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Studies towards the total synthesis of taxoids: a rapid entry into bicyclo[6.4.0]dodecane ring system. Part 1

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Abstract

We report a short and stereocontrolled synthesis of the taxoid BC-subunit (+)-**5** embodying the whole carbon framework and most of the required oxygen functionalities for further elaboration. Enantiomeric purity was secured at an early stage by resolution involving derivatization with (*S*)-2-acetoxypropionyl chloride on (±)-**10b**.

1. Introduction

Previous studies from this laboratory concerned with the synthesis of taxoid analogues have revealed a three-reaction based strategy, the aldol–annulation–fragmentation methodology,[1] for stereoselectively constructing taxoid[2] BC-subunits. These early studies have established the feasibility of producing the 20-carbon framework of the taxoid diterpene skeleton **I** in relatively few steps from inexpensive starting materials.

We detail herein a full account of our approach, built around methylcyclopentenone, to which were attached the atoms destined to become the taxoid subunit embodying the whole carbon framework and suitable oxygen functionalities. Methyl acetoacetate, methyllithium, benzoic acid, methyl iodide and formalin together with methylcyclopentenone would provide the entire taxoid diterpene skeleton using our three-reaction sequence.

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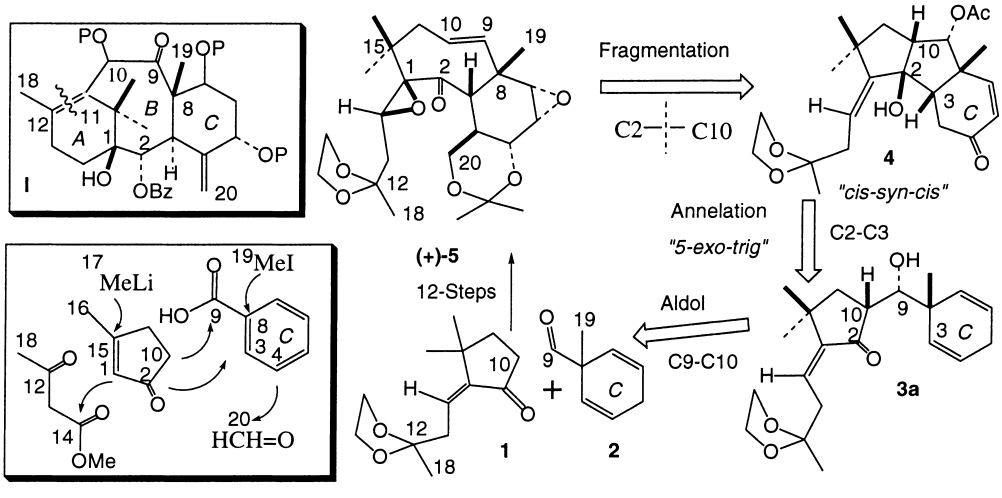
2. Synthetic planning

In the light of the results obtained during our synthetic studies aimed at the preparation of a homochiral taxoid BC-subunit,[3] the general strategy for the formation of the target molecule (+)-**5**, centered around the generation of fragmentation precursor **4** which would provide the A-seco taxoid skeleton in a step-efficient manner. Working backwards, the key tricyclic system **4** could, in principle, be assembled from an intramolecular annulation of **3a** which, in turn, could be derived from the left and right half aldol partners **1** and **2**. Recognition that tricyclic intermediate **4** could be derived from a close derivative of *threo* aldol **3a** via a 5-*exo*-trig cyclization was a key element of the synthetic scheme. According to the strategy formulated in Scheme 1 it was necessary to evaluate several issues. First, it was mandatory to establish the feasibility of the key annulation step. Critical to the success of this approach was the construction of the 'folded' *cis-syn-cis* annulated intermediate **4** that would guarantee the stereoselective production of the requisite relationship between the centers at C-1 and C-8. This retrosynthesis did not account for the stereogenic center at C-3; however, we anticipated that this center could be controlled by equilibration after closure to the taxoid ABC system (for precedents see literature[2]). As it was necessary to define those stereochemical control elements that would ensure a series of 'single isomer' transformations, we chose to use achiral aldol partners to simplify stereochemical issues. Had we used chiral aldol partners as in our previous approach, any lack of selectivity in the aldol process could have been magnified during the annulation step, producing a complex mixture of isomers. Single *threo* aldol formation **3a**, set the stage for a single *cis-syn-cis* annulated tricyclic enone **4**, which in turn secured a single fragmentation precursor **17**. The sequence begins with the aldol partners **1** and **2** and leads in four steps to the annulated intermediate **4**. Five straightforward steps are required for the incorporation of the C-20 hydroxymethyl substituent and the required oxygen functionalities at C-1 and C-7. Installation of the appropriate leaving group at C-9 and subsequent Grob type fragmentation completes the synthesis of the target bicyclo[6.4.0]dodecane (+)-**5** in its enantiomerically pure arrangement in three additional steps. In the present letter we document the ease with which the 6+8 fused substructure of taxoids can be constructed with complete stereocontrol.

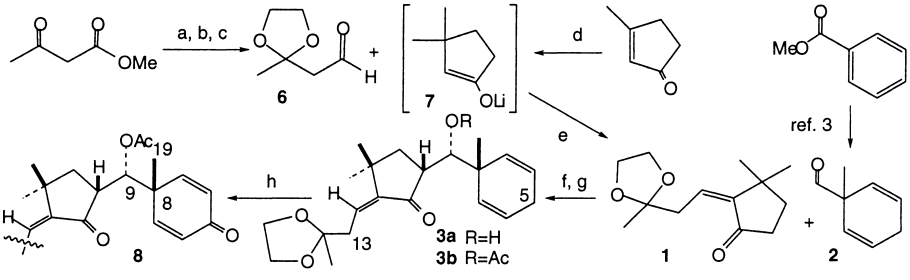


Scheme 1. Target, ingredients, bond forming operations and the three-reaction sequence

3. Results and discussion

3.1. Preparation of the aldol partners: the C9–C10 bond formation (aldolization)

The first stage of the synthesis required the left-half aldol partner **1**, the right-half aldol partner **2** being already reported in our earlier work.[3] To that end we undertook the synthesis of aldehyde **6** which was synthesized in 85% yield from methyl acetoacetate by a three-step sequence using literature conditions. Protection of the ketone carbonyl (ethylene glycol, *p*TosOH, PhMe, reflux, 1 h, 90%) followed by $LiAlH_4$ reduction in THF (rt, 10 min, 100%) and oxidation of the resulting primary alcohol via the usual Swern protocol (DMSO, $(COCl)_2$, CH_2Cl_2, −78°C, then Et_3N, 95%) afforded **6**. Coupling of the latter with the methyl cuprate generated enolate[4] **7** (MeLi, CuI, Et_2O, −10°C, 15 min, then methylcyclopentenone, 0°C, 20 min) at −20°C, in the presence of 1.6 equiv. of $ZnCl_2$ (1.0 M in ether) gave the corresponding aldol (as a 7:1 mixture) which was directly acetylated (Ac_2O, Py, DMAP, rt) and crotonized immediately after (DBU) in one-pot to afford the desired enone **1** in 75% overall yield. With the two carbonyl components from methylcyclopentenone and benzoic acid methyl ester (conveniently prepared on a 100 g scale), we proceeded to the aldol reaction in order to join the left and right half fragments (C10–C9 bonding) as outlined in Scheme 2. Aldol condensation was carried out at −78°C, by addition of the aldehyde **2** to a solution of the *threo*-selective *E*-enolate[5] generated from **1** [LDA, THF, −40°C, 2 h for enolate formation, and a further 15 min stirring upon tetramethylethylenediamine (TMEDA) addition]. 5 min after addition the reaction was quenched with a saturated solution of $NaHCO_3$ to give, exclusively, the required *threo* aldol **3a** as the sole product in 90% isolated yield (EtOAc:heptane, 1:3).



Scheme 2. (a) $HO(CH_2)_2OH$, *p*TsOH. (b) $LiAlH_4$, THF. (c) Swern. (d) Me_2CuLi, Et_2O. (e) $ZnCl_2$, Et_2O, −20°C, Ac_2O, Py, DMAP, then DBU. (f) LDA, THF, −78°C, 5 min. (g) Ac_2O, Py, DMAP. (h) CrO_3–DMP, *t*BuOOH, CH_2Cl_2, 0°C to rt

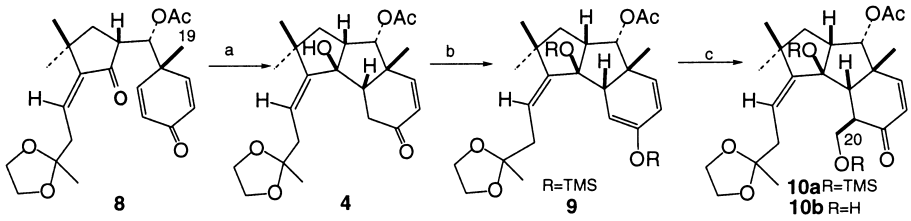
Acetylation at C-9 of the aldol thus obtained (Ac_2O, Py, DMAP, 0°C, 1 h) afforded 95% of the corresponding C-9 acetate **3b**. For the conversion of the latter to the annulation precursor **8**, a site selective allylic oxidation at C-5 was required. This was efficiently accomplished by the CrO_3–dimethyl pyrazole (DMP) protocol.[6] Thus, treatment of **3b** with CrO_3, in the presence of 3,5-dimethyl pyrazole, and *t*BuOOH, in CH_2Cl_2, at 0°C to room temperature for 5 h, afforded the desired annelation precursor **8**, in 85% isolated yield, while no trace of the undesired C-13 oxidation was detected.

3.2. The C2–C3 bond formation (annulation) and the installation of C-20

Having successfully achieved the *threo*-selective aldol reaction and the regioselective allylic oxidation, which sets up conditions for the annulation sequence (C2–C3 bonding), we turned our attention to the subsequent ring closure. In principle, this step could occur via two stereoisomeric transition states; that is, the closure could occur from either the conformation in which the angular methyl at C-8 (Me-19) and the C-9 acetate are in *gauche* relationship, leading to the desired *cis-syn-cis* product, or in

severe eclipsing relationship, leading to the unwanted *cis-anti-cis* product. Annulation was achieved by samarium diiodide[7] promoted intramolecular reductive coupling via a 5-*exo*-trig process according to our previous work.[1] Treatment of **8** with SmI_2 in THF in the presence of HMPA and MeOH at −85°C for 15 min followed by quenching with aqueous $NaHCO_3$ (2 ml/mmol) gave, after flash chromatography (EtOAc:heptane, 1:1) the *cis-syn-cis* tricyclic enone **4** as the sole product in 70% isolated yield. Within the limits of detection by 400 MHz ^{1}H NMR spectroscopy, no stereoisomer was produced. The single isomer formation could be rationalized from a consideration of the developing eclipsing interactions between the angular methyl group at C-8 and the C-9 acetoxy group.

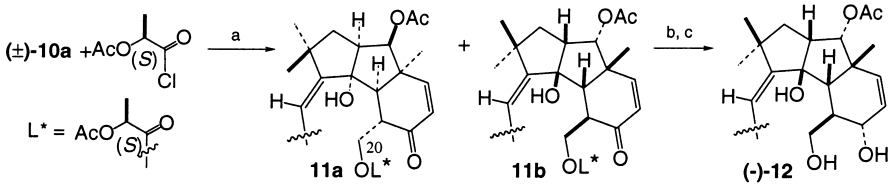
Incorporation of the last carbon (C-20) of the diterpene skeleton was first achieved by deprotonation of the tricyclic enone **4** with LDA at −78°C followed by cyanomethyl formate addition at −78°C in the presence of HMPA, and further reduction (LAH, THF, −20°C). This sequence afforded low yields and a number of by-products and thus was abandoned. An alternative route for the introduction of the C-20 was then established in which the enone **4** was transformed into the aldol **10** in a sequence of reactions involving generation of its silylenol ether **9** (Scheme 3) (by quenching its LDA generated lithium enolate with TMS-Cl) and subsequent aldol condensation in the presence of $Yb(OTf)_3$, a water tolerant Lewis acid catalyst, affording ca. 70% isolated yield of the target aldol. In a search for other routes to TMS-dienol ethers aiming at practicality and better yields, we investigated the TMSOTf (trimethylsilyl trifluoromethane sulfonate) protocol; however, attempted TMS-dienol formation using TMSOTf in CH_2Cl_2 was complicated by enolization of the O-acetyl group and, more importantly, opening of the ketal at C-12 to give an enol ether. To circumvent this problem, the tricyclic enone **4** reacted smoothly with TMSOTf (1.5 equiv.) in the presence of collidine (4.4 equiv.) in dry toluene (6.5 ml/mmol), at −40°C under argon, cleanly affording the desired TMS-dienol ether **9**, in quantitative yield. Regular TLC monitoring of the TMS-dienol ether formation reaction was required since extended reaction times led to lower yields because of the possible formation of the earlier cited side products. Nevertheless, by carrying out the reaction in toluene and operating at −40°C, complications can be easily avoided. The ^{1}H NMR of the crude material indicated no side products (such as enol ether formation at C-12 or silylation on the methyl of the C-9 acetate), and the desired product **9** was easily purified by silica gel flash chromatography and could be safely stored under argon for long periods. The conversion of **9** to **10** proceeds cleanly through the $Yb(OTf)_3$ catalyzed aldol condensation with formalin (37% HCH=O in water), and subsequent desilylation (nBu$_4$NF, THF, rt) with the only by-product observed being the starting enone, resulting from TMS-enol hydrolysis. SiO_2 flash chromatography (EtOAc:heptane, 1:1) removed the unreacted starting enone and provided **10b** in 85% yield. The relative stereochemistry of **10b** was assigned on the basis of the observed diagnostic NOEs.



Scheme 3. (a) SmI_2–MeOH/THF/HMPA, −85°C, 15 min. (b) TMSOTf, collidine, PhMe, −40°C. (c) $Yb(OTf)_3$, HCH=O, rt, then nBu$_4$NF, THF, rt

3.3. Introduction of enantiomeric purity

Aldol **10b**, embodying the whole carbon framework of the taxoid diterpene skeleton, was obtained in its enantiomerically pure arrangement through a resolution sequence outlined in Scheme 4 as follows: diastereomeric derivatization with (*S*)-2-acetoxypropionyl chloride[8] in the presence of triethylamine and DMAP in dry CH_2Cl_2 at 0°C afforded the corresponding esters **11a** and **11b** as a mixture of diastereomers which were then separated by HPLC using heptane:ethyl acetate, 2:1 and 0.1% AcOH as eluent.



Scheme 4. (a) (*S*)-O-Acetyllactyl chloride, DMAP, CH_2Cl_2, 0°C. (b) K_2CO_3, MeOH:H_2O, 10:1, −30°C. (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, CH_2Cl_2–EtOH

The absolute configuration of the (*S*)-O-acetyllactyl derivative **11a** was assigned by a single crystal X-ray crystallographic study (Fig. 1).

Thus, **11b** having the required absolute stereochemistry, was used in the synthetic scheme towards taxoid series in the transformation sequence: **11b→12→13→14→17**. To this end, the C-9 acetyl group had to be removed selectively in the presence of the C-9 acetate; this was successfully achieved using potassium carbonate in methanol:water, 10:1, at −30°C. A non-selective one step reduction would free the C-9 OAc, the C-20 lactate and would also reduce the C-5 carbonyl, thus saving two additional steps. However, low yields obtained through this way were discouraging and thus we adopted the somehow longer but more efficient method portrayed in Scheme 4.

3.4. Preparation of fragmentation precursor and B-ring formation: C2–C10 fragmentation

In order to prepare intermediates in which the C2–C10 bond could provide access to cleavage, we have studied several alternative strategies portrayed in Scheme 5. Reports from this laboratory have demonstrated the feasibility of an ozonolytic approach (type I cleavage) for the preparation of an

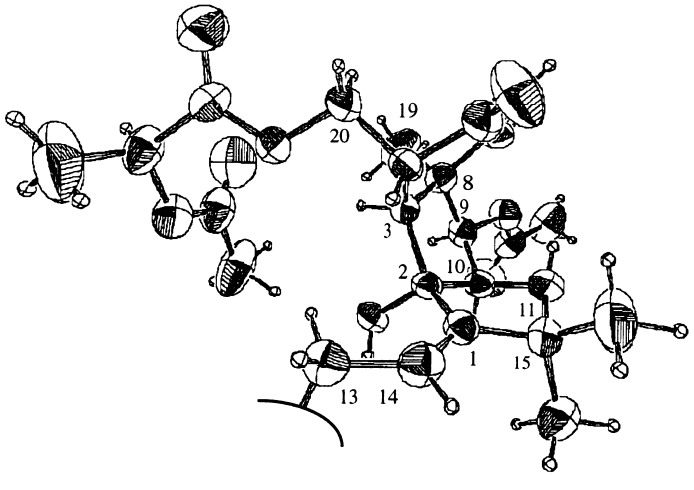
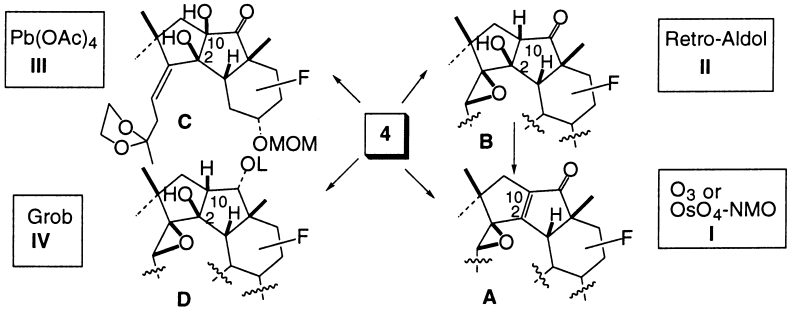


Figure 1. Perspective drawing of the X-ray structure of **11a** (dioxolane part omitted to simplify the presentation)

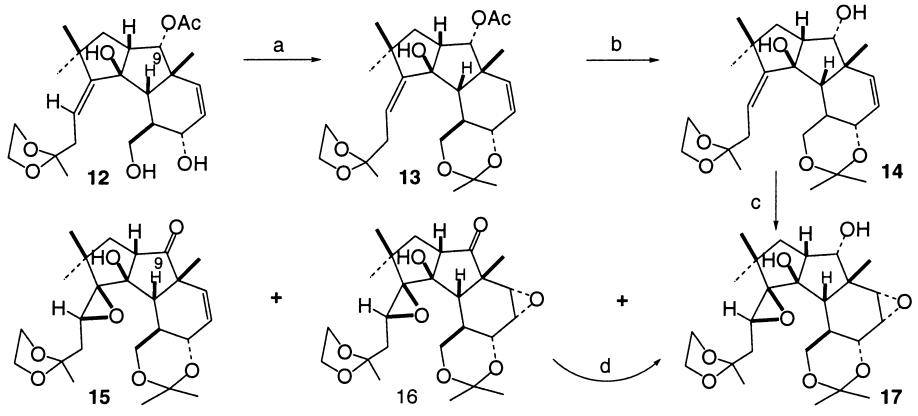
advanced, enantiomerically pure, taxoid BC-substructure.[9] Attempted ozonolytic cleavage of several A type substrates failed; proceeding as in our previous studies, ozonolysis has repeatedly proved to be complex and not synthetically valuable. The retro-aldol fragmentation on B-like substrates, which are obtained as recyclable by-products during Sharpless epoxidation (type II cleavage) was attempted next, unsuccessfully. Various conditions targeting retroaldolization failed, affording instead the corresponding crotonized A-like compounds, used in the unsuccessful ozonolytic type I fragmentation mode. At this point an alternative approach to the B-ring formation through a C2–C10 diol fragmentation (type III cleavage) was attempted. In principle, treatment of an enolate derived from B-like substrates with one of the known electrophilic hydroxylation reagents could produce the C-like diol, a logical precursor for the construction of BC-subunit via a lead tetra-acetate mediated oxidative cleavage. Despite an extensive search for suitable reaction conditions that would accommodate the C-like C2–C10 diol, none were found to be synthetically useful.



Scheme 5. Looking for the appropriate C2–C10 fragmentation mode; the B-ring formation

These unpromising results forced a change in strategy for the construction of the eight-membered B-ring. The objective became to effect a Grob fragmentation (type IV cleavage)[10] to construct the fully functional eight-membered B-ring. Thus we needed an efficient route which targeted the elaborated D-like analogues as key intermediates. The proposed route to the target compound **17** is outlined in Scheme 6. Chemoselective saponification of **11b** hydrolyzed the C-20 lactate, while the C-9 acetate remained intact (K_2CO_3, MeOH,H_2O, 10:1, −30°C) affording **10**. Further elaboration of the resulting enantiomerically pure (−)-**10b** to the acetonide (−)-**13**, common intermediate for all fragmentation precursors was achieved through diol (−)-**12** in two steps. Enone reduction of **10b** with $NaBH_4$, (4 molar equiv.) in the presence of $CeCl_3$ (1.2 equiv.), in EtOH:CH_2Cl_2 (1:1, 5 ml/mmol), at −78°C afforded **12** (98%). Subsequent treatment with acetone, 2,2-dimethoxy propane (DMP), and a catalytic amount of *p*TsOH, at 0°C, for 20 min under argon, furnished the corresponding acetonide **13** (88%).

As the stereochemistry of the fragmentation precursor **13** should ensure that the stereogenic centers at C-8, C-1 have the desired configuration, we relied on the hydroxyl group-directed epoxidation protocol for the introduction of the C-1 oxygen to secure the correct stereochemistry at C-1 stereocenter. Moreover, by carrying out the hydroxyl directed epoxidation after saponification at C-9, we could expect an increased functionalization. This was achieved by using Sharpless conditions; thus $VO(acac)_2$ (0.03 equiv.), *t*BuOOH (5 M solution in decane, 1.15 equiv.), benzene (25 ml/mmol), 15 min reflux, afforded the target compound, the bis-epoxide **17** (C1–C14 β- and C6–C7 α-epoxide, 61%) along with the corresponding bis-epoxy aldol **16** (20%) where the C-9 OH position was oxidized to the ketone, and the mono-epoxy aldol **15** (14%) in high combined yield (95%). The bis-epoxy aldol, once reduced at C-9 ($LiAlH_4$, Et_2O, 0°C, 10 min, 96%) afforded the desired compound **17**. However, **15** was also recycled via two additional steps (reduction and Sharpless epoxidation as above), thus increasing the yield.



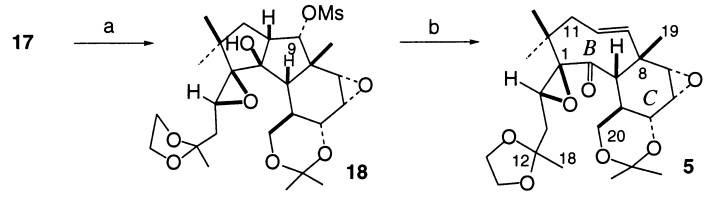
Scheme 6. (a) Acetone, 2,2-DMP, cat. *p*TsOH, 0°C. (b) 2 N NaOH, MeOH–H_2O, 0°C to rt. (c) $VO(acac)_2$, *t*BuOOH in decane, PhH, reflux. (d) $LiAlH_4$, Et_2O, 0°C

The overall sequence portrayed in Scheme 6 can be readily modified to produce the required carbon/oxygen skeleton offering several distinct ways for further elaboration. The stereochemical outcome of the epoxidation process was assessed by extensive NMR studies. The ^1H and ^{13}C NMR features of **17** are well resolved and readily amenable to assignment on the basis of 1 and 2D experiments, which allowed the tracing of the entire atomic connectivity. In particular, diagnostic NOEs established the spatial proximities and confirmed the folded *cis-syn-cis* relationship in the key tricyclic intermediate, and the stereochemistry of the two epoxides (α-configuration of the epoxide at C6–C7, β-configuration of the epoxide at C1–C14). The α-stereochemistry of C6–C7 epoxide was confirmed by 1D-NOEDIFF experiments. Irradiation of the C-8 angular methyl group, Me-19, singlet at 1.39 ppm, showed NOE to H-7 at 3.19 ppm (confirms epoxide stereochemistry) as well as to H-9, H-3 at 4.26 and 1.51 ppm, respectively (confirms *cis-syn-cis* ring junction) and H-5 proton at 3.99 ppm. No enhancement was observed for the H-4 proton confirming the β-stereochemistry of the C-20 hydroxymethyl group. Likewise, when H-9 was irradiated, an NOE was seen to the epoxidic proton H-7 at 3.19 ppm, to H-10 at 2.61 ppm and Me-19 at 1.39 ppm. Irradiation of both α- and β-methyl groups at C-15, showed NOE to H-14 at 3.20 ppm. These data, along with additional information given in the experimental part, establish the stereochemical relationship of all ring substituents. **17** can also serve for resolution purposes using (*S*)-O-acetyllactyl chloride as above, even though the former resolution, carried out four steps earlier, is synthetically more interesting.

The C-9 mesylate **18** obtained quantitatively using standard procedures (MsCl, pyridine, DMAP cat., 0°C, 30 min) was efficiently fragmented to the BC-taxoid substructure. Thus, treatment with *t*BuOK:*t*BuOH (6 equiv. of 1 M solution of *t*BuOK in *t*BuOH), in dry THF (10 ml/mmol), at 70°C (oil bath temperature), for 1.5 h, afforded after SiO_2 flash chromatography (ethyl acetate:heptane, 1:2) an 88% isolated yield of (+)-**5** (Scheme 7). Similarly, upon subjection to fragmentation conditions using NaH (4 equiv.), in THF (10 ml/mmol), at reflux for 1 h, led to the desired eight-membered ring containing BC-subunit (+)-**5** in comparable yields, so establishing the viability of this approach for taxoid synthesis.

4. Conclusion

We developed a three reaction sequence of [6+8]-fused taxoid BC-system based on the aldol-annulation sequence as the critical steps. The synthetic strategy relied on the simple diastereoselection offered by the enolate geometry during the aldol reaction and the feasibility of efficient 5-*exo*-trig



Scheme 7. (a) MsCl, pyridine, DMAP cat., 0°C. (b) *t*BuOK/*t*BuOH–THF, 70°C

annulation using SmI_2. A kinetic aldol reaction created the stereogenic center at C-9 leading to **3a**, whilst a highly stereoselective 5-*exo*-trig cyclization provided the folded *cis-syn-cis* tricyclic enone **4**, which in turn secured the installation of the quaternary centers at C-8 and C-1 with the required relative and absolute configuration. From the standpoint of efficiency of stereocontrolled bond construction, the result is truly remarkable: note that during the aldol–annelation sequence, starting from two achiral precursors, two new bonds are formed, five chiral centers are generated, and only one diastereomer is obtained out of 16 possible enantiomeric pairs of diastereoisomers. The flexibility of the current method to efficiently introduce and further modify various substituents around the core tricyclic intermediate allows scope for novel fragmentation precursors, while opening up routes to new functionalized [6+8]-fused bicyclics.

5. Experimental section

5.1. General

Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (400 and 75 MHz, respectively, 1D and 2D experiments) and were corroborated by spatial proximity (NOE) studies. Molecular mechanics calculations were run using Still's Macromodel program version 5.5 operated on a Silicon Graphics workstation. Structures were constructed by means of the interactive graphics input and then subjected to the MM3 minimization using the Monte Carlo option of the program for the search of all conformers and the evaluation of their energy (indicated solvent: chloroform). Experiments which required an inert atmosphere were carried out under dry argon or nitrogen in a flame dried glass system. THF and benzene were freshly distilled from $LiAlH_4$ and sodium wire, respectively, and were transferred via syringe. Methylene chloride was distilled from P_2O_5. Triethyl and diisopropyl amines were distilled from KOH pellets. Commercial reagents were purchased from Aldrich Chemicals and used as received. 'Usual work up' means washing of the organic layer with brine, drying on anhydrous $MgSO_4$, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Optical rotations were recorded in $CHCl_3$ solution in a 1 dm cell using a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Nicolet 205 FTIR instrument, neat or in chloroform. Melting points are uncorrected. ^1H NMR spectra were obtained on Bruker AM400, AM300, AC250 (400, 300 and 250 MHz, respectively) instruments in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS The ^1H NMR data are presented in the order: δ value of the signal, integrated number of protons, peak multiplicity (abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and coupling constants in hertz. Nuclear Overhauser enhancements by the NOEDIFF method[11] were obtained with the aid of the Aspect 3000 microprograms, which allow direct accumulations of difference FIDs. NOEs were successfully obtained with extremely low irradiating power levels (40 dB); 320 transients were acquired in NOE experiments, and an exponential line broadening of 0.3 Hz was used. ^{13}C spectra were measured at 62.5 and 75 MHz and the chemical shifts are reported relative to $CDCl_3$ triplet centered at 77.00 ppm. For all compounds investigated, multiplicities of ^{13}C resonances were

assigned by the SEFT technique.[12] Two-dimensional homo and heteronuclear correlation experiments were performed with standard Bruker software. Mass spectra (MS), recorded on an AEI MS-50 (electron impact spectra, EI), an AEI MS-9 (chemical ionization spectra, CI), or a Kratos MS-50 (high resolution mass spectra, HR) instruments are reported in the form: 'm/z (intensity relative to base peak)=100%'. Flash chromatographies were run on silica gel (Merck 60, 230–400 mesh) with the solvent mixture indicated. Thin layer chromatography was performed on commercial silica gel glass plates that were developed by immersion in 5% phosphomolybdic acid in 95% ethanol.

5.2. Preparation of left-half aldol partner **1**

A dry flask was charged with copper(I) iodide (17.7 g, 93.15 mmol) which was dried under high vacuum pressure for 12 h. Methyllithium (120 ml of a 1.55 M solution in ether, 186 mmol) was added dropwise to a stirring suspension of the copper(I) iodide in ether (180 ml) at −20°C under argon. After 20 min, the mixture was allowed to warm to 0°C and 3-methylcyclopent-2-enone (6.72 g, 69.9 mmol) was added. After a further 20 min, the mixture was cooled to −20°C and zinc chloride (95.12 ml of a 1.0 M solution in ether, 95.12 mmol) was added. After 5 min, the aldehyde **6** (8.65 g, 66.54 mmol) was added and the mixture was stirred for a further 20 min. The reaction mixture was quenched by addition of a saturated solution of ammonium chloride and diluted with EtOAc. After being allowed to warm to room temperature, ammonia was added to solubilize the precipitate. The organic layer was washed with 1 N hydrochloric acid, water and brine, and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give 16 g of crude product which, upon chromatography, furnished 81% yield of the corresponding aldol as a mixture of two diastereomers, used as such in the next step.

Acetic anhydride (26.4 g, 258.6 mmol) was added dropwise to a stirring solution of the latter crude (12.2 g, 50.4 mmol) and DMAP (1.3 g, 10.8 mmol) in pyridine (50 ml) at 0°C under argon. After 15 min the mixture was allowed to warm to room temperature and stirred for an additional 1 h. DBU (24.84 g, 163.2 mmol) was added to the mixture and it was then stirred overnight. The mixture was ice cooled, diluted with CH_2Cl_2, washed with dilute hydrochloric acid, saturated with sodium bicarbonate and brine, and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, heptane:EtOAc, 4:1) to give 10.49 g of **1** (93%) along with a small amount (0.45 g, 4%) of the *Z*-isomer, separable by chromatography. **1**: IR (film): 2957, 2864, 1716, 1643, 1457, 1377, 1291, 1218, 1111, 1058, 870 cm^{-1}. ^1H NMR (250 MHz): 1.18 (6H, s), 1.31 (3H, s), 1.74 (2H, t, *J*=7.8), 2.33 (2H, t, *J*=7.8), 3.08 (2H, d, *J*=7.4), 3.96 (4H, bs), 5.90 (1H, t, *J*=7.4). ^{13}C NMR (62.9 MHz): 23.8, 28.9 (2×Me), 34.8, 36.4 (2×CH_2), 40.4 (Cq-15), 64.5 (OCH_2CH_2O, 2×C), 109.3 (C-12), 132.3 (C-14), 146.5 (C-1), 208.6 (C-2). EIMS: 224 (M^+, 2), 209 (65), 190 (14), 175 (18), 163 (14), 149 (18), 137 (12), 123 (26), 87 (100). HREIMS: calcd for $C_{13}H_{20}O_3$ m/z 224.1412, found: 224.1398.

5.3. Preparation of **3a**: aldol condensation

A solution of diisopropylamine (5.12 g, 50.64 mmol) in 80 ml of dry THF was cooled to −78°C and *n*BuLi (2.5 M in hexanes, 18.6 ml, 46.4 mmol) was added dropwise under argon. After 30 min, **1** (9.45 g, 42.2 mmol) was added dropwise. The solution was allowed to stir for 2 h (enolate formation) at −78°C, and TMEDA (11.5 ml, 76.0 mmol) was added in one portion. After 15 min the aldehyde **2** (5.12 g, 76.6 mmol) was added dropwise. The mixture was allowed to stir for 5 min at −78°C and the reaction was quenched with 45 ml of saturated aqueous $NaHCO_3$. The mixture was rapidly extracted in EtOAc, washed with ice-cold 1% HCl and then a $NaHCO_3$ solution. After drying and removal of solvent the aldol was obtained as a light yellow oil. Purification was effected by flash chromatography only for

characterization purposes, (SiO_2, heptane:EtOAc, 4:1 as eluent) to give a single *threo* aldol (±)-**3a** as the sole product in nearly quantitative yield. The crude reaction profile of the aldol reaction step showed a single product by 400 MHz ^{1}H NMR without any detectable trace of an *erythro* aldol.

(±)-**3a**: IR (film): 3440, 3018, 2958, 2924, 2863, 2820, 1692, 1623, 1451, 1425, 1382, 1304, 1279, 1210, 1158, 1115, 1037, 1020, 943, 900, 865, 719 cm^{-1}. ^{1}H NMR (400 MHz): 1.07 (3H, s), 1.16 (3H, s), 1.19 (3H, s), 1.31 (3H, s), 1.39 (1H, t, *J*=12.6), 1.87 (1H, dd, *J*=8.5, 12.6), 2.49 (1H, dt, *J*=8.5, 12.6), 2.65 (2H, bd, *J*=1.0), 3.07 (2H, d, *J*=7.4), 3.54 (1H, dd, *J*=1.5, 8.5), 3.92–3.99 (4H, m), 5.27 (1H, d, *J*=1.5, OH), 5.43 (1H, dd, *J*=1.0, 10.2), 5.65 (1H, dt, *J*=2.8, 10.2), 5.80 (2H, bs), 5.98 (1H, t, *J*=7.4). ^{13}C NMR (75 MHz): 24.0, 26.6, 26.7, 28.6, 29.9, 37.0, 38.6, 41.1, 41.4, 49.7, 64.7 (OCH_2CH_2O, 2×C), 79.4, 109.3, 123.3, 124.1, 129.7, 133.0, 134.9, 146.3, 213.3. CIMS: 347 ([M+H]$^+$, 60), 343 (10), 329 (40), 253 (20), 225 (10), 191 (11), 105 (6), 87 (76). HRCIMS: calcd for $C_{21}H_{31}O_4$ m/z 347.2222, found: 347.2231.

5.4. Acetylation of the aldol

Acetic anhydride (27.05 g 265 mmol) was added to a stirring mixture of aldol (±)-**3a** (14.6 g, 42.2 mmol) and DMAP (0.5 g, 4.1 mmol) in pyridine (80 ml) at 0°C under argon. After 30 min, the mixture was diluted with DCM and washed with dilute hydrochloric acid, saturated sodium bicarbonate, water, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, heptane:EtOAc, 4:1) to give 14.4 g of (±)-**3b** (88%) along with 7% of the corresponding crotonized product which was discarded.

(±)-**3b**: IR (film): 2960, 2932, 2872, 1742, 1711, 1639, 1450, 1151, 1369, 1243, 1138, 1115, 1051, 1029, 949 cm^{-1}. ^{1}H NMR (300 MHz) 1.03 (3H, s), 1.05 (3H, s), 1.18 (3H, s), 1.29 (3H, s), 1.65 (1H, t, *J*=12.5, H-11), 1.84 (1H, dd, *J*=8.6, 12.5, H-11), 2.12 (3H, s, OCOMe), 2.58 (1H, ddd, *J*=7.3, 8.5, 11.8, H-10), 2.63 (2H, m, H-5), 2.99 (2H, m, H-13), 3.95 (4H, m, OCH_2CH_2O), 4.86 (1H, d, *J*=7.3, H-9), 5.45 (1H, dd, *J*=1.7, 10.0), 5.7–5.9 (4H, m). ^{13}C NMR (75 MHz) 21.0 (CH_3CO), 23.7 (Me), 26.3 (C-5), 26.7 (Me), 28.6 (Me), 29.7 (Me), 36.5 (C-13), 38.0 (Cq), 40.5 (Cq), 41.1 (C-11), 47.8 (C-10), 64.5 (OCH_2CH_2O, 2×C), 79.0 (C-9), 107.4 (C-12), 124.2, 124.5, 129.6, 131.3, 132.4, 146.5, 170.7, 205.7. EIMS: 388 (M$^+$, 2), 328 (8), 237 (16), 221 (10), 191 (26), 175 (30), 105 (43), 91 (51), 87 (100). CIMS: 389 ([M+H]$^+$, 9), 343 (34), 329 (100), 285 (11), 214 (9), 87 (46). HRCIMS: calcd for $C_{33}H_{33}O_5$ m/z 389.2328, found: 389.2333.

5.5. Allylic oxidation

t-Butylhydroperoxide (60 ml of a 70% w/v solution in water, 435.6 mmol) was added to a stirring solution of 3,5-dimethylpyrazol (4.19 g, 43.56 mmol) and chromium trioxide (1.74 g, 17.42 mmol) in dichloromethane (200 ml) at 0°C. (±)-**3b** (16.9 g, 43.56 mmol) in dichloromethane (50 ml) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was diluted with ether, washed with dilute hydrochloric acid, dilute sodium hydroxide, water, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, heptane:EtOAc, 2:1 to 1:3) to give 14.89 g (85%) of of the fragmentation precursor (±)-**8**: IR (film): 3058, 2969, 2884, 1744, 1710, 1666, 1628, 1457, 1371, 1267, 1236, 1141, 1053, 1030, 864, 738, 703 cm^{-1}. ^{1}H NMR (300 MHz): 0.99 (3H, s), 1.15 (3H, s), 1.23 (3H, s), 1.29 (3H, s), 1.45 (1H, t, *J*=12.3), 1.67 (1H, dd, *J*=8.5, 12.3), 2.19 (3H, s), 2.44 (1H, ddd, *J*=7.1, 8.5, 12.3), 2.99 (2H, d, *J*=7.4), 3.92–4.00 (4H, m), 5.20 (1H, d, *J*=7.1), 5.89 (1H, t, *J*=7.4), 6.30 (1H, dd, *J*=1.8, 10.1), 6.39 (1H, dd, *J*=1.8, 10.2), 6.88 (1H, dd, *J*=3.0, 10.1), 7.18 (1H, dd, *J*=3.0, 10.2). ^{13}C NMR (75 MHz): 20.7, 23.7 (2×Me), 28.3, 29.5, 36.5, 37.9, 40.2, 45.4, 47.7, 64.4 (OCH_2CH_2O, 2×C), 76.1, 109.0, 129.1, 129.5,

133.7, 145.6, 151.2, 151.7, 170.2, 185.3, 204.2. CIMS: 403 ([M+H]$^+$, 1), 343 (98), 295 (33), 281 (30), 251 (40), 191 (41), 109 (13), 105 (14), 87 (100). HRCIMS: calcd for $C_{23}H_{31}O_6$ m/z 403.2120, found 403.2132, calcd for m/z 343.1909 ([MH]$^+$–AcOH) found: 343.1892.

5.6. Annelation

HMPA (30 ml, 172.5 mmol) was added dropwise to a stirring solution of samarium iodide (330 ml of a 0.1 M solution in THF, 33 mmol) at −85°C under argon (the dark blue coloration turns to purple). After 30 min at this temperature, a solution of (±)-**8** (2.98 g, 7.41 mmol) in dry methanol (6 ml) and THF (18 ml) was added dropwise over 5 min. After a further 10 min at −85°C, the mixture was quenched by the addition of a saturated solution of potassium sodium tartrate (60 ml) followed by dilution with EtOAc. Water was added and the organic layer was separated. The aqueous layer was re-extracted with EtOAc and the combined organic layers were washed with 1 N HCl, water, brine and dried ($MgSO_4$). The crude residue was chromatographed (SiO_2, heptane:EtOAc, 1:1) to give 2.093 g of the required product (±)-**4** (70% isolated yield).

(±)-**4**: IR ($CHCl_3$) 3436, 2951, 3938, 2878, 1736, 1682, 1377, 1238, 1045, 952, 746 cm^{-1}; ^{1}H NMR (400 MHz) 1.10 (3H, s, Me-17), 1.18 (3H, s, Me-16), 1.37 (3H, s, Me-18), 1.56 (3H, s, Me-19), 1.59 (1H, d, *J*=9.9, H-11α), 1.60 (1H, d, *J*=11.1, H-11β), 1.97 (3H, s, OCOMe), 2.15 (1H, dd, *J*=13.4, 16.8, H-4βax), 2.25 (1H, dd, *J*=6.2, 16.8, H-4αequiv.), 2.52 (2H, m, H-13), 2.56 (1H, dd, *J*=6.2, 13.4, H-3), 3.27 (1H, ddd, *J*=8.1, 9.9, 11.1, H-10), 3.85–4.01 (4H, m, OCH_2CH_2O−), 4.58 (1H, OH-2), 5.16 (1H, d, *J*=8.1, H-9), 5.39 (1H, dd, *J*=6.5, 10.7, H-14), 5.98 (1H, d, *J*=10.1, H-6), 6.55 (1H, d, *J*=10.1, H-7). Diagnostic NOEs: {Me-17}: Me-16 (NOE gem), H-11α, H-14; {Me-16}: Me-17 (NOE gem), H-11β, H-10, H-14; {Me-19}: H-3, H-9, H-7; {H-10}: H-11β, Me-16, H-9; {H-9}: H-10, Me-19, H-7; {H-14}: Me-16, Me-17, Me-18; ^{13}C NMR (75 MHz) 20.9 (*CH*$_3$CO), 24.9 (Me-18), 27.1 (Me-19), 27.5 (Me-17), 32.1 (Me-16), 38.8 (C-11), 39.2 (C-13), 39.5 (C-4), 44.9 (C-15), 51.3 (C-8), 54.9 (C-3), 55.4 (C-10), 65.1, 65.2 (OCH_2CH_2O), 79.8 (C-9), 92.4 (C-2), 109.7 (C-12), 117.3 (C-14), 128.5 (C-6), 153.3 (C-7), 157.5 (C-1), 169.8 (MeC=O), 199.3 (C-5); EIMS: m/z 404 (M$^+$, 3), 389 (M−Me, 13), 371 ([M−Me]−H_2O, 7), 191 (39), 121 (59), 87 (100). HRCIMS: calcd for $C_{23}H_{33}O_6$ m/z 405.2276, found 405.2249. Anal. calcd for $C_{23}H_{32}O_6$: C 68.29, H 7.97, found: C 68.16, H 7.90.

5.7. Incorporation of C-20 via TMS-dienol ether (±)-*9*

To a stirred solution of 3.71 g (9.18 mmol) of (±)-**4** and 24.3 ml (184 mmol) of collidine in dry toluene (60.0 ml) at −40°C under argon, was added 8.1 ml (45 mmol) of TMSOTf. The mixture was stirred at −40°C for 20 min, diluted with heptane, washed with 1 M hydrochloric acid, water and brine, dried over sodium sulfate, and concentrated under reduced pressure to give a crude, which upon purification on silica gel (heptane:EtOAc, 1:1 as eluent), yielded 4.76 g (94%) of (±)-**9**: IR (film): 3050, 2957, 2897, 1741, 1665, 1457, 1413, 1375, 1252, 1215, 1156, 1099, 1066, 949, 903, 843, 751 cm^{-1}. ^{1}H NMR (300 MHz): 0.18 (9H, s), 0.19 (9H, s), 0.99 (3H, s), 1.07 (3H, s), 1.23 (3H, s), 1.38 (3H, s), 1.58 (2H, t, *J*=5.9), 2.08 (3H, s), 2.59 (1H, dd, *J*=7.3, 15.8), 2.78 (1H, dd, *J*=6.2, 15.8), 2.91 (1H, d, *J*=5.4), 2.98 (1H, dt, *J*=5.9, 6.5), 3.90–4.02 (4H, m), 4.86 (1H, dd, *J*=1.9, 5.4), 5.17 (1H, d, *J*=6.5), 5.37 (1H, dd, *J*=6.2, 7.3), 5.54 (1H, dd, *J*=1.9, 10.1), 5.66 (1H, d, *J*=10.1). ^{13}C NMR (75 MHz): 0.2 (3×Me), 1.8 (3×Me), 20.8, 24.5, 28.4, 31.2, 32.2, 36.7, 38.1, 41.7, 43.0, 52.1, 59.2, 64.6 (OCH_2CH_2O, 2×C), 84.8, 96.6, 102.5, 109.8, 119.1, 122.0, 133.1, 144.4, 154.0, 170.4. CIMS: 548 (M$^+$, 3), 533 (3), 488 (3), 473 (4), 440 (9), 368 (49), 308 (20), 223 (14), 195 (16), 180 (14), 165 (33), 73 (100).

(±)-**9** (4.67 g, 8.5 mmol) thus obtained was dissolved in 100 ml of THF at room temperature. 50 ml of 37% aqueous HCHO and 4.7 g (7.65 mmol) of $Yb(OTf)_3$ were added and the reaction mixture stirred for 40 h. Quenching with a saturated aqueous solution of sodium bicarbonate (2 ml per mmol) followed by extraction with EtOAc, washing with 1 N aqueous HCl, water and brine afforded 4.8 g of crude, containing partially silylated compounds of type (±)-**10a**, the desired (±)-**10b** and the starting material (±)-**4**, which was then desilylated. Thus, the crude material was dissolved in THF (100 ml); 1 M Bu_4NF in THF (13 ml, 13 mmol) was added at room temperature and the mixture stirred for 10 min. Dilution with EtOAc, washing with brine and drying over $MgSO_4$ furnished a residue which was subsequently purified on silica gel (heptane:EtOAc, 1:2 to 1:4) to yield 0.368 g (11%) of recovered (±)-**4** and 2.95 g (80%) of (±)-**10b**. Spectral data for enantiomerically pure **10b** will follow after the resolution step (vide infra).

*5.8. Resolution of (±)-**10b**: preparation of lactate derivatives **11a** and **11b***

Racemic **10b** (708 mg, 1.63 mmol) was dissolved in dry CH_2Cl_2 (24 ml) at 0°C; Et_3N (1.6 ml, 11.5 mmol), DMAP (500 mg, 4.1 mmol) and 10 min later (*S*)-O-acetyllactyl chloride ((*S*)-2-acetoxypropionyl chloride, 1.2 ml, 10.4 mmol) were added at 0°C. After 25 min at this temperature (TLC monitoring), the reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$. Extraction with CH_2Cl_2, washings with 1 N aq. HCl, $NaHCO_3$, water and brine and finally drying over $MgSO_4$ afforded a crude residue which was purified on silica gel (heptane:EtOAc, 1:1) to yield 832 mg (93%) of a mixture of lactates **11a** and **11b** along with 28 mg (4%) of the starting alcohol (±)-**10b**. The lactates **11a** and **11b** were separated by HPLC (heptane:ethyl acetate 2:1, in the presence of 0.1% acetic acid).

11a (ent-taxoid series): mp 54–57°C (ether:heptane). $[\alpha]_D$ 36.5 (*c* 1.15). IR (film): 3454, 3055, 2987, 2962, 2894, 1742, 1671, 1422, 1375, 1266, 1240, 1195, 1136, 1101, 1066, 1051, 895 cm^{-1}. ^1H NMR (400 MHz): 0.91 (3H, s), 1.06 (3H, s), 1.28 (1H, dd, *J*=8.4, 13.4), 1.36 (3H, s), 1.43 (3H, s), 1.50 (3H, d, *J*=7.1), 1.57 (1H, t, *J*=13.4), 2.12 (3H, s), 2.14 (3H, s), 2.43 (1H, dd, *J*=5.5, 13.6), 2.65 (1H, bs), 2.86 (1H, dd, *J*=11.7, 13.5), 2.88–2.96 (2H, m), 3.85–3.96 (4H, m), 4.13 (1H, s, OH), 4.19 (1H, dd, *J*=6.0, 10.7), 4.42 (1H, dd, *J*=7.7, 10.7), 5.03 (1H, q, *J*=7.1), 5.24 (1H, d, *J*=7.0), 5.52 (1H, dd, *J*=5.5, 11.7), 5.99 (1H, d, *J*=10.5), 6.99 (1H, dd, *J*=1.0, 10.5). ^{13}C NMR (75 MHz): 16.9, 20.5, 20.8, 24.7, 28.1, 28.7, 33.5, 37.6, 38.7, 41.9, 44.4, 45.8, 54.1, 55.7, 64.9, 65.0, 66.6, 68.6, 81.7, 91.3, 109.5, 121.5, 126.9, 154.7, 157.5, 170.1, 170.3, 170.5, 196.4. Anal. calcd for $C_{29}H_{40}O_{10}$: C 63.49, H 7.35, found: C 63.32, H 7.56.

X-Ray structure determination of **11a**: $C_{29}H_{39}O_{10}$, $C_4H_{10}O$: Mr=621.75, monoclinic, $P2_1$, *a*=13.434(9), *b*=10.461(9), *c*=12.381(5) Å, β=95.33(5)°, *V*=1735(2) $Å^{-3}$, *Z*=2, D_x=1.190 Mg m^{-3}, λ(MoKα)=0.71073 Å, μ=0.828 cm^{-1}, *F*(000)=670, *T*=294 K. The sample (0.25×0.25×0.30 mm) was studied on an automatic diffractometer CAD4 ENRAF–NONIUS with graphite monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$=50°, scan ω/2θ=1, t_{max}=60 s, range HKL: H −17,17 K 0,13 L 0,15, intensity controls without appreciable decay (0.2%) gave 4175 reflections from which 2457 were independent (R_{int}=0.013) with $I>3.0\sigma(I)$. After Lorenz and polarization corrections the structure was solved with SIR-92 which revealed the non-hydrogen atoms of the structure and the solvent molecule. After anisotropic refinement, the hydrogen atoms were found with a Fourier difference (between 0.56 and 0.24 e $Å^{-3}$). The whole structure was refined by the full-matrix least-square techniques (use of *F* magnitude; *x*, *y*, *z*, β_{ij} for C and O atoms and *x*, *y*, *z* fixed for H atoms; 489 variables and 2457 observations; $w=1/\sigma(F_o)^2=[\sigma^2(I)+(0.04F_o^2)^2]^{-1/2}$) with the resulting *R*=0.052, R_w=0.049 and S_w=0.778 (residual Δρ=0.23 e $Å^{-3}$). Atomic scattering factors are from *International Tables for X-Ray Crystallography*

(1974). All the calculations were performed on a Silicon Graphics Indy computer with the MOLEN package (Enraf–Nonius, 1990).

11b (taxoid series): $[\alpha]_D$ −73.3 (*c* 0.85). IR (film): 3444, 2962, 2919, 2856, 1744, 1669, 1462, 1375, 1225, 1200, 1110, 1050 cm^{-1}. ^1H NMR (400 MHz): 0.91 (3H, s), 1.06 (3H, s), 1.27 (1H, dd, *J*=8.6, 13.5), 1.36 (3H, s), 1.43 (3H, s), 1.50 (3H, d, *J*=7.0), 1.58 (1H, t, *J*=13.5), 2.12 (6H, s), 2.44 (1H, dd, *J*=5.5, 13.5), 2.65 (1H, bs), 2.84 (1H, dd, *J*=11.8, 13.5), 2.88–2.96 (2H, m), 3.84–3.97 (4H, m), 4.12 (1H, s, OH), 4.30 (1H, dd, *J*=7.0, 10.9), 4.34 (1H, dd, *J*=7.4, 10.9), 5.08 (1H, q, *J*=7.0), 5.24 (1H, d, *J*=7.1), 5.52 (1H, dd, *J*=5.5, 11.8), 5.97 (1H, d, *J*=10.5), 6.96 (1H, dd, *J*=1.1, 10.5). ^{13}C NMR (62.9 MHz): 16.8, 20.5, 20.7, 24.6, 27.9, 28.5, 33.5, 37.6, 38.7, 41.8, 44.4, 46.0, 54.0, 55.6, 64.8, 64.9, 66.1, 68.4, 81.6, 91.1, 109.4, 121.4, 126.9, 154.3, 157.3, 170.0, 170.2, 170.3, 196.4. The 400 MHz ^1H NMR spectra were easily integrated, and compared to the racemic mixture; enantiomeric excesses were measured with ±2% precision.

5.9. Selective hydrolysis of C-20 lactyl functionality in the presence of C-9 acetate

11b (1.33 g, 2.4 mmol) was dissolved in MeOH (60 ml), K_2CO_3 (840 mg, 6.1 mmol) and then water (6 ml) were added at −30°C. After stirring for 55 min at −30°C (TLC monitoring), MeOH was evaporated under reduced pressure and the residue was taken into CH_2Cl_2. Following washing with brine, the organic layer was dried over $MgSO_4$ and flash chromatographed (heptane:EtOAc, 1:3) to yield 920 mg (88%) of **10b** along with 30 mg (2%) of recovered starting material. **10b**: $[\alpha]_D$ −73, (*c* 2.1). IR (film) 3449, 2959, 2934, 2884, 1741, 1664, 1376, 1240, 1053 cm^{-1}. ^1H NMR (400 MHz) 0.92 (3H, s, Me-17), 1.06 (3H, s, Me-16), 1.29 (1H, dd, *J*=8.4, 13.2, H-11b), 1.35 (3H, s, Me-18), 1.39 (3H, s, Me-19), 1.57 (1H, t, *J*=13.2, H-11a), 2.12 (3H, s, OCOMe), 2.49 (1H, dd, *J*=5.8, 13.7, H-13), 2.56 (1H, br s, H-3), 2.61 (1H, OH-20), 2.74 (1H, ddd, *J*=1.5, 6.1, 8.3, H-4), 2.85 (1H, dd, *J*=11.2, 13.7, H-13), 2.94 (1H, ddd, *J*=7.0, 8.4, 12.8, H-10), 3.80 (2H, m, H-20), 3.94 (4H, m, OCH_2CH_2O−), 5.25 (1H, d, *J*=7.0, H-9), 5.54 (1H, dd, *J*=5.8, 11.2, H-14), 5.98 (1H, d, *J*=10.4, H-6), 7.00 (1H, dd, *J*=0.6, 10.4, H-7). Diagnostic NOEs: {Me-17}: Me-16 (NOE gem), H-11α, H-14; {Me-16}: Me-17 (NOE gem), H-11β, H-10, H-14; {Me-19}: H-3, H-9, H-7; {H-11α}: H-11β (NOE gem), Me-17, H-7; {H-9}: H-3, H-10, Me-19. ^{13}C NMR (75 MHz) 20.8 (CH_3CO), 24.8 (Me-18), 28.1 (Me-17), 29.0 (Me-19), 33.5 (Me-16), 37.6 (C-11), 38.7 (C-13), 41.8 (C-15), 44.5 (C-8), 49.3 (C-4), 54.2 (C-10), 56.0 (C-3), 64.9, 65.0 (OCH_2CH_2O), 65.9 (C-20), 81.8 (C-9), 91.5 (C-2), 109.5 (C-12), 121.3 (C-14), 126.6 (C-6), 155.0 (C-7), 157.3 (C-1), 170.1 (MeC=O), 200.0 (C-5); EIMS: m/z 434 (M^+, 4), 419 (9), 401 (7), 313 (29), 295 (40), 191 (43), 151 (47), 87 (100). HRCIMS: calcd for $C_{24}H_{35}O_7$ m/z 435.2382, found 435.2359.

*5.10. Reduction of the C-5 carbonyl and preparation of the isopropylidene derivative (−)-**13***

Cerium chloride heptahydrate (0.51 g, 1.36 mmol) was added to a solution of **10b** (536 mg, 1.24 mmol) in CH_2Cl_2 (15 ml) and ethanol (15 ml) at −78°C. After 5 min, sodium borohydride (117 mg, 3.1 mmol) was added and the mixture was stirred for 1.5 h at −78°C and then quenched by careful addition of brine followed by dilution with ether. After being allowed to warm to room temperature, the organic layer was separated and the aqueous layer was extracted with ether (×3). The combined organic fractions were washed with brine and dried over $MgSO_4$, the solvent was evaporated under reduced pressure to give a crude residue which was purified by SiO_2 flash chromatography, eluent EtOAc, 534 mg (98%) of (−)-**12**. $[\alpha]_D$ −128 (*c* 2.35). IR (film): 3429, 3046, 2966, 2923, 2892, 1737, 1663, 1465, 1379, 1249, 1140, 1045, 950, 852, 730 cm^{-1}. ^1H NMR (300 MHz): 1.08 (3H, s), 1.11 (3H, s), 1.16 (3H, s), 1.20–1.35 (1H, m), 1.36 (3H, s), 1.66–1.79 (3H, m), 2.12 (3H, s), 2.48 (1H, dd, *J*=6.3, 13.8), 2.70–2.82 (1H, m),

3.10 (1H, dd, *J*=10.6, 13.8), 3.16 (1H, bs, OH), 3.51–3.65 (1H, m), 3.56 (1H, s, OH), 3.72 (1H, bs, OH), 3.94–4.05 (5H, m), 4.29 (1H, bd, *J*=6.6), 5.12 (1H, d, *J*=6.5), 5.52 (1H, dd, *J*=6.3, 10.6), 5.69 (1H, d, *J*=10.1), 6.04 (1H, dd, *J*=2.5, 10.1). ^{13}C NMR (75 MHz): 21.0, 24.8, 28.6, 29.6, 34.0, 37.1, 38.2, 41.5, 44.6, 46.7, 55.6, 55.7, 64.9, 65.0, 68.5, 71.5, 81.0, 91.9, 109.8, 120.5, 129.3, 132.7, 157.7, 170.6. CIMS: (419 $[(M+H)-H_2O]^+$, 100), 401 (6), 375 (56), 359 (24), 357 (27), 87 (98).

Diol (−)-**12** thus obtained was dissolved in 22 ml of acetone and 2.2 ml of 2,2-DMP, and catalytic *p*TsOH·H_2O was added at 0°C. After 20 min stirring, the mixture was first filtered on Al_2O_3 which was rinsed with EtOAc. The residue was purified by chromatography on silica gel (heptane:EtOAc, 3:1) to give 512 mg (88%) of (−)-**13**: $[\alpha]_D$ −141 (*c* 2.03). IR (film): 3441, 2954, 2895, 1733, 1675, 1463, 1364, 1240, 1193, 1111, 1047, 875 cm^{-1}. ^{1}H NMR (300 MHz): 1.10 (3H, s), 1.18 (3H, s), 1.22–1.32 (1H, m), 1.32 (3H, s), 1.35 (3H, s), 1.40 (3H, s), 1.47 (3H, s), 1.54–1.67 (3H, m), 1.92 (1H, d, *J*=12.3), 2.10 (3H, s), 2.32 (1H, dd, *J*=5.3, 13.5), 2.76–2.90 (1H, m), 3.04 (1H, dd, *J*=12.0, 13.5), 3.58 (1H, t, *J*=10.9), 3.84–3.94 (4H, m), 4.01 (1H, bs, OH), 4.10–4.22 (2H, m), 5.13 (1H, d, *J*=7.0), 5.45 (1H, dd, *J*=5.3, 12.0), 5.66 (1H, d, *J*=10.6), 5.85 (1H, dd, *J*=2.6, 10.6). ^{13}C NMR (75 MHz): 18.9, 21.0, 24.8, 28.3, 29.7, 31.1, 33.3, 37.6, 38.4, 41.7, 41.8, 46.8, 56.4, 56.7, 64.9, 65.0, 69.1, 81.5, 90.8, 98.1, 109.6, 119.8, 127.6, 132.9, 158.5, 170.5.

5.11. Hydrolysis of the C-9 acetate

Sodium hydroxide (54 mmol, 9 ml of a 6 N solution) was added dropwise to a stirring solution of (−)-**13** (2.45 g, 5.15 mmol) in methanol (110 ml) at 0°C. After 1 h, the mixture was allowed to warm to room temperature and then stirred for an additional 1 h (TLC monitoring). Methanol was evaporated under reduced pressure and the residue was taken up in ethyl acetate. The solution was washed with water, saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$ to give 2.3 g (100%) of (−)-**14**. An analytical sample was purified on SiO_2 gel (heptane:EtOAc, 1:2). (−)-**14**: $[\alpha]_D$ −163 (*c* 2.11). IR (film): 3451, 3050, 2989, 2957, 2927, 1652, 1460, 1381, 1293, 1267, 1223, 1199, 1149, 1107, 1052, 997, 950, 870, 737 cm^{-1}. ^{1}H NMR (200 MHz): 1.08 (3H, s), 1.15 (3H, s), 1.24 (3H, s), 1.32 (3H, s), 1.30–1.60 (3H, m), 1.36 (3H, s), 1.44 (3H, s), 1.84 (1H, d, *J*=12.0), 2.10 (1H, OH, bs), 2.29 (1H, dd, *J*=5.4, 13.5), 2.51–2.65 (1H, m), 2.99 (1H, dd, *J*=12.0, 13.5), 3.55 (1H, t, *J*=10.8), 3.81–3.94 (4H, m), 4.03–4.16 (3H, m), 4.15 (1H, d, *J*=6.9), 5.42 (1H, dd, *J*=5.4, 12.0), 5.69 (1H, d, *J*=10.0), 6.02 (1H, dd, *J*=2.5, 10.0). ^{13}C NMR (50.33 MHz): 19.0, 24.8, 28.3, 29.7, 31.0, 33.5, 36.8, 38.5, 41.7, 42.4, 46.7, 56.8, 58.7, 64.9, 65.0, 65.4, 69.1, 79.9, 90.2, 98.1, 109.7, 119.3, 128.2, 132.8, 158.8. CIMS: 435 ($[M+H]^+$, 6), 417 (23), 377 (100), 373 (31), 359 (24), 315 (33), 227 (11), 87 (99).

5.12. Sharpless epoxidation

A mixture of diol (−)-**14** (1.9 g, 4.2 mmol) and $VO(acac)_2$ (16 mg, 0.06 mmol) in benzene (100 ml) was refluxed for 10 min under argon. Addition of 5–6 M *t*BuOOH in decane (1.0 ml, 5.5 mmol) followed, and stirring continued at this temperature for 15 min. After cooling, dilution with EtOAc, and washing with a saturated aqueous solution of $NaHCO_3$, water and brine, the residue was dried, concentrated and chromatographed on silica gel (heptane:EtOAc, 1:1 to 1:3) to yield 265 mg (14%) of **15**, 390 mg (20%) of **16** and 1.19 g (61%) of the desired bisepoxy-1,3-diol **17**. The C-9 oxidized derivatives **15** and **16** were then easily recycled by $LiAlH_4$ reduction in dry Et_2O, at 0°C, (10 min, 96%) for the latter and $LiAlH_4$ reduction followed by Sharpless epoxidation as above for the former, thus considerably increasing the yield.

Elution with heptane:ethyl acetate, 2:1, afforded first the C-9 oxidized derivatives **15** and **16** which served as B-like substrates (Scheme 5) in, otherwise unsuccessful, retro-aldol type II fragmentation experiments.

15: mp: 188–190°C (heptane:ether). IR (film): 2987, 2967, 2939, 2875, 1737, 1460, 1381, 1372, 1226, 1199, 1112, 1001, 871 cm^{-1}. ^1H NMR (400 MHz): 0.92 (3H, s), 1.19 (3H, s), 1.41 (3H, s), 1.42 (3H, s), 1.45 (3H, s), 1.51 (3H, s), 1.72 (1H, t, *J*=13.8), 1.86 (1H, dd, *J*=9.5, 13.8), 1.92–2.08 (1H, m), 2.11–2.14 (2H, m), 2.22 (1H, dd, *J*=1.9, 13.6), 2.76 (1H, ddd, *J*=1.9, 9.5, 13.8), 3.31 (1H, bs, OH), 3.33 (1H, dd, *J*=4.5, 8.3), 3.77 (1H, t, *J*=11.1), 3.96–4.03 (4H, m), 4.16–4.24 (2H, m), 5.66 (1H, d, *J*=10.0), 5.84 (1H, dd, *J*=2.4, 10.0). ^{13}C NMR (62.9 MHz): 18.9, 24.3, 25.7, 27.2, 28.3, 29.6, 37.1, 39.3, 39.5, 41.5, 52.4, 53.8, 57.5, 59.9, 64.6, 64.7, 65.3, 69.6, 72.7, 85.3, 98.5, 109.2, 128.1, 131.6, 218.1. Anal. calcd for $C_{25}H_{36}O_7$: C 66.94, H 8.09, found: C 66.89, H 8.12.

16: mp: 224–226°C (heptane:ether). $[\alpha]_D$ −14.3 (*c* 1.29). IR (film): 3469, 2987, 2968, 2939, 2876, 1737, 1465, 1382, 1374, 1301, 1268, 1230, 1219, 1200, 1168, 1115, 1084, 1052, 1000, 948, 918, 896, 857 cm^{-1}. ^1H NMR (300 MHz): 0.93 (3H, s), 1.20 (3H, s), 1.44 (6H, s), 1.45 (3H, s), 1.51 (3H, s), 1.76 (1H, dd, *J*=9.1, 13.9), 1.94 (1H, dd, *J*=1.8, 13.4), 2.03 (1H, dd, *J*=13.5, 13.9), 2.04–2.09 (2H, m), 2.39 (1H, dddd, *J*=4.1, 9.5, 11.1, 13.5), 2.71 (1H, ddd, *J*=1.8, 9.1, 13.5), 3.19 (1H, OH, s), 3.29 (1H, dd, *J*=3.7, 9.1), 3.33 (1H, d, *J*=4.5), 3.37 (1H, d, *J*=4.5), 3.64 (1H, t, *J*=11.1), 3.96–4.04 (4H, m), 4.03 (1H, d, *J*=9.5), 4.11 (1H, dd, *J*=4.1, 11.1). ^{13}C NMR (62.9 MHz): 18.8, 24.3, 25.2, 25.6, 27.3, 29.5, 33.7, 36.3, 37.1, 39.3, 50.7, 52.7, 54.3, 57.2, 57.3, 60.1, 64.6, 64.8, 64.9, 70.7, 72.5, 86.1, 98.7, 109.2, 218.4. CIMS: 465 ($[M+H]^+$, 100), 447 (24), 407 (24), 403 (53), 389 (30), 345 (40), 87 (99). HRCIMS: calcd for $C_{25}H_{37}O_8$ m/z 465.2488, found: 465.2479. Anal. calcd for $C_{25}H_{36}O_8$: C 64.64, H 7.81, found: C 64.39, H 7.97.

17: mp: 210–212°C (heptane:EtOAc). $[\alpha]_D$ −45 (*c* 1.31). IR (film): 3451, 2991, 2981, 2875, 1460, 1384, 1374, 1268, 1255, 1230, 1217, 1196, 1170, 1101, 1055, 1039, 996, 755 cm^{-1}. ^1H NMR (300 MHz): 0.91 (3H, s, Me-16), 1.17 (3H, s, Me-17), 1.39 (3H, s, Me-19), 1.42 (3H, s, Me-18), 1.43 (3H, s, Me-eq acetonide), 1.45–1.52 (2H, m, H-11, H-3), 1.48 (3H, s, Me-ax acetonide), 1.94 (1H, t, *J*=13.4, H-11), 1.98–2.05 (2H, m, H-13), 2.35 (1H, m, H-4), 2.61 (1H, ddd, *J*=7.4, 8.0, 13.4, H-10), 2.89 (1H, s, OH), 3.20 (1H, d, *J*=4.7, H-7), 3.22 (1H, dd, *J*=4.5, 8.1, H-14), 3.33 (1H, d, *J*=4.7, H-6), 3.53 (1H, t, *J*=11.1, H-20ax), 3.92–4.03 (4H, m, -OCH_2CH_2O-), 3.98 (1H, d, *J*=9.8, H-5), 3.99 (1H, dd, *J*=4.7, 11.1, H-20eq), 4.27 (1H, d, *J*=7.4, H-9). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-14, H-11β, H-10; {Me-19}: H-3, H-9, H-7, H-5; {Me-βax of acetonide}: H-20β-ax, H-5; {H-5}: H-3, H-6, Me-ax acetonide, H-20ax; {H-6}: H-7, H-5; {H-7}: Me-19, H-6; {H-14}: Me-16, Me-17, H-13. ^{13}C NMR (62.9 MHz): 18.7 (Me-ax acetonide), 24.1 (Me-18), 25.4 (Me-17), 27.5 (Me-16), 29.4 (Me-eq acetonide), 29.6 (Me-19), 34.2 (C-4), 34.7 (C-11), 37.0 (C-13), 37.9 (Cq), 46.3 (Cq), 53.6 (C-6), 54.3 (C-3), 56.8 (C-14), 57.0 (C-10), 57.6 (C-7), 64.4, 64.6 (-OCH_2CH_2O-), 65.0 (C-20), 70.6 (C-5), 72.6 (Cq-O), 82.2 (C-9), 87.3 (Cq-O), 98.4 (C-12), 109.2 (Cq-acetonide). CIMS: 467 ($[M+H]^+$, 96), 449 (54), 409 (17), 405 (79), 391 (57), 347 (55), 329 (23), 87(100). HRCIMS: calcd for $C_{25}H_{37}O_8$ m/z 467.2645, found: 467.2640. Anal. calcd for $C_{25}H_{38}O_8$: C 64.36, H 8.21, found: C 64.31, H 8.29.

5.13. Setting the stage for the B-ring formation: mesylation protocol

To a stirred solution of **17** (550 mg, 1.18 mmol) in pyridine (10 ml), in the presence of DMAP as catalyst (few crystals), methanesulfonyl chloride (MsCl, 0.8 ml, 8.2 mmol) was added at 0°C and stirring continued for 1 h at this temperature (TLC monitoring, CH_2Cl_2:MeOH, 96:4 as eluent). The reaction was quenched with a saturated aqueous solution of sodium bicarbonate, and extracted with methylene chloride. The combined extracts were washed with 1 N hydrochloric acid, water, sodium bicarbonate and

brine, and then dried over sodium sulfate, and concentrated under reduced pressure to give 642 mg of the required mesylate **18**. As a sensitive compound it was taken into the next step without purification. Spectral characteristics of this crude material (purified on silica gel, heptane:EtOAc, 1:1 to 1:1.5 as eluent) are as follows: $[\alpha]_D$ −32.3 (*c* 1.16). IR (film): 3387, 3035, 2985, 2872, 1655, 1461, 1384, 1342, 1331, 1271, 1234, 1220, 1200, 1172, 1116, 1104, 1056, 961, 896, 861 cm^{-1}. ^1H NMR (300 MHz): 0.90 (3H, s), 1.18 (3H, s), 1.41 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 1.48 (3H, s), 1.56 (1H, dd, *J*=7.8, 13.8), 1.57 (1H, d, *J*=13.1), 1.97–2.06 (2H, m), 2.13 (1H, t, *J*=13.8), 2.32–2.51 (1H, m), 2.71 (1H, ddd, *J*=7.5, 7.8, 13.8), 2.97 (1H, s, OH), 3.08 (3H, s), 3.19 (1H, d, *J*=4.7), 3.23 (1H, dd, *J*=3.6, 8.8), 3.28 (1H, d, *J*=4.7), 3.53 (1H, t, *J*=11.1), 3.94–4.02 (6H, m), 5.14 (1H, d, *J*=7.5). ^{13}C NMR (75 MHz): 18.6, 24.1, 25.2, 27.4, 28.8, 29.3, 33.9, 35.3, 36.9, 37.8, 37.9, 46.0, 52.9, 54.2, 55.4, 56.6, 56.9, 64.4, 64.5, 64.7, 70.3, 72.3, 87.7, 87.8, 98.3, 109.0. CIMS: 545 ($[M+H]^+$, 6), 527 (7), 483 (28), 449 (100), 425 (28), 391 (18), 347 (11), 329 (13), 143 (7), 103 (98), 87 (37).

5.14. Fragmentation

For the synthesis of the BC fragment **5** we report two routes, both of which are efficient and allow access to multigram quantities of material.

(a) Mesylate **18** (1.15 mmol) was dissolved in THF (15 ml) and *t*BuOK (1 M in *t*BuOH, 3.5 ml, 3.5 mmol) was added at room temperature. The temperature was then raised to 70°C (bath temp.) and the reaction mixture was stirred for 45 min. After cooling, then dilution with ether, water was added. Extraction with EtOAc, followed by washing with brine, drying of the organic layer on $MgSO_4$ and concentration under reduced pressure furnished 529 mg (92%) of (+)-**5** as a crude. A rapid filtration on SiO_2 (heptane:EtOAc, 2:1 to 1:1) gave pure (+)-**5** in 88% isolated yield.

(b) Sodium hydride (60% suspension in oil) was washed with dry hexane (3×5 ml) under inert atmosphere (septum), vacuum dried and then slurried in anhydrous THF. Mesylate **18** (1.1 mmol) in THF (12 ml) was added to a suspension of NaH (4 mmol) in THF (8 ml). The resulting slurry was heated at reflux for 1 h, quenched with water and extracted with methylene chloride. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification as above gave 75% of the desired compound (+)-**5**: mp 168–170°C (heptane:ether). $[\alpha]_D$ +21 (*c* 1.29). IR (film): 2989, 2968, 2937, 2877, 2853, 1702, 1476, 1459, 1442, 1382, 1370, 1320, 1305, 1268, 1239, 1229, 1199, 1177, 1156, 1118, 1106, 1062, 1036, 1020, 951, 937, 917, 888, 857, 765, 741 cm^{-1}. ^1H NMR (300 MHz): 0.82 (3H, s, Me-16), 1.19 (3H, s, Me-17), 1.20 (1H, dd, *J*=7.9, 14.7, H-13), 1.33 (3H, s, Me-18), 1.40 (3H, s, Me-acetonide), 1.41 (3H, s, Me-acetonide), 1.68 (1H, dd, *J*=3.2, 14.7, H-13), 1.70 (1H, dd, *J*=8.8, 13.8, H-11), 1.78 (3H, s, Me-19), 2.38 (1H, dddd, *J*=4.3, 10.5, 10.6, 12.2, H-4), 2.75 (1H, d, *J*=12.2, H-3), 2.80 (1H, dd, *J*=8.8, 13.8, H-11), 2.95 (1H, d, *J*=4.4, H-7), 3.16 (1H, t, *J*=10.5, H-20ax), 3.18 (1H, dd, *J*=3.2, 7.9, H-14), 3.31 (1H, d, *J*=4.4, H-6), 3.80 (1H, dd, *J*=4.3, 10.5, H-20eq), 3.91–3.97 (4H, m, OCH_2CH_2O), 4.04 (1H, d, *J*=10.6, H-5), 5.68 (1H, dt, *J*=8.8, 12.2, H-10), 5.77 (1H, dd, *J*=1.3, 12.2, H-9). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-14; {Me-19}: H-3, H-9, H-7; {Me-βax of acetonide}: H-20β-ax, H-5; {H-3}: Me-19, H-5, H-20ax; {H-5}: H-3, H-6, Me-ax acetonide, H-20ax; {H-6}: H-7, H-5; {H-7}: Me-19, H-6, H-9; {H-14}: Me-16, H-13. ^{13}C NMR (75 MHz): 18.9 (Me ax acetonide), 24.0 (Me-17), 24.4 (Me-18), 25.0 (Me-16), 26.1 (Me-19), 29.6 (Me-eq acetonide), 30.4 (C-4), 37.0 (Cq), 38.0 (C-11), 38.5 (Cq), 38.6 (C-13), 55.2 (C-6), 55.6 (C-3), 56.2 (C-14), 61.3 (C-7), 63.7 (C-20), 64.7, 64.8 (OCH_2CH_2O), 69.7, 70.5 (C-5), 98.7, 108.4, 129.9 (C-10), 135.6 (C-9), 205.1 (C-2). CIMS: 449 ($[M+H]^+$, 49), 391 (93), 387 (16), 329 (31), 261 (51), 87 (100). HRCIMS: calcd for $C_{25}H_{37}O_7$: 449.2539, found: 449.2544. Anal. calcd for $C_{25}H_{36}O_7$: C 66.94, H 8.09, found: C 66.68, H 7.91.

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References

1. Arseniyadis, S.; Brondi Alves, R.; Pereira de Freitas, R.; Muñoz-Dorado, M.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Heterocycles* **1997**, *46*, 727–764; Arseniyadis, S.; Rico Ferreira, M.; Quilez del Moral, J.; Yashunsky, D. V.; Potier, P. *Tetrahedron Lett*. **1998**, *39*, 571–574 and references cited therein.
2. Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 15–44; Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemporary Organic Synthesis* **1994**, *1*, 47–75. von Neh, H.; Kühling, A.; Blechert, S. *Helv. Chim. Acta* **1989**, *72*, 101–109.
3. Arseniyadis, S.; Yashunsky, D. V.; Muñoz Dorado, M.; Brondi Alves, R.; Wang, Q.; Potier, P.; Toupet, L. *Tetrahedron* **1996**, *52*, 6215–6232.
4. Lipshutz, B. H.; Sengupta, S. *Organic Reactions*, Paquette, L. et al., Eds; John Wiley & Sons, 1992; Vol. 41.
5. Heathcock, C. H. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press Inc.: New York, 1984; Vol. 3, 111–212.
6. Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem*. **1978**, *43*, 2057–2059; Muzart, J. *Tetrahedron Lett*. **1987**, *28*, 4665–4668.
7. (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc*. **1980**, *102*, 2693–2698. (b) Kagan, H. B. *Nouveau J. Chim*. **1990**, *14*, 453–460.
8. Arseniyadis, S.; Rodriguez, R.; Muñoz Dorado, M.; Brondi Alves, R.; Ouazzani, J.; Ourisson, G. *Tetrahedron* **1994**, *50*, 8399–8426.
9. Petasis, N. A; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.
10. (a) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594. (b) Clayton, R. B.; Henbest, H. B.; Smith, M. *J. Chem. Soc*. **1957**, 1983–1993. (c) Wharton, P. S. *J. Org. Chem*. **1961**, *26*, 4781–4782. (d) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem*. **1965**, *30*, 3254.
11. Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703–5711.
12. LeCocq, C.; Lallemand, J. Y. *J. Chem. Soc., Chem. Commun*. **1981**, 150–152.