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TETRAHEDRON: *ASYMMETRY*

A convenient preparation of taxoid right-half building blocks

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Abstract

Wieland–Miescher ketone derived unsaturated diols **4** reacted with $Pb(OAc)_4$ to furnish tricyclic enolether intermediate **6** which upon ozonolysis gave access to useful synthetic intermediates such as bicyclic lactone **7**, methyl furanoside **8** and triol **9** (taxoid right-half precursors), depending on the solvent used during the ozonolysis and the nature of the following synthetic operation. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Elaborated six-membered ring systems containing multiple stereogenic centers constitute the backbone of several biologically important natural compounds. The need for constructing such derivatives for the synthesis of A- and C-ring components of taxoids, provided a strong incentive for the development of improved synthetic methods[1] during the era of taxol synthesis and considerable efforts have been devoted to meet this challenge.[2]

Through our efforts towards the total synthesis of taxoids, using the (*S*)-(+)-Hajos–Parrish ketone **1** as precursor for the entire taxoid framework,[3] we investigated the lead tetraacetate mediated oxidative cleavage of the unsaturated diols **3**. This provided a convenient route for elaboration of the right half (C2–C10) of the taxoid diterpene skeleton **I** and prompted us to use similar methodology for the preparation of the taxoid C-ring subunit starting from its higher analog **4**, itself obtained from the (*S*)-(+)-Wieland–Miescher ketone **2**. As we pointed out,[4] two main differences were observed in the oxidative fragmentations of the unsaturated diols **3** and **4**. The one of interest is related to the stability of the intermediate tricyclic enol ether (or enol acetal) **6** which unlike its lower homolog is perfectly stable. The latter, obtained in one synthetic operation upon treatment of **4** with 1.2 equiv. of $Pb(OAc)_4$ in acetonitrile, can be easily isolated and stored without any special care, thus allowing for a

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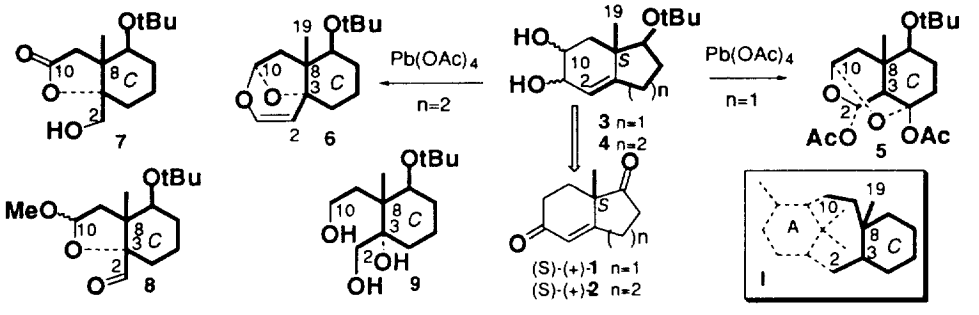
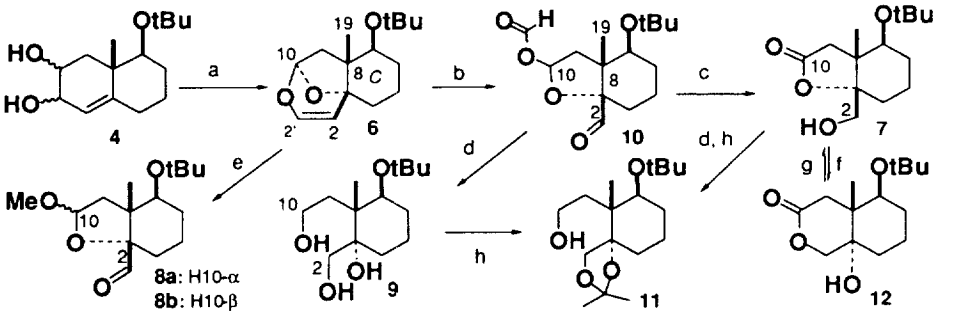
differential functional group interconversion. This clearly means that the cascade can be 'interrupted' on the Wieland–Miescher series while this is not the case in the Hajos–Parrish series, where the full cascade product **5** is obtained straightforwardly (Scheme 1). In a preliminary communication, dealing with the $Pb(OAc)_4$ mediated one-pot multi-stage transformations, we reported that if the sequence is interrupted after the intramolecular bis-hetero Diels–Alder reaction, the method also serves, following ozonolytic cleavage, for the preparation of methyl furanoside **8** or formylacetal-aldehyde **10** depending on the solvent used (Scheme 2).[5] Reported here is the synthesis and characterization of the bicyclic lactone **7**, methyl furanoside **8** and triol **9**, homochiral taxoid C-ring precursors, offering linking possibilities at C-2 and C-10. The key to these transformations is the $Pb(OAc)_4$ mediated oxidative cleavage of the Wieland–Miescher ketone derived bicyclic diol **4**, allowing the synthesis of tricyclic enol ether **6**. Ozonolytic cleavage of the latter leading to **10**, sets the stage for an intramolecular Cannizzaro type oxidoreduction[6] which proceeds under very mild conditions allowing for the construction of the bicyclic lactone **7**.



Scheme 1. Reactions of unsaturated 1,2-diols with lead tetraacetate; taxoid C-ring precursors



Scheme 2. (a) 1.2 equiv. $Pb(OAc)_4$, CH_3CN, −10°C for 5 min, then rt, 3 h; (b) O_3, CH_2Cl_2, −78°C then Me_2S; (c) K_2CO_3–MeOH–H_2O, rt, 6 h; (d) $LiAlH_4$, THF, reflux; (e) O_3, MeOH, −78°C then Me_2S, rt; (f) LiOH–MeOH–H_2O, rt; (g) SiO_2, heptane:ethyl acetate (2:1), 12 h; (h) acetone, *p*TsOH, rt

2. Results and discussion

The preparation of the requisite tricyclic enol ether **6** was accomplished by lead tetraacetate mediated oxidative cleavage of the unsaturated bicyclic diol **4**. Treatment of the latter with $Pb(OAc)_4$ (1.2 equiv.), in dry acetonitrile (5 ml per mmol) at −10°C to rt, for 3 h under an inert atmosphere, afforded **6** in 91% yield after silica gel flash chromatography (heptane:ether, 1:1).

This one-pot sequence leading to **6** (the 'interrupted cascade'), also works well at room temperature or at below zero temperatures, though longer periods of stirring are needed for low temperature runs

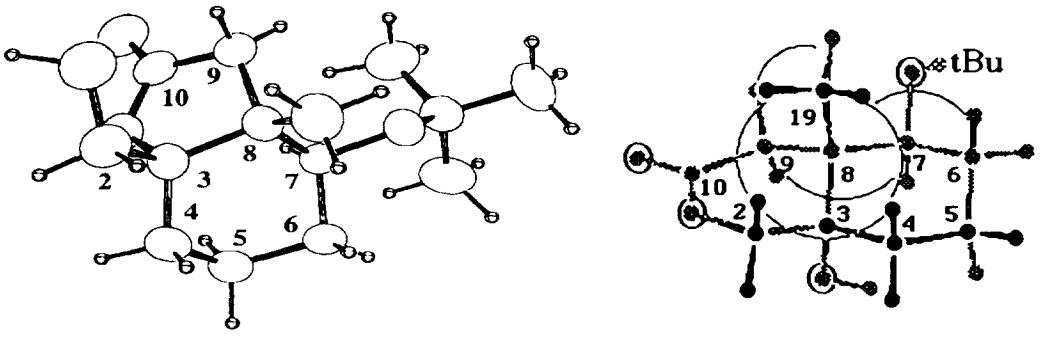
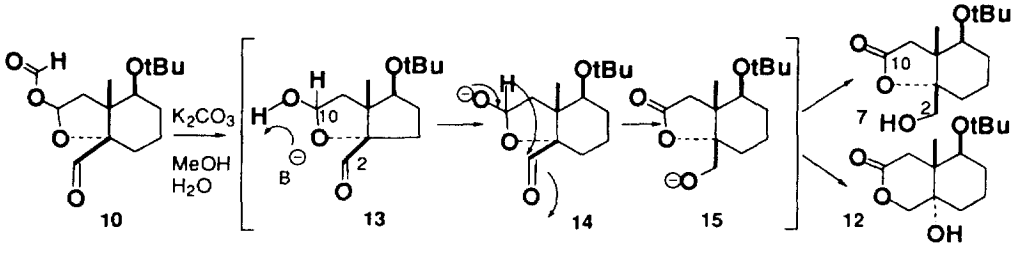


Fig. 1. Perspective drawing of the X-ray structure of **7** and spatial proximities (diagnostic NOEs) of **12** shown on the lowest energy conformer as determined by molecular mechanics calculations

(−40°C for example), and tolerates various solvents. By appropriate selection of the next operation, taxoid C-ring building blocks such as **7**, **8**, **9** and **11** could then be prepared. The procedure used to prepare these C-ring precursors is outlined in Scheme 2. When ozonolysis of **6** was carried out in methanol (10 ml per mmol), at −78°C, a diastereomeric mixture of methyl furanosides **8a** and **8b** (ca. 1:4 ratio) was obtained following reductive treatment with excess Me_2S, in 78% combined yield. On the other hand, when ozonolysis was performed in dichloromethane, formylacetal-aldehyde **10** was obtained. Reduction of the latter with $LiAlH_4$ in refluxing THF afforded triol **9** which upon room temperature treatment with dry acetone in the presence of a catalytic amount of *p*-toluenesulfonic acid led to the corresponding isopropylidene derivative **11** in 68% overall yield (from **6**). Upon mild base treatment (K_2CO_3, MeOH–H_2O, 6 h at room temperature), formylacetal-aldehyde **10** afforded bicyclic lactone **7** as a crystalline solid in 67% yield, along with **12** (11%), via an intramolecular Cannizzaro type oxidoreduction. The two bicyclic lactones, **7** and **12**, could be separated by silica gel column chromatography (eluent: heptane:ethyl acetate, 3:1). However, we observed that **12**, originally obtained as a minor product, was gradually transformed into **7** upon a prolonged stay in an SiO_2 column. Isopropylidene derivative **11** could also be obtained in comparable yields from bicyclic lactone **7** using the same protocol as from **10**. Complete acid promoted transesterification could also be achieved by stirring pure bicyclic lactone **12** in heptane:ethyl acetate (2:1) in the presence of silica gel for a few hours at room temperature, resulting in the exclusive formation of **7**. On the other hand, upon subjection of pure bicyclic lactone **7** to a basic treatment (10 equiv. of LiOH or KOH or NaOH, in MeOH:H_2O (10:1), 10 ml/mmol), at room temperature, an equilibrium mixture of **7**:**12** (ca. 1:1.1) resulted. Interestingly, treatment of **10** with $LiCO_3$–MeOH–H_2O at room temperature for up to 48 h produced solely lactol aldehyde **13** as an unseparable epimeric mixture at the C-10 position, which was characterized as such. Briefly, bicyclic lactone **7** was the final product of acid promoted transesterification, while the base promoted transesterification led to an equilibrium mixture of **7** and **12** (nearly 1:1), regardless of the starting point, which could be pure **7**, pure **12**, or any random mixture of **7** and **12**. Single-crystal X-ray diffraction analysis of bicyclic lactone **7** enabled unequivocal stereochemical assignment and further confirmed the correctness of previous assignments by NMR techniques. The ORTEP representation of **7** along with the lowest energy conformer of **12** is shown in Fig. 1.

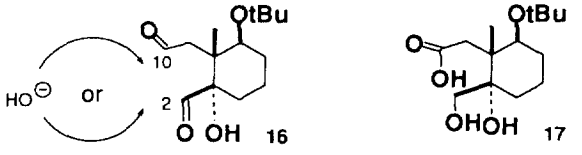
Repeated in the presence of a tenfold excess of formalin (37% HCH=O in H_2O) or paraformaldehyde, basic treatment of **10** did not furnish any crossed-Cannizzaro product; a mixture of the two bicyclic lactones **7** and **12** was obtained instead, in an approximately 1:1 ratio. The site-selective disproportionation of the Cannizzaro oxidoreduction is consistent with direct hydride shift on the lactol-aldehyde **13**, leading to the bicyclic lactone **7** which in turn in a basic medium suffers ring opening followed by partial translactonization affording the bicyclic lactone **12**. A mechanistic framework that accounts for these sequential

transformations is portrayed in Scheme 3. Saponification of the starting formyl acetal **10**, obtained from ozonolysis of **6** in methylene chloride, occurs in the presence of base to give the lactol-aldehyde **13**. Removal of the acidic proton then generates **14** which undergoes a subsequent intramolecular hydride transfer leading to **15**. The proposed sequence can be monitored by TLC (heptane:ethyl acetate, 2:1), with intermediates **10**, **13**, **17**, **7** and **12** possessing distinct R_f values. Soon after addition of the base in MeOH–H_2O, two new lower R_f spots appear on the TLC plate; the higher one is lactol-aldehyde **13**, the lower being bicyclic lactone **7**. The spot corresponding to lactol-aldehyde **13** is gradually transformed to **7** upon 6–7 h stirring at room temperature. Further stirring then gives rise to a third spot, lower than the bicyclic lactone **7**, corresponding to the transesterified bicyclic lactone **12**.



Scheme 3. Proposed mechanism for the base induced disproportionation of formyl-aldehyde **10**

On the other hand, dihydroxy-carboxylic acid intermediate **17** can be observed by TLC as a spot characteristic to acids, near the baseline, upon treatment with KOH–H_2O or LiOH–H_2O. The formation of bicyclic lactones **7** and **12** could also be envisioned to occur via ring-opened intermediate **16** shown below.



This second pathway, which involves disproportionation on the open form of the lactol-aldehyde **13**, could be reasonably discarded as selectivity in disproportionation is complete. Neither the ring-opened dihydroxy-acid corresponding to the Cannizzaro product resulting from HO^- addition to the C-2 carbonyl of **16**, nor its hydroxy-lactone form were detected. Furthermore, it should be pointed out that the nature of the counter ion (Li^+, Na^+, K^+ and Cs^+ were used) does not effect selectivity in disproportionation.

3. Conclusion

In summary, we have described a facile preparation of bicyclic lactone **7**, methylfuranoside **8** and triol **9** from the unsaturated bicyclic 1,2-diol **4**, thus proving that a large number of skeletal and functional changes can be obtained in a few synthetic operations. Tricyclic enol ether **6** proved to be a useful intermediate for preparing the above cited taxoid C-ring building blocks. The observed site-selective oxidoreduction is noteworthy, since it appears to have little, if any, precedence in the literature, insofar as the extremely mild conditions are concerned.

Obtained in three (for **7**), two (for **8**) and three (for **9**) steps, respectively, from bicyclic diol **4**, they can serve as either C-10 nucleophiles or C-2 electrophiles (and *vice versa*) in an 'A+C' approach towards the total synthesis of taxoid analogs.[7]

4. Experimental

Experimental protocols such as the drying and purification of reaction solvents, instrumentation and other such details are identical with those previously described.[8] Key intermediate **6** was prepared according to our earlier work.[8]

4.1. Ozonolysis of **6** *in* CH_2Cl_2

Ozone was passed into a stirred solution of **6** (805 mg, 3.19 mmol) in 40 ml of methylene chloride and 1 ml of pyridine at −78°C until a blue color persisted, the reaction stirred for 5 additional minutes at this temperature after which 6.4 mmol of Me_2S were added dropwise. It is worth mentioning that although it caused no harm, reductive work up of the ozonides (either Ph_3P or Me_2S) is unnecessary; TLC control before Me_2S addition indicated total destruction of the ozonides before reductive treatment. The mixture was allowed to reach room temperature within approximately 30 min, concentrated under reduced pressure, and filtered through silica gel with heptane:ethyl acetate (4:1) to give crude formyl-aldehyde **10** which, although unstable, can be isolated through rapid SiO_2 column chromatography (heptane:ether, 9:1) in 66% yield, and characterized. **10**: IR (film): 2975, 2948, 2875, 1731, 1467, 1390, 1366, 1255, 1191, 1174, 1161, 1130, 1104, 1073, 1057, 1024, 1010, 966, 938, 881 cm^{-1}. ^{1}H-NMR (250 MHz): 1.07 (3H, s, Me-19), 1.21 (9H, s, *t*Bu), 1.10–1.90 (7H, m), 2.75 (1H, dd, *J*=6.2, 14.1, H-9), 3.28 (1H, dd, *J*=3.6, 10.9, H-7), 6.55 (1H, t, *J*=5.9, H-10), 8.14 (1H, s, H-2′), 9.82 (1H, s, H-2). ^{13}C-NMR (62.5 MHz): 13.0 (Me-19), 19.0 (C-4), 24.9 (C-5), 29.2 (*t*Bu), 29.0 (C-6), 43.0 (C-9), 49.0 (Cq-8), 72.1 (C-7), 73.2 (*C*q-*t*Bu), 93.7 (Cq-3), 97.4 (C-10), 160.4 (C-2′), 202.2 (C-2). Formyl-aldehyde **10** needs no purification and can be carried out as such thus increasing the yields.

4.2. Cannizzaro type base-catalyzed oxidoreduction of **10**; *preparation of the bicyclic lactones* **7** *and* **12**

Formylacetal-aldehyde **10** (224 mg, 0.78 mmol) was dissolved in a mixture of methanol (5 ml) and water (0.5 ml), and 200 mg (1.45 mmol, 1.17 equiv.) of potassium carbonate was added. The mixture was stirred at room temperature for 6 h, diluted with water, and extracted with ether. Note that in large scale preparations methanol should be removed first under reduced pressure. Following usual work up the residue was purified by flash chromatography on silica gel to afford 134 mg (0.522 mmol, 67%) of **7** and 22 mg (0.086 mmol, 11%) of **12**. Elution with heptane:ethyl acetate (3:1) easily separated the two bicyclic lactones. (3*S*)-(7*S*)-(8*R*)-**7**: Mp 104–105°C (ether–heptane): $[\alpha]_D$ +34 (*c* 1.4). IR ($CHCl_3$): 3409, 3020, 2978, 2944, 2938, 1765, 1216 cm^{-1}. ^{1}H-NMR (300 MHz): 1.15 (3H, s, Me-19), 1.23 (9H, s, *t*Bu), 1.45–1.95 (6H, m), 2.42 (1H, A of AB, J_{AB}=17.2), 2.75 (1H, B of AB, J_{AB}=17.2, H-9), 3.50 (1H, dd, *J*=2.6, 6.8, H-7), 3.71 (2H, s, H-2). ^{13}C-NMR (62.5 MHz): 15.6 (Me-19), 18.5 (CH_2), 28.2 (CH_2), 28.8 (*t*Bu), 29.1 (CH_2), 42.0 (C-9), 45.9 (Cq-8), 66.2 (C-2), 72.3 (C-7), 74.1 (*C*q-*t*Bu), 89.3 (Cq-3), 176.7 (C-10). EIMS: 256 (M^+, 1), 200 (60), 182 (96), 169 (100), 138 (66), 57 (72). HREIMS: calcd for $C_{14}H_{24}O_4$ m/z 256.1674, found 256.1660. Anal.: calcd for $C_{14}H_{24}O_4$ C 65.60, H 9.44, found: C 65.44, H 9.46. (3*S*)-(7*S*)-(8*R*)-**12**: Mp 146–148°C (heptane). $[\alpha]_D$ +18 (*c* 0.51). IR ($CHCl_3$): 3402, 2979, 1705, 1466, 1389, 1359, 1246, 1192, 1067, 1031, 900, 864 cm^{-1}. ^{1}H-NMR (400 MHz): 1.05 (3H, s, Me-19), 1.17 (9H, s, *t*Bu), 1.33 (1H, m, H-4αeq), 1.43 (1H, m, H-6βax), 1.55 (1H, m, H-4βax), 1.63 (1H, m, H-5), 1.74 (1H, m, H-6αeq), 1.80 (1H, m, H-5), AB-system at 2.49 (1H, d, *J*=17.6, H-9βeq), and 2.72 (1H, d, *J*=17.6, H9αax), 3.69 (1H, dd, *J*=4.3, 11.4, H-7), AB-system at 4.00 (1H, A of AB, J_{AB}=12.2, H-2αeq), 4.30 (1H, B of AB J_{AB}=12.2, H-2βax). Diagnostic NOEs: {Me-19}: H-9βeq, H-6βax, H-2βax, H-4βax; {H-9αax}: H-7; {H-2βax}: H-2αeq (NOE gem), Me-19, H-4βax. ^{13}C-NMR (75 MHz): 16.1 (Me-19),

18.8 (C-5), 28.4 (C-4), 28.9 (*t*Bu), 29.6 (C-6), 39.1 (C-9), 40.4 (Cq-8), 70.9 (C-7), 71.6 (Cq-3), 73.3 (Cq-*t*Bu), 76.2 (C-2), 171.7 (C-10). EIMS: 256 (M^+, 2), 200 (36), 182 (100), 57 (46). CIMS: 257 (M+1, 100). HRCIMS: calcd for $C_{14}H_{25}O_4$ m/z 257.1753, found 257.1755.

4.3. X-Ray structure determination of 7

$C_{14}H_{24}O_4$: Mr=256.35, triclinic, P-1, a=7.876(4), b=9.020(4), c=10.705(3) Å, α=89.95(2), β=102.29(3), γ=106.77(3)°, V=710.0(5) $Å^{-3}$, Z=2, D_x=1.199 Mg m^{-3}, λ(MoKα)=0.70926 Å, μ=0.81 cm^{-1}, F(000)=280, T=294 K. The sample (0.45×0.45×0.55 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 $\omega/2\theta$=1, t_{max}=60 s, range HKL: H 0,9 K −10,10 L −12,12, intensity controls without appreciable decay (0.2%) gave 2504 reflections of which 1693 were independent with $I>3.0\sigma(I)$. After Lorenz and polarization corrections the structure was solved with Direct Methods which revealed the non-hydrogen atoms of the molecule. After isotropic (R=0.12), then anisotropic refinement (R=0.10), the hydrogen atoms were found with a Fourier difference (between 0.50 and 0.27 $eÅ^{-3}$). 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 for H atoms; 236 variables and 1693 observations; $w=1/\sigma(F_o)^2=[\sigma^2(I)+(0.04F_o^2)^2]^{-1/2}$) with the resulting R=0.035, R_w=0.033 and S_w=0.85 (residual $\Delta\rho$=0.14 $eÅ^{-3}$). Atomic scattering factors were taken from *International Tables for X-Ray Crystallography* (1974). All the calculations were performed on a Digital MicroVAX 3100 computer with the MOLEN package (Enraf–Nonius, 1990).

4.4. Attempted crossed-Cannizzaro reactions in the presence of formalin and paraformaldehyde

To a stirred solution of formylacetal-aldehyde **10** (1.4 mmol) in 20 ml of MeOH, and 2 ml of H_2O, were added 10 equiv. of K_2CO_3 and 10 equiv. of paraformaldehyde, and stirring at room temperature was continued for 46 h (TLC monitoring). Work up as above gave an 80% isolated yield of **7** and **12** in nearly a 1:1 ratio. Repeated in the presence of formalin (37% in H_2O) the same experiment furnished the intramolecular Cannizzaro products **7** and **10** in the same yield and ratio while, again, no crossed-Cannizzaro products were detected.

4.5. Translactonization experiments

Pure bicyclic lactone **12** (0.39 mmol, 100 mg) was stirred at 25°C, for 12 h (until lactone **12** had been consumed) in the presence of SiO_2 (ca. 100 mg) in heptane:ethyl acetate (2:1, 10 ml). The reaction mixture was filtered and concentrated under reduced pressure to give quantitatively compound **7**. In a parallel experiment, 1.4 mmol of pure bicyclic lactone **7**, in 20 ml of MeOH and 2 ml of H_2O, was treated with 10 equiv. of KOH (14 mmol) until the equilibrium ratio, 1.1:1, **12**:**7** was established upon stirring for 4.5 h at rt. The ratio remains unchanged upon prolonged room temperature stirring (2 days). The same equilibrium mixture was enriched upon subjection of either pure **7** or any random mixture of **7** and **12**.

4.6. Ozonolysis of 6 in MeOH

Ozone was passed into a stirred solution of 102 mg (0.40 mmol) of **6** in methanol (8 ml) at −78°C until a purple–blue color persisted. Me_2S (ca. 3 ml) was added. The reaction mixture was allowed to

reach room temperature within 1 h, concentrated under reduced pressure, and the residue was flash chromatographed on silica gel. Elution with heptane:ether (10:1) afforded 17 mg (16%) of **8a** (H-10α) and 67 mg (62%) of **8b** (H-10β) in 78% combined yield and ca. 1:4 ratio. (3*S*)-(7*S*-)(8*R*)-(10*R*)-**8a**: Mp 59–61°C (heptane–ether). $[\alpha]_D$ −30 (*c* 0.8). IR ($CHCl_3$): 2973, 2945, 1728, 1466, 1388, 1365, 1190, 1131, 1099, 1051, 1016, 973 cm^{-1}. ^{1}H-NMR (250 MHz): 0.99 (3H, s, Me-19), 1.20 (9H, s, *t*Bu), 1.30–1.85 (7H, m), 2.63 (1H, dd, *J*=6.0, 14.0, H-9′), 3.26 (1H, dd, *J*=3.5, 11.0, H-7), 3.50 (3H, s, OCH_3), 5.23 (1H, t, *J*=5.8, H-10), 9.88 (1H, s, H-2). ^{13}C-NMR (75 MHz): 13.0 (Me-19), 19.2 (C-4), 24.8 (C-5), 29.1 (*t*Bu), 29.4 (C-6), 44.1 (C-9), 49.1 (Cq-8), 56.1 (OCH_3), 72.3 (C-7), 73.3 (Cq-*t*Bu), 92.4 (C-3), 105.2 (C-10), 204.8 (C-2). CIMS: m/z 271 [(M+H), 7], 239 [(M+H)−MeOH, 100], 183 (82), 165 (32), 57 (64). Anal.: calcd for $C_{15}H_{26}O_4$ C 66.64, H 9.69, found: C 66.34, H 9.76. (3*S*)-(7*S*)-(8*R*)-(10*S*)-**8b**: Mp 58–60°C (heptane–ether). $[\alpha]_D$ +115 (*c* 1.0). IR ($CHCl_3$): 3019, 2977, 2943, 2915, 2872, 1729, 1466, 1391, 1365, 1216, 1192, 1127, 1099, 1069, 1024, 970 cm^{-1}. ^{1}H-NMR (400 MHz): 1.03 (3H, s, Me-19), 1.20 (9H, s, *t*Bu), 1.50 (1H, m, H-6β), 1.61 (1H, m, H-4), 1.70–1.82 (3H, m, H-5, 6α, 4), 1.77 (1H, dd, *J*=13.7, 6.6, H-9β), 2.26 (1H, dd, *J*=2.2, 13.7, H-9α), 3.43 (3H, s, OCH_3), 3.87 (1H, dd, *J*=2.5, 7.9, H-7), 5.28 (1H, dd, *J*=2.2, 6.6, H-10), 9.61 (1H, s, H-2). Diagnostic NOEs: {Me-19}: H-6β, H-9β, H-10; {H-10}, H-9β, Me-19. ^{13}C-NMR (75 MHz): 15.8 (Me-19), 19.0 (C-4), 26.8 (C-5), 29.1 (C-6), 29.0 (*t*Bu), 43.2 (C-9), 46.6 (Cq-8), 55.7 (OCH_3), 71.1 (C-7), 73.6 (Cq-*t*Bu), 92.0 (C-3), 104.8 (C-10), 202.5 (C-2). CIMS: m/z 271 [(M+H), 1], 241 (15), 239 [(M+H)−MeOH, 27], 183 (100), 165 (17), 57 (99). Anal.: calcd for $C_{15}H_{26}O_4$ C 66.64, H 9.69, found: C 66.51, H 9.64.

*4.7. Reduction of **10** and selective acetonide formation*

To a stirred solution of **10** (284 mg, 1.0 mmol) in THF (20 ml), $LiAlH_4$ (114 mg, 3 mmol) was added slowly at room temperature. The mixture was stirred under reflux for 1 h, cooled to ambient temperature, quenched with 0.2 ml of water, 0.2 ml of 15% NaOH, 0.6 ml of water, and stirring was continued at room temperature for 1 h. Filtration and concentration under reduced pressure afforded crude triol **9**, which was purified through silica gel column chromatography, using ethyl acetate:methanol (9:1) as eluent, to yield 68% (two steps; ozonolysis+reduction) of (3*S*)-(7*S*)-(8*R*)-**9**: mp 96–98°C (CH_2Cl_2). $[\alpha]_D$ +35 (*c* 1.0). IR: 3252, 2969, 2934, 2872, 1451, 1423, 1363, 1226, 1191, 1086, 1018, 974, 908, 878, 754 cm^{-1}. ^{1}H-NMR (300 MHz): 0.90 (3H, s, CH_3-19), 1.17 (9H, s, *t*Bu), 1.40–2.12 (8H, m), 3.50–3.75 (5H, m). ^{13}C-NMR (75 MHz): 17.2 (Me-19), 18.7 (CH_2), 29.1 (CH_2), 29.2 (*t*Bu), 30.2 (CH_2), 37.4 (CH_2), 44.3 (C-9), 58.6 (C-10), 65.4 (C-2), 72.0 (C-7), 73.3 (Cq-*t*Bu), 76.4 (C-3). CIMS: m/z 261 [(M+H), 100], 243 [(M+H)−H_2O, 14], 205 [(M+H)−Me_2C=C, 16]. HRCIMS: calcd for $C_{14}H_{29}O_4$ m/z 261.2065, found 261.2069. Anal.: calcd for $C_{14}H_{28}O_4$ C 64.58, H 10.84, found: C 64.67, H 10.76. Triol **9** thus obtained, was dissolved in dry acetone (5 ml) and a catalytic amount of *p*-toluenesulfonic acid (ca. 20 mg) was added. The mixture was stirred under argon at room temperature for 5–10 min, diluted with ethyl acetate and filtered through aluminum oxide to give acetonide **11** in quantitative yield. (3*S*)-(7*S*)-(8*R*)-**11**: $[\alpha]_D$ +1 (*c* 0.9). IR: 3423, 2973, 2941, 2872, 1465, 1368, 1252, 1212, 1197, 1111, 1065, 1049, 1017, 1007, 977, 918, 874 cm^{-1}. ^{1}H-NMR (300 MHz): 1.05 (3H, s), 1.17 (9H, s), 1.35 (3H, s), 1.41 (3H, s), 1.20–1.82 (8H, m), 2.22 (1H, m), 3.33 (1H, d, *J*=3.2, OH), 3.60 (1H, m), 3.79 (1H, m), 3.87 (1H, d, *J*=9.7), 4.10 (1H, dd, *J*=1.2, 9.7). ^{13}C-NMR (75 MHz): 17.2 (Me), 19.0 (CH_2), 26.0 (Me), 27.0 (CH_2), 27.9 (Me), 28.7 (*t*Bu), 32.4 (CH_2), 39.1 (CH_2), 42.8 (Cq-8), 58.9 (C-10), 69.8 (C-2), 73.6 (Cq-*t*Bu), 76.2 (C-7), 85.7 (C-3), 107.1 (Cq-acetonide). CIMS: m/z 301 [(M+H), 100], 245 [(M+H)−Me_2C=C, 40], 169 (53). HRCIMS: calcd for $C_{17}H_{33}O_4$ m/z 301.2378, found 301.2340. Triol **9** and hence acetonide **11** were also obtained from **7** using the same procedure as above.

4.8. *Intermediate hemiacetal-aldehyde* **13**

To a solution of **10** (450 mg, 1.58 mmol) in MeOH (20 ml) and H_2O (2 ml) was added $LiCO_3$ (1.17 g, 15.8 mmol). The resulting mixture was stirred at room temperature for 24 h at which point no starting material remained. The reaction mixture was then diluted with ether and worked up as usual. Silica gel column chromatography (eluent: ethyl acetate:heptane, 1:4) afforded 378 mg (94%) of an unseparable 6:1 epimeric mixture of **13**. Major isomer: IR: 3427, 2972, 1727, 1467, 1391, 1361, 1190, 1095, 1060, 983 cm^{-1}. ^{1}H-NMR (300 MHz): 1.06 (3H, s, Me-19), 1.20 (9H, *t*Bu), 1.33 (1H, dd, *J*=6.0, 14.2, H-9), 1.35 (2.01, 6H, m), 2.59 (1H, dd, *J*=6.1, 14.2, H-9), 3.26 (1H, dd, *J*=3.8, 11.0, H-7), 4.07 (1H, br s, OH), 5.59 (1H, t, *J*=6.0), 9.77 (1H, s, H-2). ^{13}C-NMR (62.5 MHz): 12.8 (Me-19), 19.5 (C-4), 24.8 (C-5), 29.2 (*t*Bu), 29.6 (C-6), 45.1 (C-9), 46.6 (Cq-8), 71.6 (C-7), 73.5 (Cq-*t*Bu), 91.5 (C-3), 98.4 (C-10), 206.6 (C-2). CIMS: m/z 257 [(M+H), 7), 239 (79), 183 (100), 165 (27).

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