56 (dd, $J = 2.3$, 10.2 Hz, 1 H), 5.63 (d, $J = 10.2$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz): $\delta = 19.0$, 20.8, 24.3, 25.8, 27.4, 29.7, 32.0, 37.1, 37.6, 38.3, 41.1, 48.5, 54.0, 55.4, 57.5, 64.6, 64.7, 65.6, 70.0, 72.8, 81.7, 88.2, 98.3, 109.3, 126.6, 133.1, 170.5 ppm. IR (film): $\tilde{\nu} = 3483$, 2978, 1730, 1378, 1244, 1044, 741 cm^{-1}. ESIMS (MeOH): 515.4 $[M + Na]^+$ (100). Analysis: calcd. for $C_{27}H_{40}O_8$ (492.60): C 65.83, H 8.18; found C 65.56, H 8.19.

Hydrolysis of the C-9 Acetate. Preparation of Compound 6b: Sodium hydroxide (36 mmol, 6 mL of a 6 N solution) was added dropwise to a stirred solution of **6a** (914 mg, 1.85 mmol) in methanol (36 mL) at 0 °C. After 1 h, the mixture was allowed to warm to room temperature and was then stirred for an additional 1 h. Methanol was evaporated under reduced pressure, and the residue was taken up in ethyl acetate. The solution was washed with water and saturated aqueous $NaHCO_3$ and worked up as usual. The residue obtained was purified on SiO_2 gel (heptane/EtOAc, 1:1) to give pure **6b** (817 mg, 98%). m.p. 71 °C (heptane). ^{1}H NMR (300 MHz): $\delta = 0.90$ (s, 3 H), 1.16 (s, 3 H), 1.32 (s, 3 H), 1.41 (s, 3 H), 1.44 (s, 3 H), 1.49 (s, 3 H), 156 (dd, $J = 8.8$, 13.6 Hz, 1 H), 1.73 (t, $J = 12.9$ Hz, 1 H), 1.78 (d, $J = 13.3$ Hz, 1 H), 2.03 (m, 4 H), 2.67 (m, 1 H), 3.13 (s, 1 H), 3.26 (dd, $J = 4.1$, 8.6 Hz, 1 H), 3.68 (t, $J = 11.0$ Hz, 1 H), 3.98 (m, 4 H), 4.13 (m, 3 H), 5.75 (d, $J = 10.4$ Hz, 1 H), 5.82 (dd, $J = 2.2$, 10.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): $\delta = 19.1$, 24.3, 25.8, 27.5, 29.8, 32.0, 36.9, 37.3, 38.5, 41.5, 49.2, 54.2, 57.5, 57.4, 64.7, 64.8, 65.7, 70.0, 73.2, 80.3, 87.7, 98.4, 109.4, 128.7, 133.0 ppm. IR (film): $\tilde{\nu} = 3479$, 2963, 1461, 1381, 1199, 1110, 1045, 733 cm^{-1}. ESIMS (MeOH): 473.4 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{25}H_{38}O_7Na$ m/z 473.2515; found 473.2494.

Mesylation/Grob Fragmentation. Preparation of Compound 7: Methanesulfonyl chloride (MsCl, 1.9 mL, 25 mmol) was added at 0 °C to a stirred solution of **6b** (862 mg, 1.9 mmol) in pyridine (13 mL), in the presence of DMAP as catalyst (a few crystals), and the mixture was stirred for 1 h at this temperature. The reaction was quenched with a saturated aqueous solution of sodium hydrogen carbonate, and the mixture was extracted with dichloromethane. The combined extracts were washed with HCl (1 N), sodium hydrogen carbonate, and brine, and were then dried over magnesium sulfate and concentrated under reduced pressure to give the required mesylate **6c** (1025 mg) as a crude material that was taken into the next step without purification. An analytical sample was purified by flash chromatography (heptane/EtOAc, 1:1) on SiO_2 for characterization. **6c**: M.p. 146 °C (dec, heptane). ^{1}H NMR (300 MHz): $\delta = 0.91$ (s, 3 H), 1.17 (s, 3 H), 1.42 (s, 6 H,), 1.44 (s, 3 H), 1.49 (s, 3 H), 1.62 (dd, $J = 13.9$, 8.6, 1 H), 1.81 (d, $J = 13.6$, 1 H), 1.83 (t, $J = 13.0$, 1 H), 2.02 (m, 3 H), 2.82 (m, 1 H), 3.03 (s, 3 H), 3.18 (s, 1 H), 3.28 (dd, $J = 9.7$, 2.9, 1 H), 3.69 (t, $J = 11.0$, 1 H), 3.98 (m, 4 H), 4.11 (d, $J = 6.9$, 1 H), 4.15 (dd, $J = 11.1$, 4.2, 1 H), 4.99 (d, $J = 7.8$, 1 H), 5.69 (d, $J = 10.4$, 1 H), 5.75 (dd, $J = 10.2$, 2.2, 1 H) ppm. ^{13}C NMR (75 MHz): $\delta = 19.1$, 24.3, 25.8, 27.5, 29.8, 31.9, 37.2, 37.9, 38.0, 38.4, 41.2, 48.4, 53.7, 56.2, 57.6, 64.7, 64.8, 65.5, 69.7, 72.8, 87.8, 88.0, 98.5, 109.3, 127.5, 132.3 ppm. IR (film): $\tilde{\nu} = 3482$, 2987, 1463, 1371, 1175, 908, 733 cm^{-1}.

The crude mesylate was dissolved in THF (14 mL), and *t*BuOK (1 M in *t*BuOH, 6.7 mL, 6.7 mmol) was added at room temperature. The temperature was then raised to 70 °C (bath temperature) and the reaction mixture was stirred for 45 min. After cooling and dilution with ether, water was added. Extraction with EtOAc, followed by usual workup and rapid filtration through SiO_2 (heptane/EtOAc, 2:1 to 1:1), gave pure **7** in 82% isolated yield for two steps. **7**: M.p. 136 °C (heptane). ^{1}H NMR (300 MHz): $\delta = 0.86$ (s, 3 H), 1.24 (s, 3 H), 1.28 (dd, $J = 7.9$, 14.7 Hz, 1 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.70 (m, 2 H), 1.76 (s, 3 H), 2.09 (m, 1 H), 2.87 (dd, $J = 8.4$, 13.1 Hz, 1 H), 2.98 (d, $J = 12.3$ Hz, 1 H), 3.23 (dd, $J = 3.2$, 7.9 Hz, 1 H), 3.33 (t, $J = 10.7$ Hz, 1 H), 3.96 (m, 5 H), 4.19 (d, $J = 9.9$ Hz, 1 H), 5.57 (m, 4 H) ppm. ^{13}C NMR (75 MHz): $\delta = 19.2$, 24.3, 24.4, 24.9, 27.8, 29.8, 37.8, 38.0, 38.6 (2 C), 40.0, 55.2, 56.1, 64.2, 64.7, 64.8, 68.6, 69.9, 98.6, 108.5, 124.6, 129.1, 137.9, 138.2, 207.0 ppm. IR (film): $\tilde{\nu} = 2988$, 1702, 1460, 1382, 1269, 1199, 1047, 740 cm^{-1}. ESIMS (MeOH): 455.2 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{25}H_{36}O_6Na$ m/z 455.2410; found 455.2415.

C1–C14 Epoxide Opening. Preparation of Compound 8a: HMPA (2.13 mL, 12.2 mmol) was added to a solution of $LiNEt_2$ (prepared at 0 °C from 10.3 mmol of Et_2NH and 8.5 mmol of *n*BuLi, 1.6 M in hexanes) in dry THF (10 mL), and the reaction mixture was allowed to reach room temperature. A solution of **7** (365 mg, 0.843 mmol) in dry THF (8 mL) was then added, and stirring was continued for 20 min at room temperature, under argon. After quenching with saturated aqueous ammonium chloride and dilution with ether, the aqueous phase was extracted with EtOAc. Following usual workup, the residue was filtered through SiO_2 (heptane/EtOAc, 2:1) to give **8a** (357 mg, 98%). m.p. 222 °C (heptane). ^{1}H NMR (300 MHz): $\delta = 0.88$ (s, 3 H), 1.08 (s, 3 H), 1.40 (s, 3 H), 1.45 (s, 3 H), 1.47 (s, 3 H), 1.56 (s, 3 H), 1.61 (dd, $J = 8.0$, 13.8 Hz, 1 H), 2.01 (m, 2 H), 2.98 (dd, $J = 10.7$, 13.7 Hz, 1 H), 3.43 (m, 2 H), 3.65 (d, $J = 12.1$ Hz, 1 H), 3.80 (m, 2 H), 3.95 (m, 2 H), 4.21 (d, $J = 10.2$ Hz, 1 H), 5.41 (td, $J = 7.9$, 10.3 Hz, 1 H), 5.53 (d, $J = 15.9$ Hz, 1 H), 5.62 (d, $J = 10.2$ Hz, 1 H), 5.63 (d, $J =$

9.9 Hz, 1 H), 5.70 (d, J = 10.6 Hz, 1 H), 6.26 (d, J = 15.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 19.1, 22.2, 24.6, 25.3, 29.7, 30.2, 36.0, 39.6, 41.1, 41.4, 53.0, 64.3, 64.5, 64.6, 67.9, 84.3, 98.5, 107.2, 127.4, 128.0, 129.8, 132.7, 138.7, 140.6, 211.4 ppm. IR (film): $\tilde{\nu}$ = 3477, 2991, 1687, 1367, 1267, 1198, 1037, 867 cm^{-1}. ESIMS (MeOH): 455.2 $[M + Na]^+$ (100). Analysis: calcd. for $C_{25}H_{36}O_6$ (432.55): C 69.42, H 8.39; found C 69.63, H 8.63.

Protection of the C-1 Hydroxy Group as Its Methyl Ether. Preparation of Compound 8b: Freshly powdered KOH (1.29 g, 23.1 mmol) was added to DMSO (14 mL) and the mixture was stirred for 1 h at room temperature. A solution of **8a** (665 mg, 1.54 mmol) in DMSO (20 mL) was then added, followed after 2 minutes by an excess of MeI (26 mL, distilled and filtered through basic alumina, under argon, just before use). The reaction mixture was stirred for 30 min. Dilution with CH_2Cl_2, and usual workup, followed by silica gel chromatography (heptane/EtOAc, 3:1), afforded the title compound **8b** (659 mg, 96%). m.p. 106 °C (heptane). ^{1}H NMR (800 MHz): δ = 0.91 (s, 3 H), 1.00 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 6 H), 1.54 (dd, J = 8.4, 14.1 Hz, 1 H), 1.69 (s, 3 H), 2.20 (qd, J = 3.0, 11.0 Hz, 1 H), 3.13 (d, J = 11.0 Hz, 1 H), 3.16 (d, J = 12.4 Hz, 1 H), 3.39 (s, 3 H), 3.46 (t, J = 10.8 Hz, 1 H), 3.57 (dd, J = 3.1, 10.6 Hz, 1 H), 3.83 (m, 2 H), 3.97 (m, 2 H), 4.20 (d, J = 10.0 Hz, 1 H), 5.40 (q, J = 9.8 Hz, 1 H), 5.49 (d, J = 11.9 Hz, 1 H), 5.59 (d, J = 10.0 Hz, 1 H), 5.63 (d, J = 10.0 Hz, 1 H), 5.70 (d, J = 16.2 Hz, 1 H), 5.81 (d, J = 16.2 Hz, 1 H) ppm. ^{13}C NMR (200 MHz): δ = 19.0, 22.1, 25.2, 26.1, 29.3, 29.7, 35.9, 39.7, 40.5, 42.3, 53.5, 56.5, 64.4, 64.6 (2 C), 68.3, 90.3, 98.5, 107.2, 125.6, 126.3, 129.0, 135.3, 138.8 (2 C), 212.2 ppm. IR (film): $\tilde{\nu}$ = 2989, 1702, 1473, 1371, 1268, 1198, 1041, 866 cm^{-1}. ESIMS (MeOH): 469.2 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{26}H_{38}O_6Na$ m/z 469.2566; found 469.2560. Analysis: calcd. for $C_{26}H_{38}O_6$ (446.58): C 69.93, H 8.58; found C 69.77, H 8.53.

Reduction of the C-2 Carbonyl. Preparation of Compound 9: $LiAlH_4$ (76 mg, 2 mmol) was added, under argon atmosphere, to an ice-cold, stirred solution of **8b** (110 mg, 0.25 mmol) in dry THF (8 mL). The mixture was stirred at reflux for 4 h, cooled to 0 °C, and diluted with diethyl ether, and a small amount of water, aqueous NaOH (6 N), and water again were added successively (for each 1 g of $LiAlH_4$, 1 mL of water, 1 mL of 6 N NaOH and 3 mL more water were added), and stirring was continued at room temperature for 45 minutes. Rapid filtration through SiO_2 (eluent: EtOAc) and removal of solvent gave a residue, which was purified by silica gel chromatography (heptane/EtOAc, 2:1) to yield **9** (72 mg, 64%). m.p. 76 °C (heptane). ^{1}H NMR (300 MHz): δ = 0.96 (s, 3 H), 1.04 (s, 3 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 1.49 (s, 3 H), 1.59 (dd, J = 7.7, 13.6 Hz, 1 H), 1.79 (qd, J = 4.0, 10.6 Hz, 1 H), 2.39 (d, J = 9.5 Hz, 1 H), 2.60 (d, J = 12.7 Hz, 1 H), 3.01 (dd, J = 11.1, 13.1 Hz, 1 H), 3.24 (s, 3 H), 3.71 (t, J = 11.2 Hz, 1 H), 3.90 (m, 6 H), 4.32 (d, J = 10.1 Hz, 1 H), 5.68 (m, 3 H), 5.87 (d, J = 16.3 Hz, 1 H), 5.96 (d, J = 11.3 Hz, 1 H), 6.06 (d, J = 16.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 19.0, 24.9, 25.2, 29.2, 29.8 (2 C), 36.2, 39.0, 45.4, 45.5, 48.5, 53.0, 64.5 (2 C), 65.4, 68.8, 80.2, 83.1, 98.3, 107.6, 127.9, 131.6, 131.8, 133.5, 139.6, 141.2 ppm. IR (film): $\tilde{\nu}$ = 3538, 2987, 1458, 1370, 1268, 1198, 1042, 867 cm^{-1}. ESIMS (MeOH): 471.2 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{26}H_{40}O_6Na$ m/z 471.2723; found 471.2717.

Transannular Epoxide Opening. Preparation of Compound 10: MTO (0.8 mg, 0.003 mmol) was added at room temperature to a stirred solution of **9** (122 mg, 0.27 mmol) and pyridine (8 µL, 0.10 mmol) in CH_2Cl_2 (2 mL), followed by aqueous H_2O_2 (30%, 0.03 mL, 0.45 mmol). After 12 h the solution was diluted with CH_2Cl_2, washed with a solution of $Na_2S_2O_3$, and, following usual workup, purified through a short column of silica gel (heptane/EtOAc, 1:1) to yield **10** (119 mg, 91%). **10**: M.p. 102 °C (heptane). ^{1}H NMR (800 MHz): δ = 0.95 (s, 3 H), 1.02 (s, 3 H), 1.31 (dd, J = 2.5, 14.2 Hz, 1 H), 1.39 (s, 3 H), 1.44 (s, 3 H), 1.49 (s, 6 H), 1.68 (s, 1 H), 2.10 (dddd, J = 4.5, 7.9, 11.2, 11.5 Hz, 1 H), 2.27 (m, 2 H), 3.14 (d, J = 4.8 Hz, 1 H), 3.18 (d, J = 4.8 Hz, 1 H), 3.22 (s, 3 H), 3.60 (t, J = 11.4 Hz, 1 H), 3.77 (dd, J = 4.5, 11.3 Hz, 1 H), 3.86 (m, 2 H), 3.98 (m, 2 H), 4.16 (ddd, J = 3.7, 4.9, 13.8 Hz, 1 H), 4.27 (d, J = 10.8 Hz, 1 H), 4.28 (d, J = 4.1 Hz, 1 H), 4.39 (d, J = 4.6 Hz, 1 H), 5.79 (d, J = 16.2 Hz, 1 H), 6.11 (d, J = 16.2 Hz, 1 H) ppm. Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H11, OMe, H14; {Me17}: Me-16 (NOE gem), H10, H14; {Me19}: H3, H5, H7; {Meβ-ax of acetonide}: H5, H20β-ax; {H2}: H4, H13; {H7}: H9. ^{13}C NMR (200 MHz): δ = 19.0, 19.6, 25.4, 27.8, 28.7, 29.7, 40.3, 40.8, 44.3, 45.5, 46.1, 51.9, 53.4, 61.6, 64.6, 64.7, 65.4, 69.8, 70.3, 81.5, 88.2, 94.3, 99.2, 107.6, 130.2, 133.2 ppm. IR (film): $\tilde{\nu}$ = 3479, 2940, 1463, 1383, 1370, 1197 cm^{-1}. ESIMS (MeOH): 503.3 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{26}H_{40}O_8Na$ m/z 503.2621; found 503.2631.

Periodinane Oxidation of 10: Periodinane (503 mg, 1.186 mmol) was added to a solution of **10** (19.0 mg, 0.395 mmol) in dry dichloromethane (15 mL) and pyridine (0.32 mL, 3.95 mmol), and stirring was continued at room temperature for 1 h. The reaction mixture was then diluted with dichloromethane, quenched with a saturated aqueous solution of sodium hydrogen carbonate, and worked up as usual. The product obtained was purified by chromatography (heptane/EtOAc, 2:1) to afford **11** (179.5 mg, 95%): m.p. 91 °C (heptane). ^{1}H NMR (800 MHz, C_6D_6, 318 K): δ = 0.95 (s, 3 H), 0.99 (s, 3 H), 1.06 (s, 3 H), 1.30 (s, 3 H), 1.48 (s, 3 H), 1.52 (s, 3 H), 1.92 (dd, J = 3.8, 8.4 Hz, 1 H), 2.01 (d, J = 13.4 Hz, 1 H), 2.35 (dddd, J = 4.5, 8.4, 10.4, 11.3 Hz, 1 H), 2.67 (d, J = 4.7 Hz, 1 H), 2.92 (d, J = 13.4 Hz, 1 H), 2.93 (s, 3 H), 2.96 (d, J = 4.7 Hz, 1 H), 3.36 (t, J = 11.4 Hz, 1 H), 3.50 (m, 2 H), 3.58 (m, 2 H), 3.83 (dd, J = 4.5, 11.3 Hz, 1 H), 3.95 (d, J = 10.6 Hz, 1 H), 4.06 (s, 1 H), 4.38 (d, J = 3.4 Hz, 1 H), 6.07 (d, J = 16.1 Hz, 1 H), 6.12 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (200 MHz, C_6D_6): δ = 19.0, 19.1, 25.7, 30.1, 30.2 (2 C), 39.7, 41.1, 44.3, 48.4, 51.9, 52.7, 53.9, 61.2, 64.7 (2 C), 65.6, 70.2, 82.5, 90.3, 94.6, 99.4, 107.8, 130.5, 134.9, 212.1 ppm. IR (film): $\tilde{\nu}$ = 2988, 1705, 1456, 1370, 1264, 1197, 1080, 869, 736 cm^{-1}. ESIMS (MeOH): 501.3 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{26}H_{38}O_8Na$ m/z 501.2464; found 501.2420. Analysis: calcd. for $C_{26}H_{38}O_8$ (478.58): C 65.25, H 8.00; found C 65.38, H 7.98.

C-11 Hydroxylation and C-9 Silylation: A solution of *n*-butyllithium in hexanes (1.6 M, 0.549 mL, 0.878 mmol) was added at –70 °C to a solution of diisopropylamine (0.146 mL, 1.045 mmol) in THF (4 mL). The mixture was stirred at –70 °C for 1 h, and chlorotrimethylsilane (0.318 mL, 272.5 mmol) was then added, followed 5 min later by dropwise addition of **11** (200 mg, 0.418 mmol) in THF (1 mL). The mixture was stirred at the same temperature for 30 minutes and then diluted with pentane (15 mL). After rapid filtration of the salts, the solution was concentrated under vacuum and the products were separated from the starting material by flash chromatography (SiO_2, heptane/EtOAc, 1:1).

The less polar product was a 1:1 mixture of **12** (160 mg, 69%) and **13** and the more polar product was recovered staring material **11** (60 mg, 28%).

$NaHCO_3$ (88 mg, 1.01 mmol) and *m*CPBA (33 mg, 0.189 mmol) were as added at 0 °C to the mixture of **12** and **13** (160 mg, 0.29 mmol) in dichloromethane (5 mL). The mixture was stirred for 20 minutes at 0 °C, diluted with dichloromethane, washed successively with Na_2SO_3 solution (5%) and saturated $NaHCO_3$ solution, and worked up as usual. Column chromatography (SiO_2, heptane/EtOAc, 1:1) gave **13** (78 mg) and **14** (70 mg). **13**: M.p. 86 °C (heptane). ^{1}H NMR (800 MHz, C_6D_6): δ = 0.26 (s, 9 H), 0.87 (s, 3 H), 1.14 (s, 3 H), 1.20 (s, 3 H), 1.31 (s, 3 H), 1.56 (s, 3 H), 1.56 (s, 3 H), 1.85 (d, J = 11.9 Hz, 1 H), 1.99 (t, J = 6.3 Hz, 1 H), 2.35 (m, 1 H), 2.89 (s, 3 H), 3.00 (d, J = 4.9 Hz, 1 H), 3.03 (d, J = 4.9 Hz, 1 H), 3.19 (d, J = 11.9 Hz, 1 H), 3.38 (t, J = 11.4 Hz, 1 H), 3.52 (m, 2 H), 3.59 (m, 2 H), 3.99 (dd, J = 4.3, 11.3 Hz, 1 H), 4.06 (d, J = 10.7 Hz, 1 H), 4.48 (d, J = 5.2 Hz, 1 H), 6.17 (d, J = 16.3 Hz, 1 H), 6.31 (d, J = 16.3 Hz, 1 H) ppm. ^{13}C NMR (200 MHz, C_6D_6): δ = –2.3 (3 C), 19.3, 20.6, 24.3, 25.7, 30.9, 31.1, 40.5, 41.0, 46.6, 51.8, 52.3, 52.7, 54.3, 59.0, 64.6, 64.7, 65.7, 70.2, 81.6, 93.7, 95.5, 99.5, 107.9, 132.5, 134.8, 217.5 ppm. IR (film): $\tilde{\nu}$ = 2989, 1682, 1385, 1370, 1265, 1251, 1197, 1078, 847 cm^{-1}. HRESIMS: calcd. for $C_{29}H_{46}O_8NaSi$ m/z 573.2860; found 573.2856. Analysis: calcd. for $C_{29}H_{46}O_8Si$ (550.76): C 63.24, H 8.42; found C 63.03, H 8.43. **14**: M.p. 208 °C (heptane). ^{1}H NMR (800 MHz): δ = 0.75 (s, 3 H), 1.06 (s, 3 H), 1.16 (s, 3 H), 1.45 (s, 3 H), 1.49 (s, 3 H), 1.51 (s, 3 H), 1.59 (s, 1 H), 2.20 (m, 1 H), 2.27 (m, 1 H), 3.17 (d, J = 4.8 Hz, 1 H), 3.22 (d, J = 4.8 Hz, 1 H), 3.33 (s, 3 H), 3.61 (t, J = 11.5 Hz, 1 H), 3.80 (dd, J = 4.6, 11.4 Hz, 1 H), 3.88 (m, 2 H), 4.01 (m, 2 H), 4.21 (d, J = 10.8 Hz, 1 H), 4.32 (s, 1 H), 4.52 (s, 1 H), 4.69 (d, J = 3.85 Hz, 1 H), 5.92 (d, J = 16.2 Hz, 1 H), 6.29 (d, J = 16.2 Hz, 1 H) ppm. ^{13}C NMR (200 MHz): δ = 18.8, 18.9, 20.7, 22.2, 25.4, 29.6, 40.2, 43.9, 45.6, 47.2, 51.6, 53.9, 59.9, 64.6, 64.7, 65.0, 69.3, 78.7, 80.1, 91.6, 95.4, 99.3, 107.4, 128.4, 135.1, 209.3 ppm. IR (film): $\tilde{\nu}$ = 3463, 2988, 1702, 1465, 1383, 1371, 1198, 1090 cm^{-1}. HRESIMS: calcd. for $C_{26}H_{38}O_9Na$ m/z 517.2414; found 517.2437.

Preparation of α-Diketone 15: This compound was prepared by the same procedure as used for **11**. Thus, from **14** (40 mg, 0.081 mmol), Dess–Martin oxidation afforded **15** (37 mg, 93%) as a white solid. **15**: M.p. 258 °C (heptane). ^{1}H NMR (800 MHz): δ = 1.22 (s, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.44 (s, 3 H), 1.49 (s, 3 H), 1.50 (s, 3 H), 1.90 (d, J = 11.7 Hz, 1 H), 2.19 (qd, J = 4.4, 11.2 Hz, 1 H), 3.25 (d, J = 4.5 Hz, 1 H), 3.29 (d, J = 4.5 Hz, 1 H), 3.32 (s, 3 H), 3.42 (t, J = 11.3 Hz, 1 H), 3.61 (dd, J = 4.5, 11.4 Hz, 1 H), 3.87 (m, 2 H), 4.03 (m, 2 H), 4.05 (d, J = 10.6 Hz, 1 H), 4.11 (s, 1 H), 4.43 (s, 1 H), 5.68 (d, J = 16.1 Hz, 1 H), 5.85 (d, J = 16.3 Hz, 1 H) ppm. ^{13}C NMR (200 MHz): δ = 18.8, 19.1, 23.4, 24.0, 25.4, 29.6, 34.9, 46.6, 48.5, 53.1, 53.8, 55.7, 61.5, 64.8 (2 C), 65.0, 68.9, 84.7, 86.4, 91.3, 99.2, 107.0, 123.1, 135.9, 200.5, 211.7 ppm. IR (film): $\tilde{\nu}$ = 2989, 1739, 1702, 1374, 1198, 1085, 1038 cm^{-1}. ESIMS (MeOH + CH_2Cl_2): 515.2 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{26}H_{36}O_9Na$ m/z 515.2257; found 515.2233.

C-12 Deketalization. Preparation of Compound 16: pTsOH (1.2 mg, 0.006 mmol) was added to a solution of **15** (30 mg, 0.061 mmol) in acetone (3 mL). After 3 h, 4-Å molecular sieves were added and the mixture was stirred for 30 minutes. The solution was then filtered through basic alumina with ethyl acetate as eluent to give **16** (26 mg, 96%). A sample was rapidly purified by flash chromatography (heptane/EtOAc, 1:2) for analysis. **16**: M.p. 249 °C (heptane). ^{1}H NMR (800 MHz): δ = 1.28 (s, 3 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.48 (s, 3 H), 1.93 (d, J = 11.6 Hz, 1 H), 2.16 (qd, J = 4.5, 11.2 Hz, 1 H), 2.34 (s, 3 H), 3.26 (d, J = 4.6 Hz, 1 H), 3.29 (d, J = 4.6 Hz, 1 H), 3.36 (s, 3 H), 3.37 (t, J = 11.2 Hz, 1 H), 3.44 (dd, J = 4.6, 11.2 Hz, 1 H), 4.05 (d, J = 10.7 Hz, 1 H), 4.11 (s, 1 H), 4.47 (s, 1 H), 6.23 (d, J = 16.4 Hz, 1 H), 6.73 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (200 MHz): δ = 18.8, 19.0, 23.7, 24.4, 28.1, 29.5, 34.9, 46.2, 48.6, 53.0, 54.4, 55.3, 61.4, 64.7, 68.8, 85.4, 86.5, 91.2, 99.4, 132.6, 138.5, 195.9, 200.1, 210.5 ppm. IR (film): $\tilde{\nu}$ = 1738, 1703, 1678 cm^{-1}. ESIMS (MeOH): 471.2 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{24}H_{32}O_8Na$ m/z 471.1995; found 471.1992.

Reduction of the C13–C14 Double Bond. Preparation of Compound 17: An aqueous suspension of Raney-Ni (0.5 g, excess) was added at 0 °C to a stirred solution of **16** (46 mg, 0.103 mmol) in THF (4 mL) and the mixture was further stirred for 30 minutes, was then diluted with ethyl acetate and filtered through celite, and the solvents were evaporated. The crude product was diluted with dichloromethane (2 mL), and pyridine (0.08 mL, 1 mmol) and Dess–Martin periodinane (131 mg, 0.309 mmol) were then added. After 1 h, the reaction mixture was then diluted with dichloromethane, quenched with a saturated aqueous solution of sodium hydrogen carbonate, and worked up as usual. The residue obtained was purified by chromatography (heptane/EtOAc, 1:1) and afforded **17** (32 mg, 69% for two steps): m.p. 259–261 °C (heptane). ^{1}H NMR (800 MHz): δ = 1.28 (s, 3 H), 1.36 (s, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.51 (s, 3 H), 1.86 (d, J = 11.1 Hz, 1 H), 1.95 (ddd, J = 3.4, 11.7, 15.1 Hz, 1 H), 2.04 (ddd, J = 5.9, 11.3, 15.1, 1 H), 2.21 (s, 3 H), 2.24 (qd, J = 4.7, 11.0 Hz, 1 H), 2.43 (ddd, J = 3.4, 11.3, 17.9 Hz, 1 H), 2.62 (ddd, J = 5.9, 11.7, 17.9 Hz, 1 H), 3.24 (d, J = 4.6 Hz, 1 H), 3.29 (d, J = 4.7 Hz, 1 H), 3.36 (s, 3 H), 3.61 (t, J = 11.1 Hz, 1 H), 3.65 (dd, J = 4.8, 11.1 Hz, 1 H), 4.12 (d, J = 11.1 Hz, 1 H), 4.13 (s, 1 H), 4.42 (s, 1 H) ppm. ^{13}C NMR (200 MHz): δ = 18.8, 19.2, 22.7, 23.3, 24.5, 29.6, 30.3, 36.2, 38.1, 47.51, 48.4, 52.3, 53.0, 56.4, 61.4, 64.9, 68.9, 85.2, 86.9, 91.2, 99.3, 201.2, 205.7, 211.2 ppm. IR (film): $\tilde{\nu}$ = 2991, 1737, 1710, 1704, 1384, 1372, 1198, 1170, 1078, 733 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): 473.1 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{24}H_{34}O_8Na$ m/z 473.2151; found 473.2118.

The Final C–C Bonding. A-Ring Formation Affording 18: Triketone **17** (35 mg, 0.078 mmol), dissolved in THF (10 mL), was added at 0 °C, under argon, to a solution of samarium(II) iodide (3 mL of 0.1 M solution in THF, 0.3 mmol). After the mixture had been stirred for 1 h, hydrolysis with HCl (0.1 N) at –78 °C, followed by ethyl acetate extraction and washing with saturated NaCl solution, gave **18** (20 mg, 57%). More polar products were oxidized by the same procedure as used for **11**, finally to afford a 74% overall yield of **15** as a white solid with recovered **17** (2.5 mg, 7%). **18**: M.p. 245–247 °C (heptane). ^{1}H NMR (800 MHz): δ = 0.84 (s, 3 H), 0.90 (s, 3 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 1.48 (s, 3 H), 1.78 (dd, J = 7.9, 13.2 Hz, 1 H), 2.05 (dd, J = 8.2, 14.9 Hz, 1 H), 2.08 (dd, J = 3.2, 8.7 Hz, 1 H), 2.15 (td, J = 4.6, 8.7, 11.2 Hz, 1 H), 2.46 (td, J = 8.6, 12.8 Hz, 1 H), 2.70 (td, J = 8.2, 14.9 Hz, 1 H), 3.19 (d, J = 4.8 Hz, 1 H), 3.21 (d, J = 4.8 Hz, 1 H), 3.33 (s, 3 H), 3.40 (s, 1 H), 3.54 (t, J = 11.6 Hz, 1 H), 3.78 (dd, J = 4.6, 11.6 Hz, 1 H), 4.12 (d, J = 10.9 Hz, 1 H), 4.35 (s, 1 H), 4.49 (s, 1 H), 4.69 (s, 1 H) ppm. Diagnostic NOEs: {Me-16}: Me19, Me17 (NOE gem), H3, OH-11; {Me18}: H13, H9, OH-11; {Me19}: H7, H5, Me16; {Me17}: Me16 (NOE gem), H14, OMe, OH-11; {H-14α}: H14β (NOE gem), H2; {H3}: Me16, Me19, H20β-ax, H5, H2; {H20β-ax}: Meβ-ax acetonide, H3, H-20 (NOE gem), H5. ^{13}C NMR (200 MHz): δ = 18.2, 18.9, 20.6, 23.3, 28.0, 28.5, 29.7, 34.0, 40.1, 43.2, 45.9, 49.4, 51.2, 51.7, 62.1, 65.0, 68.9, 72.0, 78.6, 89.0, 89.5, 96.1, 99.4, 205.7 ppm. IR (film): $\tilde{\nu}$ = 3526, 3407, 2971, 2937, 1691 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): 475.2 $[M + Na]^+$ (100). HRESIMS: calcd. for $C_{24}H_{36}O_8Na$ m/z 475.2308; found 475.2292.

Acetonide Cleavage. Preparation of Compound 1: Aqueous HCl solution (1 N, 1 mL) and pTsOH (5 mg) were added at 0 °C to a solution of **18** (20 mg, 0.044 mmol) in THF. After 1 h, the solution was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were worked up as usual. Chromatography (heptane/EtOAc, 1:4 to 0:1) gave pure **1** (18 mg, 97%): m.p. 219 °C (heptane). ^{1}H NMR (300 MHz): δ = 0.87 (s, 3 H), 0.91 (s, 3 H), 1.20 (s, 3 H), 1.31 (s, 3 H), 1.65 (s, 2 H), 1.84 (dd, J = 7.8, 13.3 Hz, 1 H), 1.97 (qd, J = 3.8, 6.8 Hz, 1

H), 2.05 (dd, J = 7.8, 14.8 Hz, 1 H), 2.32 (dd, J = 4.2, 6.5 Hz, 1 H), 2.42 (td, J = 8.3, 12.4 Hz, 1 H), 2.69 (ddd, J = 8.4, 12.4, 14.7 Hz, 1 H), 3.19 (d, J = 4.8 Hz, 1 H), 3.31 (d, J = 4.8 Hz, 1 H), 3.33 (s, 3 H), 3.42 (s, 1 H), 3.61 (dd, J = 7.2, 10.5 Hz, 1 H), 3.90 (dd, J = 4.0, 10.5 Hz, 1 H), 4.10 (d, J = 10.1 Hz, 1 H), 4.35 (d, J = 3.9 Hz, 1 H), 4.48 (s, 1 H), 4.69 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 17.2, 21.0, 23.5, 28.1, 28.7, 34.2, 43.4, 45.9, 43.7, 49.5, 50.8, 54.1, 62.6, 65.3, 69.9, 72.0, 79.1, 89.1, 89.5, 96.3, 214.8 ppm. IR (film): $\tilde{\nu}$ = 3436, 3307, 2936, 1690, 1265 cm^{-1}. ESIMS (MeOH): 435.1 [M + Na]$^+$ (100). HRESIMS: calcd. for $C_{21}H_{32}O_8Na$ m/z 435.1995; found 435.1992.

Reduction of the C-2 Carbonyl Group. Solvent Effect: $LiAlH_4$ (95 mg, 2.5 mmol) was added under argon atmosphere to an ice-cold, magnetically stirred solution of **8b** (134 mg, 0.3 mmol) in dry Et_2O (10 mL). The mixture was stirred at reflux for 4 h (TLC monitoring). Upon disappearance of starting material, the same workup as above, rapid filtration through SiO_2 (eluent: EtOAc), and removal of solvent gave a residue, which was purified by silica gel chromatography (heptane/EtOAc, 4:1) to yield **9** (87 mg, 65%) and **19** (29 mg, 21%). **19**: M.p. 159 °C (heptane). ^{1}H NMR (300 MHz): δ = 0.89 (s, 3 H), 1.13 (s, 3 H), 1.40 (s, 3 H), 1.48 (s, 3 H), 1.49 (s, 3 H), 1.59 (dd, J = 6.7, 13.8 Hz, 1 H), 1.60 (s, 3 H), 1.92 (d, J = 3.5 Hz, 1 H), 2.00 (qd, J = 3.8, 9.6 Hz, 1 H), 2.23 (dd, J = 4.6, 10.3 Hz, 1 H), 3.23 (dd, J = 9.8, 13.5 Hz, 1 H), 3.36 (s, 3 H), 3.82 (t, J = 11.0 Hz, 1 H), 3.96 (m, 5 H), 4.11 (t, J = 3.2 Hz, 1 H), 4.30 (d, J = 9.2 Hz, 1 H), 5.47 (d, J = 16.3 Hz, 1 H), 5.60 (m, 3 H), 5.72 (d, J = 11.3 Hz, 1 H), 5.95 (d, J = 16.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 19.3, 25.1, 26.5, 27.2, 28.9, 29.8, 37.1, 40.7, 41.5, 45.4, 52.0, 53.1, 64.6, 64.7, 65.4, 71.8, 75.1, 88.4, 98.5, 107.6, 124.0, 129.0, 130.3, 132.1, 138.1, 140.8 ppm. IR (film): $\tilde{\nu}$ = 3478, 2986, 1459, 1379, 1269, 1198, 1041, 867, 737 cm^{-1}. ESIMS (MeOH): 471.2 [M + Na]$^+$ (100). HRESIMS: calcd. for $C_{26}H_{40}O_6Na$ m/z 471.2723; found 471.2738. Analysis: calcd. for $C_{26}H_{40}0_6$ (448.59): C 69.61, H 8.99; found C 69.73, H 8.97.

Preparation of Mono- and Bis-Epoxy Ketones 20 and 21: MTO (0.3 mg, 0.001 mmol) was added at room temperature to a stirred solution of **8b** (48 mg, 0.107 mmol) and pyridine (3 µL, 0.04 mmol) in CH_2Cl_2 (0.7 mL), followed by aqueous H_2O_2 (0.02 mL, 0.21 mmol, 30%). After 8 h the solution was diluted with CH_2Cl_2, washed with a solution of $Na_2S_2O_3$, worked up as usual, and purified through a column of silica gel (heptane/EtOAc, 4:1 to 1:1) to give remaining **8b** (7 mg, 14%), **20** (33 mg, 67%), and product **21** (8.4 mg, 16%).

Compound 20: M.p. 142 °C (heptane). ^{1}H NMR (800 MHz): δ = 1.02 (s, 3 H), 1.12 (s, 3 H), 1.34 (s, 3 H), 1.44 (s, 3 H), 1.47 (s, 6 H), 1.75 (dd, J = 4.7, 14.4 Hz, 1 H), 2.10 (dd, J = 11.3, 14.4 Hz, 1 H), 2.35 (qd, 1 H, J = 4.1, 10.5 Hz, 1 H), 2.76 (dt, J = 4.6, 11.3 Hz, 1 H), 2.79 (d, J = 4.4 Hz, 1 H), 2.94 (d, J = 12.7 Hz, 1 H), 3.35 (t, J = 10.7 Hz, 1 H), 3.36 (s, 3 H), 3.64 (dd, J = 4.1, 10.7 Hz, 1 H), 3.83 (m, 2 H), 3.98 (m, 2 H), 4.24 (d, J = 9.9 Hz, 1 H), 5.65 (d, J = 10.1 Hz, 1 H), 5.69 (d, J = 16.2 Hz, 1 H), 5.72 (dd, J = 2.4, 10.0 Hz, 1 H), 5.81 (d, J = 16.2 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz): δ = 19.1, 22.7, 25.0, 25.2, 26.9, 29.7, 36.7, 37.6, 39.6, 44.1, 53.2, 54.6, 55.5, 61.8, 64.1, 64.5, 64.6, 68.7, 90.0, 98.8, 107.2, 125.3, 125.7, 135.8, 136.7, 214.0 ppm. IR (film): $\tilde{\nu}$ = 2988, 1699, 1462, 1383, 1373, 1266, 1198, 1041, 737 cm^{-1}. HRESIMS: calcd. for $C_{26}H_{38}O_7Na$ m/z 485.2515; found 485.2550. Analysis: calcd. for $C_{26}H_{38}O_7$ (462.58): C 67.51, H 8.28; found C 67.17, H 8.15.

Compound 21: M.p. 216 °C (heptane). ^{1}H NMR (800 MHz): δ = 1.01 (s, 3 H), 1.11 (s, 3 H), 1.40 (s, 3 H), 1.45 (s, 6 H), 1.46 (s, 3 H), 1.77 (dd, J = 4.6, 14.5 Hz, 1 H), 2.03 (dd, J = 11.4, 14.5 Hz, 1 H), 2.72 (m, 2 H), 2.83 (dt, J = 4.6, 11.4 Hz, 1 H), 3.13 (d, J = 4.4 Hz, 1 H), 3.23 (t, J = 10.6 Hz, 1 H), 3.25 (d, J = 4.5 Hz, 1 H), 3.32 (s, 3 H), 3.39 (d, J = 4.4 Hz, 1 H), 3.49 (dd, J = 3.5, 11.0 Hz, 1 H), 3.82 (m, 2 H), 3.98 (m, 2 H), 4.11 (d, J = 6.8 Hz, 1 H), 5.68 (d, J = 16.2 Hz, 1 H), 5.78 (d, J = 16.2 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz): δ = 19.1, 22.6, 22.7, 25.2, 26.9, 29.5, 31.7, 34.5, 36.7, 44.1, 53.3, 54.6 (2 C), 55.1, 59.6, 60.5, 63.7, 64.5, 64.7, 70.4, 91.1, 99.1, 107.2, 125.0, 136, 213.0 ppm. IR (film): $\tilde{\nu}$ = 2988, 1701, 1462, 1385, 1372, 1266, 1199, 1040, 737 cm^{-1}. ESIMS (MeOH): 501.3 [M + Na]$^+$ (100). HRESIMS: calcd. for $C_{26}H_{38}O_8Na$ m/z 501.2464; found 501.2469. Analysis: calcd. for $C_{26}H_{38}O_8$ (478.58): C 65.25, H 8.00; found C 65.38, H 7.99.

Acknowledgments

Dr. J. I. Martín Hernando, Dr. J. Quílez del Moral, Dr. M. Rico Ferreira, and Dr. J. I. Candela-Lena are gratefully acknowledged for their participation in the initial steps of this study. The authors thank Professor Jean-Yves Lallemand for his kind interest and constant encouragement.

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In the Zimmermann–Traxler transition state and Newman projection for the **2**+**3** aldol reaction, C9-H points towards the inside of the chair transition structure to minimize steric interactions:

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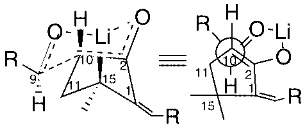

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Received May 13, 2005