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Studies towards the total synthesis of taxoids: a rapid entry into bicyclo[6.4.0]dodecane ring system. Part 2

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Abstract

We report a synthetic route that allows access into A-seco taxoid frameworks embodying the entire carbon skeleton and a large number of oxygen functionalities. The BC-subunit (−)-**4** was constructed in five steps from (+)-**3**, through a step-efficient and stereocontrolled bond construction.

1. Introduction

Recently, we have published a synthetic approach of the taxoid BC-subunit, which served the dual purpose of elucidating the stereochemistry of our aldol–annelation–fragmentation methodology and providing adequate material for further transformations.[1] We thus described the development of a synthetic strategy for advanced taxoid substructures such as (+)-**3**, establishing the feasibility of incorporating all of the 20 carbons and of essential oxygen functionalities of the taxoid[2] diterpene skeleton **I** in 12 steps starting from two achiral aldol partners **1** and **2**. With the efficient synthesis of the bicyclo[6.4.0]dodecane ring system (+)-**3** realized, the stage was now set for the completion of the synthesis. So, we went on to prepare the more advanced intermediates represented by formulas **II**, **III** and **IV**, precursors of taxoid ABC-tricyclic core of type **I**, which incorporate ring A in its seco form. An elementary retrosynthetic analysis (Scheme 1; P stands for ketal protection) of **I** would suggest two routes to achieve C11–C12 bond formation: samarium iodide[3] induced reductive coupling for precursors of types **II** and **III**, and either samarium iodide coupling or aldol chemistry for precursor **IV**. Key questions at this stage include the likelihood of obtaining chemoselectivity in epoxide-ring opening and the nature of functional group interconversion to be chosen en route towards one of the targeted A-seco taxoid frameworks of type **II**, **III** or **IV** for final ring closing (C11–C12).

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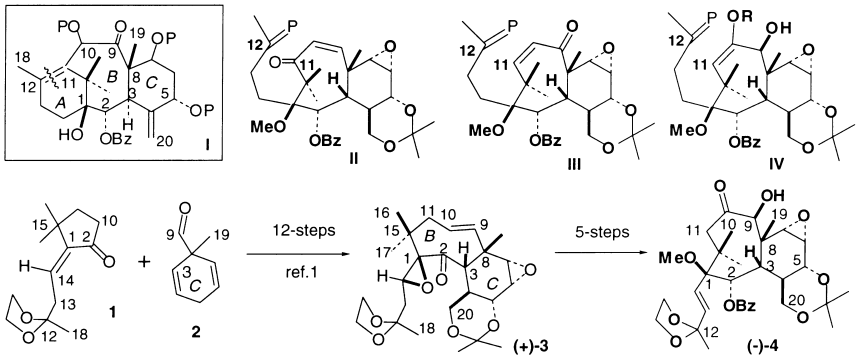


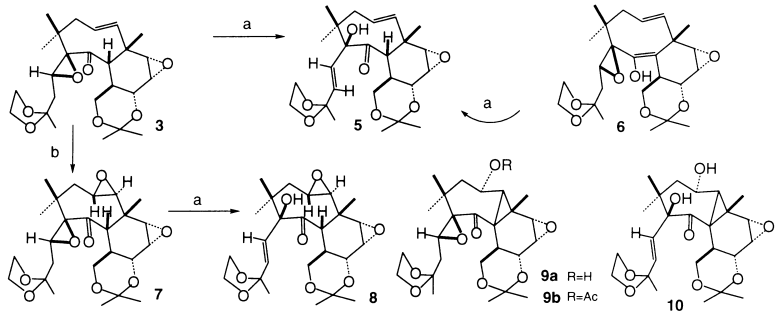
Scheme 1. Synthetic strategy options (**II**, **III**, **IV**) for completion of taxoid ABC core (**I**) via C11–C12 bonding

With the desired bis-epoxy ketone **3** in hand, our initial attention focused on the synthesis of a derivative bearing a hydroxy group, or a substituent that could be readily transformed into a hydroxy group at C-11 (type **II** precursor), with the view that intramolecular reductive coupling would be possible upon removal of the ketal protecting group at C-12. At this stage the absolute stereochemistries of all stereogenic centers were determined; based on literature precedents,[4] the required C-3 epimerization was deferred to the end of our synthetic scheme, following ABC-construction. Unfortunately, despite extensive experimentation, allylic oxidation [$Cr(CO)_6$, *t*-BuOOH, in decane; CrO_3–3,5-DMP, *t*-BuOOH 70% in H_2O; SeO_2, *t*-BuOOH, CH_2Cl_2][5] at C-11 was not realized. We therefore concentrated on the installation of the hydroxy group at C-1 via a selective epoxide opening and the reduction of C-2 carbonyl which would ultimately serve as an entry to the C2–OBz substituent. To that end, we elected to study the base-mediated rearrangement of bis-epoxide **3** and of its close relative tris-epoxide **7**, in order to assess the difference in reactivity between C1–C14, C9–C10 and C6–C7 epoxy functionalities. This was especially important since chemodifferentiation was a key issue for the following transformations. It was anticipated that compound **7** (Scheme 2), could be derived from **3** via epoxidation, and lead into a type **III** precursor for A-ring formation through some functional group manipulation. Thus, exposure of **7** to a base using known literature procedures, could conceivably offer easy chemodifferentiation between epoxides at C1–C14 and C9–C10 and further, between C6–C7. Due to the carbonyl activation at C-2, epoxide at C1–C14 would open first, which following appropriate transformations would then ensure opening of the epoxide at C9–C10, setting the stage for a C11–C12 ring closure. A prerequisite for the sequence of reactions just outlined is the successful opening of the C1–C14 epoxide leaving the remaining epoxy functions intact. Herein we report the details for the synthesis of type **IV** precursor, the A-seco taxoid framework (−)-**4**, which starts with the enantiopure bis-epoxide (+)-**3**, a compound available in quantity via our aldol–annelation–fragmentation sequence from simple building blocks **1** and **2**.

2. Results and discussion

2.1. Selective epoxy ring opening at C1–C14

With the ultimate goal of producing a suitable precursor for a C11–C12 bond forming operation, leading to the taxoid ABC-core, we first investigated routes to **5** and to its more oxygenated derivative **7**. As depicted in Scheme 2, preparation of α-ketol **5** and tris-epoxide **7** begins with bis-epoxy ketone **3**. For selective conversion of the latter into **5**, we elected to use a mild base (lithium diethyl amide) induced

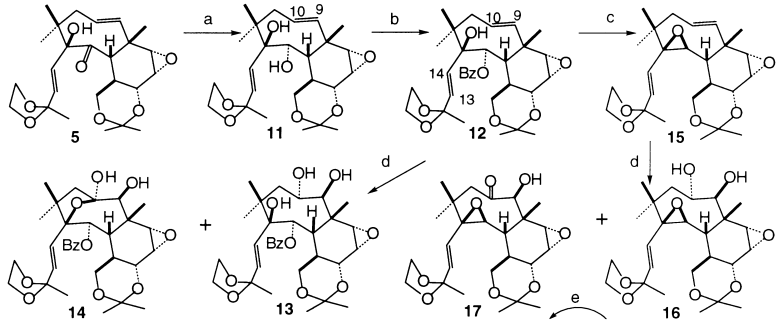


Scheme 2. (a) $LiEt_2N$, THF, HMPA, rt. (b) $MeReO_3$, pyridine, H_2O_2, CH_2Cl_2, rt

ring opening of the epoxide functionality. Numerous conditions were tried, leading to a product mixture **5** and **6**, in variable ratios depending upon reaction temperature. By the way, it should be pointed out that enol-ether **6** was, surprisingly, stable enough to be chromatographed and characterized. We can briefly summarize the effect of temperature upon product distribution as follows. Treatment of **3** with a tenfold excess of $LiEt_2N$, (prepared at −20°C) in dry THF, under argon, in the presence of a tenfold excess of dry HMPA at −78°C for 15 min, afforded enol-ether **6** along with the desired α-ketol **5** in 80% and 9% isolated yields, respectively. When opening was carried out at −40°C for 25 min, the isolated yield of the target allylic alcohol **5** increased to 68%, obtained together with the enol-ether **6** which was isolated in 30% yield. Best results were obtained by treatment with lithium diethylamide and dry HMPA, both in excess, at room temperature for 15 min, leading reproducibly to the target α-ketol **5** in >98% isolated yield, while the enol form **6** was not detected. On the other hand, resubjection of pure enol-ether **6** to the above conditions afforded cleanly α-ketol **5** via **3**. Further functionalization of compound **3** towards the highly oxygenated, [6+8] bicyclic framework containing targets such as **7** was next addressed. The well established *m*CPBA mediated epoxidation was sluggish and yields did not exceed 50%. However, when **3** was treated with methyltrioxorhenium[6] (MTO, 0.5 mol%) in the presence of 1.5 equiv. of H_2O_2 in CH_2Cl_2 under argon at room temperature for 36 h, the corresponding epoxide **7** was obtained as a single isomer, assigned as depicted in Scheme 2, in 88% isolated yield. 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. The highly elaborated polycyclic model **7** thus obtained, which contains 10 stereogenic centers and can exist in 1024 stereomeric forms, is synthesized as a single isomer, optically pure, in only 13 steps from readily available achiral aldol partners **1** and **2**. Within the limits of detection by high field NMR spectroscopy, no stereoisomer was produced throughout this 13 step transformation. The assignment of each proton and carbon resonance signal in **7** was determined from a series of 2D COSY, HMQC, and HMBC correlations.

The relative stereochemistry shown in **7** was consistent with the following 1D NOEDIFF results. Upon irradiation, the Me-16 (δ 0.86) showed NOE enhancements to the H-14 (δ 3.23) and H-11β (δ 1.98) protons; the angular Me-19 showed enhancements to the H-3 (δ 2.83), H-5 (δ 4.10) and H-7 (δ 3.06) protons while the BC-ring junction proton H-3 showed enhancements to the Me-19, H-5 and H-20 β-axial protons. These results confirmed the stereochemistry depicted in Scheme 2 for **7**. For elaboration of the epoxide opening conditions on tris-epoxy ketone **7**, we decided to carry out studies on racemic material in order to save the precious optically pure taxoid subunit **3**. Attempts to convert tris-epoxy ketone **7** into the target system **8** by using $LiEt_2N$ in the presence of HMPA, according to the procedure used above were unrewarding. Several sets of conditions were screened in an attempt to overcome the encountered problems, but all failed. Thus, epoxide opening in **7** under the usual conditions gives a cyclopropane formation of type **9a** or **10** (depending upon reaction temperature) as the major compound, along with

variable, though not exceeding 30%, amounts of the desired **8**. This is due to competing transannular processes related to C-2 carbonyl group; proton abstraction from C-3 seems easy and cyclization occurs to generate cyclopropane **9a**, whose structure was assigned on its acetate derivative **9b** by high field NMR studies (comprehensive 2D NMR experiments run at 800 MHz which included COSY, HMQC, HMBC correlations allowed all carbons and their respective protons to be assigned with confidence) and **10**. In summary, subjection of racemic **7** to epoxide ring-opening conditions at 0°C for 1 h afforded only a modest yield of the desired bis-epoxy α-ketol derivative **8** (30%) which was accompanied by the unwanted **10** (33%). When we reacted epoxide **7** under the same conditions as for **3**, at below zero temperatures (−65°C over 15 min), we found that **9a** was the major product along with unreacted starting material. Even when we left the reaction for 15 min at 65°C, we were only able to isolate a 75% yield of **9a**; from −65°C to 65°C the only difference being the presence or absence of unreacted starting material. It is noteworthy, and in complete agreement with previous work,[7] that despite the ease of enolization at C-3 no epimerization occurred during all these experiments, as was verified by exhaustive spacial proximity effect measurements by high field ^{1}H-NMR analysis using NOEDIFF and NOESY techniques. Because of the unsatisfactory results obtained from transformations involving the epoxide opening of **7**, a synthetic route targeting type **IV** precursor for C11–C12 bonding was developed (Scheme 3).



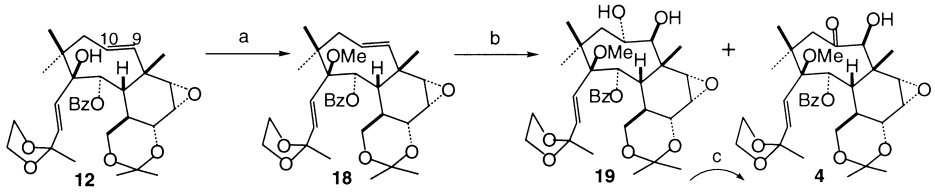
Scheme 3. (a) $LiAlH_4$–THF, 0°C. (b) BzCl, Et_3N, CH_2Cl_2, rt, 15 h. (c) KOH–DMSO. (d) OsO_4–NMO, pyridine, *t*-BuOH–H_2O. (e) Dess–Martin periodinane, CH_2Cl_2, pyridine, rt

2.2. The C9–C10 double bond functionalization

The differences in reactivity between the α-keto epoxide moiety at C1–C14 and the epoxide at C6–C7 allowed for selective manipulation just as required for the synthetic scheme. The elaboration of α-ketol **5** so-formed began with reduction of the C-2 carbonyl group; the latter was treated with lithium aluminum hydride and the ensuing reaction produced the corresponding diol **11**. Treatment of diol **11** with benzoyl chloride in anhydrous methylene chloride in the presence of triethylamine afforded the α-hydroxy benzoate **12**; only one chromatographic separation was used in the synthesis of **12** from **3**. To introduce the requisite C9–C10 substitution pattern, several options were available. A possible competing side reaction could have been the cleavage of the C9–C10 oxygenated moiety under extreme conditions. Yet another complication could arise from the presence of the C13–C14 double bond, during the C9–C10 functionalization. To address this problem we elected to carry out oxidation by osmium tetroxide; a reagent known to be highly susceptible to steric effects. In this case, attack should take place selectively at the more accessible C9–C10 double bond, as required. Attempted osmylation of **12** (cat. OsO_4, NMO, Py, *t*-BuOH, H_2O, 75°C, 4.5 h) in the presence of a free hydroxy group at C-1, afforded the desired diol **13** (57% isolated yield) which was accompanied by the unwanted transannular hemi-acetal **14** (34%). However, we were pleased to find that the first formed diol **13** underwent oxidation at C-10

exclusively (just as required) leading selectively to **14** and that the alkene groups in **12** could be easily chemodifferentiated (the C13–C14 double bond remained intact).

To circumvent the problematic formation of the undesired hemi-acetal **14**, protection of the free hydroxyl group at C-1 before effecting the osmylation step was then investigated. For this purpose we report two routes, both of which are efficient and allow access to conveniently functionalized material for further transformation. The two alternative strategies for hydroxyl group protection at C-1 utilized powdered KOH in DMSO both for the 1,2-transposed epoxide **15** (Scheme 3) and for the methyl ether **18**; for the latter MeI was used as an electrophile (Scheme 4). Accordingly, conversion of **12** to **15** was quite rapid (1.5 h). Brief treatment of benzoyl-alcohol **12** with 12 equiv. of freshly powdered potassium hydroxide in DMSO (10 ml per mmol) led to the formation of the corresponding C1–C2 epoxide **15** in 82% isolated yield which was subsequently subjected to a dihydroxylation with catalytic osmium tetroxide to furnish the C9–C10 diol **16** along with the desired acyloin **17**. Treatment of the resulting diol **16** with Dess–Martin periodinane in dry methylene chloride and pyridine at room temperature then provided additional **17** thus increasing the yield to the 80% levels; no other isomer was detected. On the other hand, the C-1 tertiary alcohol of **12** was converted to its corresponding methyl ether **18** by treatment with 12 equiv. of powdered KOH in DMSO (10 ml per mmol) and, immediately after, addition of excess, freshly distilled, MeI (30 min at room temperature with stirring) in 40% isolated yield along with 40% of recovered starting material. When di-olefin **18** was brought into reaction with a catalytic amount of osmium tetroxide in the presence of NMO, a product mixture containing the expected diol **19** (52%) and the desired acyloin (−)-**4** (32%) resulted. Oxidation of the C9–C10 diol **19** thus obtained with the Dess–Martin periodinane reagent at room temperature in dry CH_2Cl_2 and pyridine as above gave α-ketol **4** as the sole product in quantitative yield. Presumably, the neopentylic nature at C-9 of diol **19** disfavors oxidation at this position, thus allowing for a selective preparation of the desired acyloin.



Scheme 4. (a) KOH, DMSO, MeI, 18°C. (b) Catalytic OsO_4, NMO, pyridine, *t*-BuOH–H_2O, 50–70°C. (c) Dess–Martin, pyridine, CH_2Cl_2, rt

The synthetic scheme starting from **1**+**2** proceeded affording a single isomer for all transformations and no detectable side compound. The first undesired byproduct was obtained in the attempted osmylation of **12** in the presence of a free hydroxyl group at C-1. To obviate this complication we had to protect the C-1 position before effecting the osmylation step which directly affords the desired acyloin. Using **15** and **18**, containing no free hydroxyl group at the C-1 position, the C9–C10 functionalization was much more convenient, dihydroxylation being complete within less then 2 h when the reaction was performed from room temperature to 70°C (oil bath temperature); under these conditions the target acyloins **17** and **4**, were obtained directly in ca. 40% yield (Scheme 4). Also noteworthy is the regioselectivity observed in oxidation reactions with Swern, TPAP–NMO and Dess–Martin periodinane. This selectivity may be a result of the hindered nature of the OH group at C-9; such selectivity would certainly have implications in protecting group strategies (C-9 versus C-10).

3. Conclusion

In summary, an efficient synthesis of optically pure taxoid BC-subunit having peripheral functional groups suitable for appending additional substituents has been developed, making this strategy operational for taxoid construction. This five-step reaction sequence: (i) selective epoxide opening (**5**); (ii) reduction (**11**); (iii) benzoylation (**12**); (iv) protection (**15** and **18**); and (v) osmylation, provided (−)-**17** and (−)-**4** with excellent selectivity, as none of the unwanted byproducts were detected. A noteworthy feature of this synthesis pertains to the formation of only one stereoisomer out of many possible throughout, as shown by the detection of a single set of signals in the high-field (400 and 800 MHz for ^{1}H, 75 and 200 MHz for ^{13}C) NMR spectra of all investigated intermediates. Acyloins (−)-**4** and (−)-**17** are attractive synthetic intermediates because they contain the entire carbocyclic framework of the taxoid diterpene skeleton, a suitably functionalized 'C'-ring and sufficient functionality within the 'B'-ring to permit 'A'-ring formation and ensure the C-3 epimerization. Although they have a keto transposed arrangement, they are promising for the next operation, the C11–C12 bond formation. Our current efforts are concerned with the further elaboration of BC-subunits into the taxoid diterpene ABC core. Among the tasks remaining is the reduction of the double bond at C13–C14 and subsequent A-ring formation via either an intramolecular aldol reaction or samarium iodide mediated reductive coupling.

4. Experimental

General experimental details were as previously described.[8] NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform, unless otherwise noted. NMR experiments (800 MHz) were carried out on a Bruker Avance DRX-800 spectrometer, equipped with a triple resonance H/C/N probehead 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 using adiabatic WURST-40 pulses. For the proof of stereochemistry of investigated products we carried out an elaborate series of nuclear Overhauser enhancement (NOE) experiments using difference spectra, in order to establish the configuration of the key centers in the target products. 'Usual work up' means washing of the organic layer with brine, drying over anhydrous magnesium sulfate, and evaporating in vacuo with a rotary evaporator at aspirator pressure.

*4.1. Preparation of α-ketol **5** via selective epoxide opening*

To a magnetically stirred solution of $LiEt_2N$ (prepared at 0°C from 5.80 mmol of Et_2NH and 4.75 mmol of BuLi 2.5 M in hexanes) in 4 ml of dry THF, HMPA (1.0 ml, 5.7 mmol), was added and the reaction mixture was allowed to reach room temperature. A solution of bis-epoxy ketone **3** (227 mg, 0.51 mmol) in 3 ml of dry THF was then added and stirring continued for 15 min at room temperature, under an argon atmosphere. After quenching with a saturated aqueous solution of ammonium chloride and dilution with ether, the aqueous phase was extracted with EtOAc. Following usual work up, the residue was filtered on SiO_2 (eluent heptane:EtOAc 1:1) to remove the remaining HMPA and used without further purification (227 mg, 100%). An analytical sample of **5** was characterized as follows: $[\alpha]_D$ +2 (*c* 2.32, THF). Mp 212–214°C (ether–heptane). IR (Nujol): 3463, 1702, 1265, 1230, 1199, 1174, 1100, 1064, 1036 cm^{-1}. ^{1}H-NMR (300 MHz): 0.86 (3H, s, Me-17), 1.11 (3H, s, Me-16), 1.41 (3H, s, Me-18), 1.44 (3H, s, Me α-eq acetonide), 1.45 (3H, s, Me β-ax acetonide), 1.62 (1H, dd, *J*=8.1, 13.5, H-11), 1.68 (3H, s, Me-19), 1.95 (1H, br s, OH), 2.53 (1H, dddd, *J*=4.5, 5.4, 10.6, 10.8, H-4), 2.97 (1H, dd, *J*=10.7, 13.5,

H-11), 3.05 (1H, d, *J*=4.5, H-7), 3.22 (1H, t, *J*=10.8, H-20 β-ax), 3.25 (1H, dd, *J*=5.4, 10.8, H-20 α-eq), 3.31 (1H, d, *J*=4.5, H-6), 3.38 (1H, d, *J*=12.2, H-3), 3.73–3.85 (2H, m, OCH_2CH_2O), 3.91–4.00 (2H, m, –OCH_2CH_2O–), 4.09 (1H, d, *J*=10.6, H-5), 5.49 (1H, d, *J*=15.9, H-13), 5.53 (1H, ddd, *J*=8.1, 10.7, 11.9, H-10), 5.94 (1H, d, *J*=11.9, H-9), 5.77 (1H, d, *J*=15.9, H-14). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-14, H-10; {Me-18}: H-13; {Me-19}: H-3, H-7, H-5; {H-3}: H-5, Me-19; {H-5}: H-3, H-6, Me-19, Me β-ax acetonide; {H-6}: H-5, H-7; {H-7}: H-6, H-9, Me-19. ^{13}C-NMR (62.9 MHz): 19.0, 22.0, 24.6, 25.3, 27.0, 29.5, 31.5, 36.2, 37.0, 41.4, 53.2, 54.5, 62.2, 63.9, 64.4, 64.6, 69.6, 84.5, 98.9, 107.2, 129.5, 129.8, 132.9, 137.5, 209.5. CIMS: 449 ($[M+H]^+$, 100), 431 (10), 391 (48), 387 (26), 373 (17), 329 (20), 87 (27). Analysis: calcd for $C_{25}H_{36}O_7$: C 66.93; H 8.09; O 24.97, found: C 66.76; H 8.21. HRCIMS: calcd for $C_{25}H_{37}O_7$: 449.2539, found: 449.2528.

Running the same reaction at −78°C for 15 min and proceeding as above, allowed for the synthesis and characterization of the 'expected to be' rather unstable enol-ether **6** (purification on SiO_2 using heptane:EtOAc 2:1 as eluent): IR (film): 3342, 2984, 1704, 1667, 1453, 1378, 1271, 1222, 1070, 939, 738 cm^{-1}. ^{1}H-NMR (250 MHz): 0.80 (3H, s), 1.13 (3H, s), 1.24 (3H, s), 1.34 (3H, s), 1.46 (3H, s), 1.47 (3H, s), 1.52–1.66 (2H, m, H-11, H-13), 2.45 (1H, dd, *J*=2.1, 14.7, H-13), 2.79 (1H, dd, *J*=2.1, 10.6, H-14), 2.85–2.95 (1H, m, H-11), 2.92 (1H, d, *J*=4.9, H-7), 3.08 (1H, dt, *J*=4.9, 10.4, H-4), 3.32 (1H, d, *J*=4.9, H-6), 3.51 (1H, t, *J*=10.4, H-20β-ax), 3.93–4.07 (4H, m, OCH_2CH_2O), 4.43 (1H, d, *J*=10.4, H-5), 4.90 (1H, dd, *J*=4.9, 10.4, H-20α-eq), 5.30 (1H, dd, *J*=1.2, 12.2, H-9), 5.57 (1H, ddd, *J*=8.0, 9.7, 12.2, H-10), 6.46 (1H, s, OH). ^{13}C-NMR (62.9 MHz, C_6D_6): 20.5, 21.8, 24.3, 26.8, 28.3, 29.1, 37.8, 38.3, 38.7, 39.3, 42.1, 49.0, 54.3, 60.2, 64.7 (2, OCH_2CH_2O), 65.5 (C-20), 69.1, 70.4, 99.7, 108.9, 116.1, 124.1, 138.9, 145.6. CIMS: 449 ($[M+H]^+$, 39), 431 (15), 391 (99), 383 (21), 329 (18), 261 (20), 87 (100).

*4.2. Preparation of the tris-epoxy ketone **7***

To a stirred solution of bis-epoxy ketone **3** (134 mg, 0.30 mmol) in 2 ml of CH_2Cl_2, pyridine (0.006 ml, 0.076 mmol), 30% H_2O_2 (0.03 ml, 0.45 mmol), and $MeReO_3$ (0.8 mg, 0.003 mmol) were added and the reaction mixture stirred under argon at room temperature for 36 h. Additional amounts of 30% H_2O_2 were added occasionally (TLC monitoring). The reaction mixture was then diluted with CH_2Cl_2, and following washings with $Na_2S_2O_3$ and brine the organic layers were dried, concentrated and chromatographed (SiO_2, heptane:EtOAc 1:1) to afford 122 mg (88% yield) of tris-epoy ketone **7**: mp 226–228°C EtOH–CH_2Cl_2 (racemic; the mp of the optically pure material could not be measured for it showed). $[\alpha]_D$ −2 (*c* 1.02, THF). IR (film): 2988, 2939, 2886, 2874, 2845, 1698, 1379, 1310, 1267, 1200, 1174, 1152, 1117, 1099, 1064, 1054, 1035, 926, 911, 871, 643 cm^{-1}. ^{1}H-NMR (300 MHz): 0.86 (3H, s, Me-16), 1.31 (1H, dd, *J*=7.7, 14.7, H-13), 1.35 (3H, s, Me-18), 1.39 (3H, s, Me-17), 1.40 (3H, s, Me-19), 1.44 (3H, s, Meα-eq acetonide), 1.45 (3H, s, Meβ-ax acetonide), 1.73 (1H, dd, *J*=3.2, 14.7, H-13), 1.82 (1H, dd, *J*=10.8, 14.7, H-11α), 1.98 (1H, dd, *J*=5.4, 14.7, H-11β), 2.56 (1H, dddd, *J*=4.2, 10.2, 10.5, 12.5, H-4), 2.83 (1H, d, *J*=12.5, H-3), 2.95 (1H, dd, *J*=5.4, 10.8, H-10), 3.06 (1H, d, *J*=4.3, H-7), 3.23 (1H, dd, *J*=3.2, 7.7, H-14), 3.24 (1H, t, *J*=10.5, H-20β-ax), 3.25 (1H, d, *J*=5.4, H-9), 3.37 (1H, d, *J*=4.3, H-6), 3.78 (1H, dd, *J*=4.2, 10.5, H-20α-eq), 3.94–4.00 (4H, m, OCH_2CH_2O), 4.10 (1H, d, *J*=10.2, H-5). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-14, H-11β; {Me-17}: Me-16 (NOE gem), H-10, H-11α; {Me-18}: H-13; {Me-19}: H-3, H-5, H-7; {Me-βax of acetonide}: H-20β-ax, H-3, H-5; {H-10}: H-11β, Me-17, Me-16; {H-11α}: H-11β (NOE gem), Me-17, H-10; {H-11β}: H-11α (NOE gem), Me-16, H-10; {H-4}: H-20α-eq; {H-3}: Me-19, H-5, H-20β-ax; {H-7}: Me-19, H-6; {H-6}: H-7, H-5; {H-5}: H-3, H-6, Meβ-ax acetonide, H-20β-ax. ^{13}C-NMR (75 MHz): 18.7 (Meβ-ax acetonide), 22.2 (Me-19), 24.2 (Me-18), 24.4 (Me-17), 25.4 (Me-16), 29.4 (Meα-eq acetonide), 30.3 (C-4), 34.1 (Cq-15), 37.6 (Cq-8), 38.6 (C-13), 38.9 (C-11), 51.3 (C-3), 54.4 (C-6), 54.8 (C-10), 55.6 (C-14), 58.2

(C-9), 59.5 (C-7), 63.1 (C-20), 64.6 and 64.7 (OCH_2CH_2O), 68.9 (C-1), 70.4 (C-5), 98.7 (Cq-12), 108.1 (Cq-acetonide), 207.0 (C-2). CIMS: 465 ($[M+H]^+$, 86), 407 (74), 403 (16), 389 (19), 345 (19), 277 (26), 87 (100). HRCIMS: calcd for $C_{25}H_{37}O_8$: 465.2488, found: 465.2471. Analysis: calcd for $C_{25}H_{36}O_8$: C 64.64; H 7.81, found: C 63.96; H 7.64.

*4.3. Selective epoxide opening on tris-epoxy ketone **7**; preparation of the desired α-ketol bis-epoxide **8** and cyclopropane-containing byproducts*

Best conditions for α-ketol **8**: $LiEt_2N$ prepared at −20°C (0.12 ml, 1.16 mmol of Et_2NH in 1 ml of dry THF; 0.42 ml, 1.05 mmol of *n*-BuLi was added at −20°C and the reaction mixture was stirred for 1 h). Then 0.37 ml (2.10 mmol) of HMPA were added and the reaction mixture was allowed to reach 0°C. At this temperature, a solution of **7** (68 mg, 0.15 mmol) in 1 ml of dry THF was added and stirring continued at 0°C for 1 h. Quenching with saturated aqueous ammonium chloride, dilution with EtOAc and usual work up afforded after chromatography (SiO_2, eluent heptane:EtOAc 1:2) 21 mg of α-ketol bis-epoxide **8** (30%) and 23 mg of diol-cyclopropane **10** (33%). **8**: IR (film): 3452, 3059, 2996, 2877, 1705, 1381, 1261, 1204, 1034, 903 cm^{-1}. ^{1}H-NMR (250 MHz): 0.88 (3H, s), 1.33 (3H, s), 1.40 (3H, s), 1.42 (6H, s), 1.45 (3H, s), 1.83 (1H, dd, *J*=5.0, 14.3), 1.95 (1H, dd, *J*=10.0, 14.3), 2.52–2.67 (1H, m), 2.87 (1H, td, *J*=5.0, 10.0), 3.10–3.31 (5H, m), 3.39 (1H, d, *J*=4.4), 3.70–3.82 (2H, m), 3.92–3.97 (3H, m), 4.15 (1H, d, *J*=10.4), 5.54 (1H, d, *J*=15.8), 6.12 (1H, d, *J*=15.8). ^{13}C-NMR (62.9 MHz): 19.0, 22.7, 23.0, 25.4, 25.6, 29.5, 30.6, 34.1, 37.0, 42.7, 49.7, 54.6, 55.3, 59.9, 60.6, 63.4, 64.6, 64.7, 70.0, 77.5, 84.4, 107.1, 131.2, 131.8, 211.0. CIMS: 465 ($[M+H]^+$, 100), 451 (23), 421 (25), 407 (74), 403 (22), 389 (20), 363 (20), 345 (20), 87 (21). HRCIMS: calcd for $C_{25}H_{37}O_8$: 465.2488, found: 465.2490.

Best conditions for cyclopropane derivative **9**: To a stirred solution of Et_2NH (0.04 ml, 0.36 mmol) in dry THF (1.5 ml), *n*-BuLi (0.13 ml, 0.32 mmol) was added at −35°C and the reaction mixture was stirred for 1 h, after which time it was cooled to −65°C. To this, HMPA (0.11 ml, 0.63 mmol) and a solution of **7** (21 mg, 0.045 mmol) in 1.5 ml of dry THF were then added and stirring was continued for 15 min. Quenching with saturated aqueous ammonium chloride, dilution with EtOAc, extraction and usual work up furnished after chromatography (SiO_2, eluent heptane:EtOAc 1:1) 11.2 mg of **9a** (53%) and 8.5 mg of recovered starting material (41%). The alcohol **9a** thus obtained, was acetylated at room temperature, using an excess of Ac_2O in dry pyridine in the presence of a catalytic amount of DMAP to afford following SiO_2 column chromatography (eluent heptane:EtOAc 1:1) an 80% yield of the corresponding C-10 acetate which was fully characterized. **9b**: IR (film): 2989, 2934, 2885, 1737, 1676, 1376, 1370, 1243, 1197, 1099, 1023, 942, 736 cm^{-1}. ^{1}H-NMR (800 MHz): 0.82 (3H, s, Me-16/17), 1.14 (3H, s, Me-19), 1.31 (3H, s, Me-acetonide), 1.35 (3H, s, Me-acetonide), 1.36 (3H, s, Me-18), 1.39 (3H, s, Me-17/16), 1.66 (1H, dd, *J*=13.1, 14.9, H-11), 1.76 (1H, dd, *J*=6.7, 14.9, H-11), 1.81 (1H, dd, *J*=3.0, 14.3, H-13), 1.96 (1H, ddd, *J*=4.7, 10.9, 12.3, H-4), 1.99 (1H, dd, *J*=7.9, 14.3), 1.99 (3H, s, C*H*$_3$C=O), 2.00 (1H, d, *J*=8.9), 3.09 (1H, d, *J*=4.4, H-6), 3.15 (1H, d, *J*=4.4, H-7), 3.21 (1H, dd, *J*=3.0, 7.9, H-14), 3.45 (1H, dd, *J*=10.8, 12.3, H-20), 3.66 (1H, dd, *J*=4.7, 10.8, H-20), 3.89–3.95 (4H, m, –OCH_2CH_2O–), 4.38 (1H, d, *J*=10.9, H-5), 5.69 (1H, ddd, *J*=6.7, 8.9, 13.1, H-10). ^{13}C-NMR (62.9 MHz): 17.7 (Me-19), 19.0 (Me-acetonide), 21.1 (Me-acetonide), 24.4 (Me-17/16), 24.5 (2C, Me-18 and C-3), 26.8 (Me-16/17), 29.4 (Me-acetonide), 33.5 (C-15), 33.7 (C-9), 36.3 (C-13), 37.7 (C-8), 39.4 (C-4), 41.6 (C-11), 54.1 (C-6), 55.8 (C-7), 59.6 (C-14), 61.0 (C-20), 64.7 (2C, –OCH_2CH_2O–), 69.6 (C-5), 69.7 (C-10), 70.7 (C-1), 99.3 (Cq-acetonide), 109.1 (C-12), 170.0 (CH_3C=O), 204.4 (C-2). CIMS: 507 ($[M+H]^+$, 70), 505 (54), 449 (100), 447 (21), 389 (28), 87 (99). HRCIMS: calcd for $C_{27}H_{38}O_9$: 507.2594, found: 507.2600.

Cyclopropane-diol ketone **10** obtained along with **8**. **10**: Purification: SiO_2, heptane:EtOAc 1:2. IR (film): 3480, 2983, 2935, 2893, 1695, 1389, 1263, 1197, 1095, 1035 cm^{-1}. ^{1}H-NMR (250 MHz): 0.85

(3H, s), 0.94 (3H, s), 1.32 (3H, s), 1.39 (6H, s), 1.47 (3H, s), 1.56 (1H, dd, *J*=3.7, 15.4), 1.72 (1H, dd, *J*=2.4, 15.4), 1.88 (1H, ddd, *J*=3.4, 4.3, 10.5), 2.01 (1H, d, *J*=5.7), 3.16 (1H, d, *J*=4.4), 3.24 (1H, d, *J*=4.4), 3.37 (1H, t, *J*=11.3), 3.81 (1H, dd, *J*=4.3, 11.3), 3.86–3.92 (3H, m), 3.96–4.04 (2H, m), 4.30 (1H, d, *J*=10.5), 4.72 (1H, ddd, *J*=2.4, 3.7, 5.7), 5.96 (1H, d, *J*=15.2), 6.16 (1H, d, *J*=15.2). ^{13}C-NMR (62.9 MHz): 16.0, 18.9, 22.8, 25.3, 26.2 (2C), 29.4, 34.6, 35.5, 36.9, 39.1, 44.1, 54.0, 56.0, 61.9, 64.7 (2C), 67.6, 71.1, 84.9, 99.1, 107.4, 128.8, 133.9, 210.4. CIMS: 465 ([M+H]$^+$, 100), 447 (28), 418 (47), 407 (70), 403 (37), 389 (61), 345 (72), 327 (14), 87 (28).

*4.4. Preparation of the C1–C2 diol **11***

To an ice cold magnetically stirred solution of **5** (227 mg, 0.51 mmol) in 6 ml of dry THF, under an argon atmosphere, $LiAlH_4$, (80 mg, 2.1 mmol) was added. The mixture was stirred at room temperature for 45 min (TLC monitoring, CH_2Cl_2:MeOH 98:2). Upon disappearance of starting material, the reaction mixture was cooled to 0°C, diluted with ether, a few drops of water, 6 N aq. NaOH and water again were added successively, and stirring continued at room temperature for 45 min. Rapid filtration on SiO_2 (eluent: EtOAc) and removal of solvent gave a residue which was clean enough to be used without further purification (231 mg). Only for characterization, a sample was purified by chromatography (eluent heptane:EtOAc 1:1) to yield **11**: $[\alpha]_D$ +65 (*c* 1.50). IR (Nujol): 3544, 3500, 2725, 2681, 1259, 1200, 1094, 1068, 1045, 930, 877, 849 cm^{-1}. ^{1}H-NMR (250 MHz): 0.87 (3H, s), 1.08 (3H, s), 1.28 (3H, s), 1.43 (3H, s), 1.48 (6H, s), 1.62 (1H, dd, *J*=7.4, 13.2, H-11), 2.02 (1H, dddd, *J*=4.5, 9.5, 10.7, 11.3, H-4), 2.40 (1H, d, *J*=9.5, H-3), 2.57 (1H, d, *J*=8.7, C2-OH), 2.70 (1H, dd, *J*=11.3, 13.2, H-11), 3.12 (1H, d, *J*=4.8, H-7), 3.23 (1H, d, *J*=4.8, H-6), 3.52 (1H, d, *J*=8.7, H-2), 3.57 (1H, t, *J*=11.3, H-20β-ax), 3.76 (1H, dd, *J*=4.5, 11.3, H-20α-eq), 3.82–4.02 (5H, m, OCH_2CH_2O and C1-OH), 4.26 (1H, d, *J*=10.7, H-5), 5.45 (1H, d, *J*=16.0, H-13), 5.62 (1H, dt, *J*=7.4, 11.3, H-10), 6.09 (1H, d, *J*=11.3, H-9), 6.48 (1H, d, *J*=16.0, H-14). ^{13}C-NMR (62.9 MHz): 19.0, 24.7, 25.1, 27.7, 28.6, 29.6, 35.1 (C-11), 37.5 (Cq), 40.9 (C-4), 42.8 (Cq), 45.1 (C-3), 53.3 (C-6), 63.1 (C-7), 64.5 and 64.6 (OCH_2CH_2O), 65.1 (C-20), 69.4 (C-5), 77.9 (C-1), 87.6 (C-2), 99.2 (Cq-acetonide), 107.5 (C-12), 126.5 (C-10), 129.4 (C-13), 136.8 (C-14), 139.5 (C-9). CIMS: 451 ([M+H]$^+$, 18), 433 (4), 393 (15), 389 (100), 375 (12), 331 (34), 87 (9). HRCIMS: calcd for $C_{25}H_{39}O_7$: 451.2696, found: 451.2691. Analysis: calcd for $C_{25}H_{38}O_7 \cdot 0.5H_2O$: C 65.34; H 8.55; O 26.11, found: C 65.75; H 8.52.

*4.5. Benzoylation of diol **11** at C-2; preparation of **12***

To a stirred solution of diol **11** (crude 231 mg, 0.51 mmol) in 10 ml of dry CH_2Cl_2, NEt_3 (1.4 ml, 10 mmol) and BzCl (0.45 ml, 3.6 mmol) were added at 0°C under an argon atmosphere. The reaction mixture was stirred at this temperature for 14 h. After quenching with ice (10 min stirring) and extraction with CH_2Cl_2, the combined organic layers were washed with 1 N HCl, a saturated aqueous solution of $NaHCO_3$, water and brine, dried and concentrated. The residue was purified by SiO_2 chromatography (eluent heptane:EtOAc 2:1) to afford 250 mg of **12**. The overall yield for three steps starting from **3** was 72%. **12**: mp 217–219°C (ether–heptane). $[\alpha]_D$ +50 (*c* 1.82, THF). IR (film): 3520, 3021, 1719, 1604, 1452, 1385, 1269, 1215, 1105, 1069, 1026, 929, 850 cm^{-1}. ^{1}H-NMR (300 MHz): 0.87 (3H, s, Me-17), 1.04 (3H, s, Me-16), 1.27 (3H, s, Me-19), 1.42 (3H, s, Meα-eq acetonide), 1.44 (3H, s, Me-18), 1.47 (3H, s, Meβ-ax acetonide), 1.65 (1H, br s, OH), 1.67 (1H, dd, *J*=7.2, 13.7, H-11α), 2.19 (1H, dddd, *J*=3.7, 9.1, 10.9, 11.4, H-4), 2.59 (1H, d, *J*=9.1, H-3), 2.75 (1H, dd, *J*=11.2, 13.7, H-11β), 2.97 (1H, d, *J*=4.9, H-7), 3.01 (1H, d, *J*=4.9, H-6), 3.62 (1H, t, *J*=11.4, H-20β-ax), 3.94 (1H, dd, *J*=3.7, 11.4, H-20α-eq), 3.80–4.03 (4H, m, OCH_2CH_2O), 4.23 (1H, d, *J*=10.9, H-5), 5.29 (1H, s, H-2), 5.52 (1H, d,

J=15.8, H-13), 5.64 (1H, ddd, *J*=7.2, 11.2, 11.4, H-10), 6.00 (1H, d, *J*=15.8, H-14), 6.18 (1H, d, *J*=11.4, H-9), 7.38–7.59 (3H, m), 8.12–8.16 (2H, m). Diagnostic NOEs: {Me-17}: Me-16 (NOE gem), H-11α, H-13, H-14; {Me-16}: Me-17 (NOE gem), H-10, H-14; {Me-19}: H-3, H-5, H-7; {Me-18}: H-13; {Me-βax of acetonide}: H-20β-ax, H-5; {H-2}: H-3, H-4, H-14, H-20αeq; {H-3}: Me-19, H-2, H-5, H-11β, H-20ax; {H-5}: H-3, H-6, Me-19, Meβ-ax acetonide, H-20βax; {H-20-βax}: H-3, H-5, H-20α-eq. ^{13}C-NMR (50.3 MHz): 19.0 (Meβ-ax acetonide), 24.6 (Me-16), 25.3 (Me-18), 27.2 (Me-17), 29.0 (Me-19), 29.5 (Meα-eq acetonide), 34.6 (C-11), 37.7 (Cq), 40.5 (C-4), 42.4 (Cq), 44.3 (C-3), 52.3 (C-6), 62.8 (C-7), 64.2 and 64.6 (OCH_2CH_2O), 65.2 (C-20), 69.3 (C-5), 77.3 (C-1), 83.6 (C-2), 99.3 (Cq-acetonide), 107.1 (Cq-12), 125.6 (C-10), 127.8 (C-13), 128.3 (2×=CH), 129.8 (2×=CH), 130.4, 132.7, 134.4 (C-14), 141.2 (C-9), 165.6 (C=O). CIMS: 555 ($[M+H]^+$, 100), 537 (16), 497 (31), 493 (66), 435 (19), 433 (15), 375 (23), 357 (21), 313 (19), 123 (46), 87 (32). HRCIMS: calcd for $C_{32}H_{43}O_8$: 555.2958, found: 555.2938.

*4.6. Osmylation of **12**; preparation of triol-benzoate **13***

To a magnetically stirred solution of **12** (29 mg, 0.052 mmol) in *t*-BuOH:H_2O 3:1 (0.8 ml), in the presence of a few drops of pyridine, *N*-methylmorpholine *N*-oxide (8 mg, 0.08 mmol) and then a *t*-BuOH solution of OsO_4 (0.13 ml, 0.003 mmol, 0.02 M in *t*-BuOH) were added at room temperature under an argon atmosphere. The mixture was stirred at 75°C (oil bath temperature) for 4.5 h and treated, after cooling to room temperature, with 6 ml of 10% aqueous solution of $NaHSO_3$. After stirring for 1 h the products were extracted with EtOAc twice; the combined organic layers were washed with brine and the solvent was dried and evaporated. This crude residue was chromatographed (SiO_2, eluent heptane:EtOAc 1:2) to yield 17.7 mg of the corresponding triol-benzoate **13** (57%) and 10.6 mg of the undesired transanullar acetal **14** (34%). **13**: mp 256–258°C (THF–heptane). $[\alpha]_D$ −10 (*c* 2.22, THF). IR (film): 3437, 2984, 2879, 1725, 1448, 1371, 1266, 1197, 1176, 1110, 1093, 1068, 1039, 1026, 1017, 953, 894, 866 cm^{-1}. ^{1}H-NMR (800 MHz): 0.85 (3H, s, Me-17), 1.14 (3H, s, Me-19), 1.16 (3H, s, Me-16), 1.36 (3H, s, Me-18), 1.37 (3H, s, Me-α eq acetonide), 1.42 (3H, s, Me-β ax acetonide), 1.54 (1H, dd, *J*=4.8, 15.1, H-11), 1.75 (1H, br s, OH), 1.78 (1H, br s, OH), 2.08 (1H, d, *J*=8.4, H-3), 2.20 (1H, m, H-4), 2.39 (1H, dd, *J*=12.8, 15.0, H-11), 2.95 (1H, d, *J*=5.2, H-6), 2.97 (1H, d, *J*=8.5, OH), 3.57 (1H, t, *J*=11.3, H-20), 3.65 (1H, dt, *J*=5.3, 7.1, OCH_2CH_2O), 3.72 (1H, dd, *J*=0.9, 5.2, H-7), 3.76 (1H, dt, *J*=5.3, 7.1, OCH_2CH_2O), 3.81 (1H, dt, *J*=5.3, 7.1, OCH_2CH_2O), 3.85–3.89 (2H, m, H-20, OCH_2CH_2O), 4.27 (1H, d, *J*=10.7, H-5), 4.27–4.31 (1H, m, H-10), 5.02 (1H, d, *J*=4.51, 8.4, H-9), 5.28 (1H, s, H-2), 5.57 (1H, d, *J*=15.7, H-13), 6.00 (1H, d, *J*=15.7, H-14), 7.42 (2H, m), 7.51 (1H, m), 7.95 (2H, m). Diagnostic NOEs: {Me-17}: Me-16 (NOE gem), H-11α; {Me-16}: Me-17 (NOE gem), H-11β, H-10; {Me-19}: H-3, H-9, H-7; {H-11α}: H-11β (NOE gem), Me-17; {Me-βax of acetonide}: H-20β-ax, H-5; {H-3}: Me-19, H-5, H-20ax, H-11β; {H-5}: H-3, H-6, Me-βax acetonide, H-20ax, Me-19; {H-6}: H-7, H-5; {H-7}: Me-19, H-6; {H-2}: H-3, H-4; H-20 α-eq. ^{13}C-NMR (75 MHz): 19.3 (Me-β-ax acetonide), 21.6 (Me-19), 22.9 (Me-16), 25.4 (Me-18), 29.7 (Me-α-eq-acetonide), 30.2 (Me-17), 37.8 (Cq-15), 38.8 (C-11), 40.3 (C-3), 42.0 (Cq-8), 41.3 (C-4), 52.0 (C-6), 56.8 (C-7), 64.3 and 64.6 (OCH_2CH_2O), 65.2 (C-20), 69.5 (C-5), 70.7 (C-9), 72.9 (C-10), 77.1 (C-1), 84.8 (C-2), 99.6 (Cq-acetonide), 107.2 (Cq-12), 128.6 (2×=CH), 129.5 (2×=CH), 130.1 (C-13), 130.4, 132.9, 133.4 (C-14), 165.8 (C=O). CIMS: 589 ($[M+H]^+$, 34), 571 (46), 553 (14), 531 (14), 527 (31), 513 (34), 469 (30), 467 (21), 451 (17), 449 (24), 405 (29), 391 (27), 347 (31), 123 (100), 87 (70). HRCIMS: calcd for $C_{32}H_{45}O_{10}$: 589.3012, found: 589.3029.

Transanular acetal-benzoate **14**: IR (film): 3419, 2988, 2962, 2876, 1718, 1603, 1450, 1384, 1373, 1270, 1246, 1200, 1175, 1092, 1070, 1027, 949, 896, 869 cm^{-1}. ^{1}H-NMR (200 MHz): 0.93 (3H, s), 1.00 (3H, s), 1.33 (3H, s), 1.37 (3H, s), 1.44 (3H, s), 1.48 (3H, s), 1.72 (1H, d, *J*=11.4), 1.78–1.97 (1H,

m), 2.00 (1H, d, *J*=13.1), 2.57 (1H, d, *J*=13.1), 3.19 (1H, d, *J*=5.1), 3.36 (1H, t, *J*=10.6), 3.55 (1H, d, *J*=5.1), 3.81–4.14 (7H, m), 4.16 (1H, d, *J*=10.3), 5.14 (1H, s), 5.51 (1H, s), 5.84 (2H, s), 7.42–7.62 (3H, m), 8.06–8.13 (2H, m). ^{13}C-NMR (62.9 MHz): 19.0, 20.4, 21.1, 25.4, 29.3, 30.8, 32.9, 42.0, 43.0, 44.3, 53.2, 57.5, 58.3, 64.5 (2×C, OCH_2CH_2O), 64.7 (C-20), 68.8, 77.3, 79.4, 88.7, 99.0, 102.7, 107.1, 128.7 (2×=CH), 128.9, 129.8, 129.9 (2×=CH), 131.8, 133.3, 167.0. CIMS: 587 ($[M+H]^+$, 96), 569 (23), 529 (24), 525 (23), 511 (21), 465 (30), 123 (100), 87 (90). HRCIMS: calcd for $C_{32}H_{43}O_{10}$: 587.2856, found: 587.2857.

*4.7. Preparation of the transposed epoxide **15***

Freshly powdered KOH (104 mg, 1.86 mmol), in dry DMSO (1 ml) was stirred at room temperature for 10 min. Hydroxybenzoate **12** (86 mg, 0.15 mmol) in DMSO (2 ml) was then added and stirring continued for 1.5 h (TLC monitoring). The reaction mixture was diluted with CH_2Cl_2, and washed with water and brine. The residue was chromatographed on SiO_2 (eluent heptane:EtOAc 3:1) to afford 55 mg (82%) of the epoxide **15**. Mp 166–168°C (heptane–ether). $[\alpha]_D$ +76 (*c* 1.79). IR (film): 2980, 2936, 2880, 1471, 1370, 1268, 1220, 1197, 1168, 1119, 1068, 1041, 919, 852, 734 cm^{-1}. ^{1}H-NMR (250 MHz): 0.97 (3H, s), 1.11 (3H, s), 1.26 (3H, s), 1.43 (1H, dd, *J*=4.2, 9.8), 1.43 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 1.81 (1H, dd, *J*=6.7, 13.3), 2.24 (1H, ddd, *J*=4.2, 4.5, 11.3), 2.33 (1H, dd, *J*=11.2, 13.3), 2.82 (1H, d, *J*=9.8), 3.16 (1H, d, *J*=4.8), 3.23 (1H, d, *J*=4.8), 3.64 (1H, dd, *J*=10.7, 11.3), 3.79–3.95 (4H, m), 4.01 (1H, dd, *J*=4.5, 10.7), 4.34 (1H, d, *J*=11.0), 5.54 (1H, d, *J*=15.3), 5.74 (1H, ddd, *J*=6.7, 10.8, 15.1), 5.94 (1H, d, *J*=15.3), 5.99 (1H, d, *J*=10.8). ^{13}C-NMR (62.9 MHz): 19.0, 25.0, 26.1, 29.2, 29.7, 30.4, 35.8, 39.4, 40.2, 41.0, 44.6, 53.1, 61.7, 64.2, 64.5, 65.1, 65.3, 69.5, 72.3, 99.4, 107.2, 127.9, 128.2, 131.9, 140.3. Analysis: calcd for $C_{25}H_{36}O_6$: C 69.42; H 8.39, found: C 69.31; H 8.34.

*4.8. The C9–C10 functionalization on **15**; preparation of diol **16** along with one-pot formation of α-ketol **17***

To a magnetically stirred solution of **15** (53 mg, 0.12 mmol) in 1.6 ml of *t*-BuOH:H_2O (3:1), 2 drops of pyridine, 20 mg (0.17 mmol) of *N*-methylmorpholine *N*-oxide and then a *t*-BuOH solution of OsO_4 (0.3 ml, 0.006 mmol, 0.02 M in *t*-BuOH) were added at room temperature under an argon atmosphere. The mixture was stirred at 70°C (oil bath temperature) for 1 h 50 min and treated, after cooling to room temperature, with 4 ml of 10% aqueous solution of $NaHSO_3$. After stirring for 1 h the products were extracted with EtOAc twice; the combined organic layers were washed with brine and the solvent was dried and evaporated. The crude residue was chromatographed (SiO_2, eluent heptane:EtOAc 1:2) to yield the corresponding diol **16** (24 mg, 42%) along with the target acyloin **17** (23 mg, 41%).

16: $[\alpha]_D$ −9 (*c* 1.12). IR (film): 3450, 2984, 2939, 2883, 1475, 1460, 1383, 1370, 1264, 1240, 1224, 1197, 1172, 1154, 1120, 1108, 1072, 1041, 979, 953, 932, 917, 894, 867, 733 cm^{-1}. ^{1}H-NMR (800 MHz): 0.96 (3H, s, Me-16/17), 1.18 (3H, s, Me-17/16), 1.20 (3H, s, Me-19), 1.29 (1H, dd, *J*=6.5, 9.4, H-3), 1.44 (3H, s, Me-18), 1.45 (3H, s, Me-acetonide), 1.50 (3H, s, Me-acetonide), 1.62 (1H, dd, *J*=3.3, 14.8, H-11), 2.10 (1H, dd, *J*=12.5, 14.8, H-11), 2.13–2.26 (1H, m, H-4), 2.78 (1H, d, *J*=3.6, OH), 2.80 (1H, d, *J*=9.4, H-2), 3.17 (1H, d, *J*=7.6, OH), 3.24 (1H, d, *J*=5.1, H-6), 3.65 (1H, t, *J*=11.1, H-20), 3.69 (1H, dd, *J*=1.2, 5.1, H-7), 3.81–3.89 (2H, m, OCH_2CH_2O), 3.92–4.00 (3H, m, H-20, OCH_2CH_2O), 4.10 (1H, dd, *J*=5.0, 7.6, H-9), 4.25 (1H, ddd, *J*=3.3, 4.9, 12.7, H-10), 4.38 (1H, d, *J*=10.9, H-5), 5.64 (1H, d, *J*=15.1, H-13), 6.05 (1H, d, *J*=15.1, H-14). ^{13}C-NMR (62.9 MHz): 19.2 (Me-acetonide), 19.6 (Me-19), 25.1 (Me-18), 29.2 (Me-16/17), 29.5 (Me-17 /16), 29.7 (Me-acetonide), 33.3 (C-15), 41.2 (C-4), 41.7 (C-8), 42.0 (C-3), 45.4 (C-11), 53.2 (C-6), 56.9 (C-7), 64.3 and 64.7 (OCH_2CH_2O), 65.1 (C-1), 65.6 (C-20),

69.5 (C-5), 71.0 (C-10), 71.5 (C-9), 72.8 (C-2), 99.7 (Cq-acetonide), 107.2 (C-12), 129.4 (C-13), 130.3 (C-14). CIMS: 467 ([M+H]$^+$, 100), 449 (66), 409 (55), 391 (41), 87 (42). HRCIMS: calcd for $C_{25}H_{39}O_8$: 467.2645, found: 467.2646.

17: $[\alpha]_D$ −91 (*c* 1.07). IR (film): 3441, 2978, 2938, 2882, 1692, 1474, 1465, 1459, 1449, 1439, 1382, 1370, 1264, 1246, 1212, 1197, 1168, 1115, 1094, 1077, 1071, 1040, 1015, 985, 967, 947, 934, 921, 912, 895, 863, 825 cm^{-1}. ^{1}H-NMR (800 MHz): 0.82 (3H, s, Me-19), 1.04 (3H, s, Me-16/17), 1.06 (3H, s, Me-17/16), 1.40 (1H, ddd, *J*=1.2, 6.2, 8.2, H-3), 1.46 (3H, s, Me-18), 1.47 (3H, s, Me-acetonide), 1.50 (3H, s, Me-acetonide), 2.22 (1H, ddd, *J*=4.5, 6.1, 10.8, H-4), 2.40 (1H, d, *J*=14.8, H-11), 2.63 (1H, d, *J*=14.8, H-11), 3.04 (1H, d, *J*=8.2, H-2), 3.27 (1H, d, *J*=5.1, H-6), 3.69 (1H, t, *J*=11.1, H-20β-ax), 3.70 (1H, dd, *J*=1.2, 5.1, H-7), 3.83–3.88 (2H, m, OCH_2CH_2O), 3.94–3.98 (2H, m, OCH_2CH_2O), 3.99 (1H, dd, *J*=4.5, 11.1, H-20α-eq), 4.03 (1H, d, *J*=4.5, OH), 4.38 (1H, d, *J*=10.8, H-5), 4.60 (1H, d, *J*=4.5, H-9), 5.77 (1H, d, *J*=15.1, H-14), 6.13 (1H, d, *J*=15.1, H-13). ^{13}C-NMR (75 MHz): 19.1 (Me-acetonide), 19.4 (Me-19), 25.1 (Me-18), 27.1 (Me-16/17), 27.3 (Me-17/16), 29.6 (Me-acetonide), 34.8 (Cq-15), 40.5 (Cq-8), 42.8 (C-4), 43.2 (C-3), 52.1 (C-11), 53.1 (C-6), 55.6 (C-7), 64.5 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 65.4 (C-20), 66.2 (C-1), 69.6 (C-5), 74.2 (C-2), 77.8 (C-9), 99.8 (Cq-acetonide), 107.1 (C-12), 128.6 (C-14), 132.0 (C-13), 209.8 (C-10). CIMS: 465 ([M+H]$^+$, 100), 447 (14), 421 (7), 407 (84), 403 (10), 389 (24), 363 (14), 345 (18), 178 (37), 87 (89). HRCIMS: calcd for $C_{25}H_{37}O_8$: 465.2488, found: 465.2487.

*4.9. Protection of the C-1 hydroxyl group as its methyl ether; preparation of C-1 methoxy benzoate **18***

Freshly powdered KOH (87 mg, 1.6 mmol) was added to DMSO (1 ml) and the mixture was stirred for 5–10 min at room temperature before being cooled using a water bath. Then a solution of **12** (70 mg, 0.13 mmol) in DMSO (2 ml) was added and an excess of MeI (distilled and filtered through basic alumina, under an argon atmosphere, just before use) immediately followed. The reaction mixture was stirred for 30–35 min at water bath temperature (ca. 18°C). Dilution with CH_2Cl_2, and usual work up followed by silica gel chromatography (eluent heptane:EtOAc 3:1 to 1:1) afforded 29 mg (40%) of methoxy benzoate **18** and 28 mg of starting material (40%). **18**: mp 204–206°C (THF–heptane). $[\alpha]_D$ +86 (*c* 0.51). IR (film): 2968, 2937, 2890, 1717, 1465, 1451, 1385, 1372, 1274, 1197, 1177, 1109, 1085, 1070, 1040, 1027, 932, 866, 853 cm^{-1}. ^{1}H-NMR (200 MHz): 0.98 (3H, s), 1.06 (3H, s), 1.28 (3H, s), 1.39 (3H, s), 1.46 (3H, s), 1.49 (3H, s), 1.65 (1H, dd, *J*=7.4, 13.7), 2.46–2.67 (2H, m), 2.85 (1H, dd, *J*=11.3, 13.7), 2.93 (1H, d, *J*=4.9), 3.03 (1H, d, *J*=4.9), 3.23 (3H, s), 3.55–3.98 (6H, m), 4.25 (1H, d, *J*=10.3), 5.63 (1H, dt, *J*=7.4, 11.3), 5.65 (1H, s), 5.82 (1H, d, *J*=16.5), 5.99 (1H, d, *J*=16.5), 6.07 (1H, d, *J*=11.3), 7.38–7.52 (3H, m), 8.08–8.12 (2H, m). ^{13}C-NMR (50.3 MHz): 19.1, 23.3, 25.0, 28.3, 29.1, 29.6, 35.1, 37.7, 40.4, 44.5, 44.7, 52.5, 54.1, 62.9, 64.1, 64.4, 65.5, 69.5, 79.7, 81.6, 99.2, 107.4, 126.2, 127.0, 128.3 (2×=CH), 129.8 (2×=CH), 130.7, 132.5, 135.0, 140.8, 165.5. CIMS: 569 ([M+H]$^+$, 100), 537 (13), 511 (19), 479 (13), 438 (34), 375 (19), 357 (14), 123 (100), 87 (91). HRCIMS: calcd for $C_{33}H_{45}O_8$: 569.3114, found: 569.3138.

*4.10. The C9–C10 functionalization on **18**; preparation of diol **19** along with one-pot formation of target α-ketol (−)-**4***

To a magnetically stirred solution of **18** (27 mg, 0.047 mmol) in 0.8 ml of *t*-BuOH:H_2O (3:1), 2 drops of pyridine, 8 mg (0.066 mmol) of *N*-methylmorpholine *N*-oxide and then a *t*-BuOH solution of OsO_4 (0.12 ml, 0.02 M in *t*-BuOH) were added at room temperature under an argon atmosphere. The mixture was stirred at 70°C (oil bath temperature) for 2.5 h and treated, after cooling to room temperature, with 4 ml of 10% aqueous solution of $NaHSO_3$. After stirring for 1 h the products were extracted with EtOAc

twice; the combined organic layers were washed with brine and the solvent was dried and evaporated. The crude residue was chromatographed (SiO_2, eluent heptane:EtOAc 3:1 to 1:1) to yield the corresponding diol **19** (14 mg, 52%) along with the target acyloin (−)-**4** (9 mg, 32%) and some recovered starting material.

19: $[\alpha]_D$ +7 (*c* 0.51, THF). IR (film): 3407, 2966, 2886, 1722, 1458, 1360, 1268, 1189, 1072, 1035, 962, 931, 857 cm^{-1}. ^{1}H-NMR (200 MHz): 1.06 (3H, s), 1.16 (3H, s), 1.19 (3H, s), 1.36 (3H, s), 1.47 (3H, s), 1.49 (3H, s), 1.60 (1H, dd, *J*=4.7, 15.3), 1.78 (1H, OH), 2.21 (1H, d, *J*=8.2), 2.53 (1H, dd, *J*=12.8, 15.3), 2.48–2.68 (1H, m), 3.01 (1H, d, *J*=5.1), 3.10 (1H, OH), 3.24 (3H, s), 3.56–3.95 (5H, m), 3.75 (1H, d, *J*=5.1), 3.91 (1H, dd, *J*=4.4, 11.1), 4.35 (1H, d, *J*=10.6), 4.26–4.42 (1H, m), 4.94–5.05 (1H, m), 5.65 (1H, s), 5.77 (1H, d, *J*=16.6), 5.90 (1H, d, *J*=16.6), 7.40–7.53 (3H, m), 7.94–7.98 (2H, m). ^{13}C-NMR (50.3 MHz): 19.3, 21.6, 22.2, 25.1, 29.6, 30.9, 38.7, 40.1, 40.5, 41.4, 42.2, 52.1, 54.4, 56.7, 64.2, 64.4, 65.6, 69.7, 70.5, 72.7, 81.2, 81.7, 99.5, 107.3, 125.5, 128.5 (2×=CH), 129.3 (2×=CH), 130.7, 132.7, 136.6, 166.0. CIMS: 603 ($[M+H]^+$, 16), 595 (34), 571 (23), 545 (18), 527 (17), 513 (34), 495 (20), 481 (17), 449 (34), 391 (43), 123 (99), 105 (37), 87 (100). HRCIMS: calcd for $C_{33}H_{47}O_{10}$: 603.3169, found: 603.3160.

(−)-**4**: $[\alpha]_D$ −24 (*c* 0.69). IR (film): 3437, 2987, 2937, 1726, 1687, 1450, 1371, 1264, 1197, 1176, 1102, 1087, 1073, 1041, 929, 863 cm^{-1}. ^{1}H-NMR (800 MHz): 0.86 (3H, s, Me-19), 1.08 (3H, s, Me-17), 1.16 (3H, s, Me-16), 1.37 (3H, s, Me-18), 1.46 (3H, s, Meα-eq acetonide), 1.49 (3H, s, Meβ-ax acetonide), 2.20 (1H, d, *J*=8.3, H-3), 2.53 (1H, d, *J*=16.4, H-11), 2.60 (1H, m, H-4), 3.04 (1H, d, *J*=5.2, H-6), 3.31 (3H, s, OMe), 3.34 (1H, d, *J*=16.4, H-11), 3.58 (2H, m, OCH_2CH_2O), 3.69 (1H, t, *J*=11.2, H-20β-ax), 3.74 (1H, d, *J*=5.2, H-7), 3.85 (2H, m, OCH_2CH_2O), 3.96 (1H, dd, *J*=4.3, 11.2, H-20α-eq), 4.23 (1H, d, *J*=4.0, OH), 4.28 (1H, d, *J*=10.8, H-5), 5.69 (1H, d, *J*=4.0, H-9), 5.76 (1H, s, H-2), 5.78 (1H, d, *J*=16.6, H-14), 5.94 (1H, *J*=16.6, H-13), 7.37–7.59 (3H, m), 7.95–8.00 (2H, m). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-9, H-14; {Me-17}: Me-16 (NOE gem), H-14; {Me-19}: H-3, H-5, H-7; {Me-βax of acetonide}: H-20β-ax, H-5; {H-2}: H-3, H-4, OMe, H-14, H-20a-eq; {H-3}: Me-19, H-11β, H-5, H-20ax; {H-9}: Me-16; {H-20βax}: H-3, H-5, H-20α-eq. ^{13}C-NMR (200 MHz): 19.2 (Meβ-ax acetonide), 21.1 (Me-19), 22.2 (Me-16), 25.1 (Me-18), 29.6 (Meα-eq acetonide), 30.6 (Me-17), 39.7 (C-3), 40.5 (Cq-8), 40.6 (Cq-15), 40.8 (C-4), 49.0 (C-11), 52.0 (C-6), 54.5 (OMe), 55.9 (C-7), 64.3 and 64.5 (OCH_2CH_2O), 65.4 (C-20), 69.5 (C-5), 77.4 (C-9), 80.9 (C-2), 81.9 (C-1), 99.6 (Cq-acetonide), 107.2 (Cq-12), 124.1 (C-14), 128.6 (2×=CH), 129.4 (2×=CH), 130.3 (Cq-Ar), 133.0, 137.6 (C-13), 166.0 (OC=O), 211.3 (C-10). CIMS: 601 ($[M+H]^+$, 61), 583 (41), 509 (47), 543 (41), 525 (19), 511 (34), 479 (100), 447 (61), 421 (40), 389 (31), 178 (81), 123 (100), 87 (98). HRCIMS: calcd for $C_{33}H_{45}O_{10}$ m/z 601.3012, found: 601.3006.

*4.11. Protocol for Dess–Martin periodinane oxidation of diols **16** and **19***

To a stirred solution of diols **16** (**19**) (1 mmol) in 15 ml of dry methylene chloride and 2 ml of dry pyridine, 2.5 equiv. of Dess–Martin periodinane reagent were added and the reaction mixture was stirred for 1.5 h at room temperature (TLC monitoring). Upon complete oxidation of the hydroxyl group at the C-10 position the mixture was diluted with CH_2Cl_2, washed with a saturated aqueous solution of sodium bicarbonate, then sodium thiosulphate solution, the organic layers were dried over magnesium sulfate, concentrated and chromatographed on SiO_2 (eluent EtOAc) to give acyloins **17** and **4** in nearly quantitative yield.

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