Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 951–973

TETRAHEDRON:
ASYMMETRY

Studies towards the taxoid diterpene ABC-ring system: practical access to highly functionalized enantiomerically pure analogues of major group representatives†

José Ignacio Martín Hernando, Maria del Rosario Rico Ferreira, José Ignacio Candela Lena, Nicolas Birlirakis and Siméon Arseniyadis *

Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France

Received 8 December 1999; accepted 14 December 1999

Abstract

Short routes for practical syntheses of enantiopure taxoid subunits which possess oxygenation at sites appropriate for further elaboration into various members of the major taxoid families are described along with detailed structure elucidation.

1. Introduction

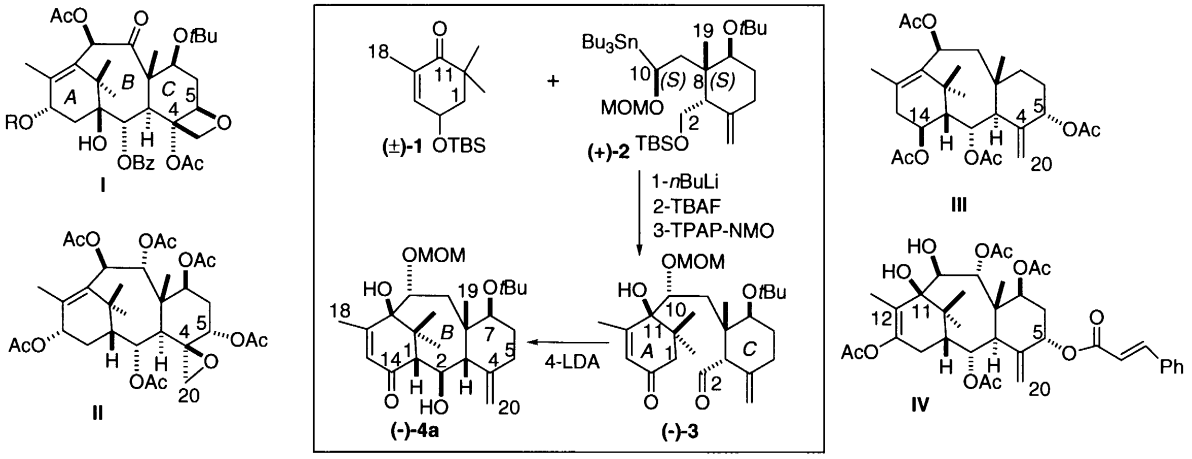
Although six total syntheses of taxol[1] have been reported, considerable effort continues to be devoted towards the development of more practical routes to conveniently access the taxoid diterpene framework. Recently,[2] we developed conditions for the four-step preparation of taxoid ABC diterpene framework **4a**, in which the isophorone-derived racemic-**1** was coupled in an A+C direction with the Hajos–Parrish ketone-derived (+)-**2**.[3] Starting from (±)-**1** and (+)-**2**, key aldol precursor (−)-**3** was produced in three steps. The published route to the key intermediate (−)-**4a** involves a transmetallation, as described by Still,[4] for the top-side linking of the left- and right-half segments, followed by a removal of TBS-protecting groups and a TPAP–NMO oxidation developed by Ley et al.[5] Intramolecular aldol[6] condensation converted the B-secotaxane **3** thus obtained to the target **4a**. (*S*)-(+)-Hajos–Parrish ketone, whose absolute stereochemistry correlates correctly with the C-8 quaternary center of taxoids, was our departure point. This stereocenter controls the relative (and consequently the absolute) configuration of the remaining stereocenters. The ease of B-secotaxane construction and the successful C-1–C-2 linkage

* Corresponding author. E-mail: simeon.arseniyadis@icsn.cnrs-gif.fr

† We dedicate this article to Professor Pierre Potier on the occasion of his 65th birthday.

0957-4166/00/$ - see front matter
PII: S0957-4166(99)00587-X

leading to the ABC skeleton underlined the feasibility of our A+C approach towards a great number of taxoid diterpene frameworks.[7] The purpose of this article is to report a convenient strategy for the synthesis of highly oxygenated, advanced taxoid ABC subunits that could be used in the total synthesis of several members of this family: those containing the bridgehead hydroxyl group at C-1, those which do not, those containing a C-4(20)-olefin, others with C-4(20)-epoxide, and finally those containing a C-12–C-13 unsaturation with a bridgehead hydroxyl group at C-11. Some examples of naturally occurring taxoids that exemplify the above-cited types are taxuspine D **IV**,[8] Taiwanxan-type taxoids such as Taxuyunnanine C **III**,[9] Baccatin I-type taxoids **II**[10] and the most well-known oxetane containing member Paclitaxel **I** (R stands for the phenylisoserine-derived side chain). The convergent synthesis of the taxoid ABC core **4a** makes this intermediate available in significant quantities (Scheme 1). As a continuation of our A+C approach we focused on the preparation of a more elaborate core tricyclic system which could be used as the starting point towards various members of the taxane family. It is worth noting that the first convergent A+C strategy to yield an ABC taxoid model embodying the whole carbon framework was reported by Kende et al.[11] while two out of six published synthetic schemes, the Nicolaou and Danishefsky routes,[1] utilized an A+C approach. We report here the syntheses of **15–33** that demonstrate the validity of this route.



Scheme 1. The four-step construction of **4a** and some of the taxoid representatives that could be accessed

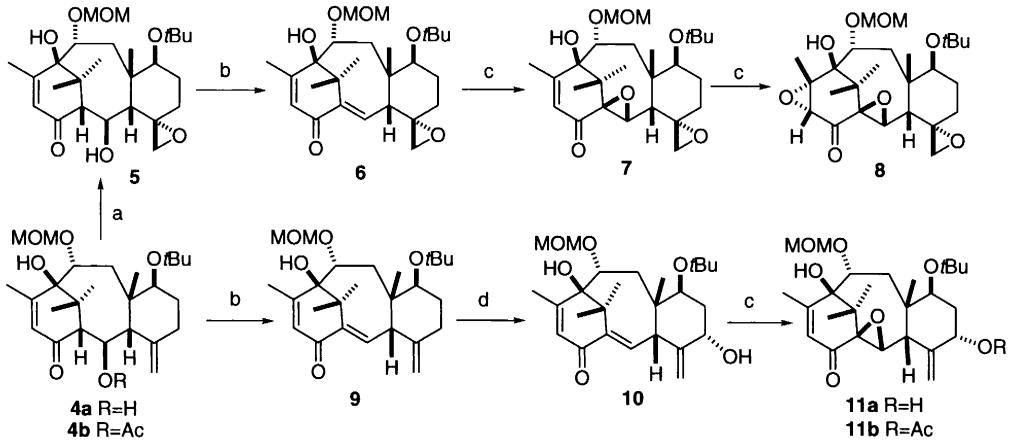
2. Results and discussion

As the left- and right-half segments had elements of the A- and C-rings in place, further transformations were devoted to the adjustment of oxygen functionality. From the foregoing results, it seemed desirable to generate a tricyclic framework that incorporates all the carbon atoms of the final taxoid skeleton and that would allow stereoselective introduction of the C-1, C-4, C-5 and C-14 hydroxyl functions. For our first model intermediate we focused on generation of the more elaborate ABC tricyclic intermediate **8** (Scheme 2). Starting from **4a**, key substrate **6** was produced in two steps. First, **4a** was transformed to **5** via a hydroxyl-directed epoxidation[12] ($VO(acac)_2$, *t*-BuOOH in decane, 10 min reflux in benzene) which led exclusively to the C-4(20)-α-epoxide in 94% isolated yield. Acetylation of the latter at C-2 using standard procedures (Ac_2O, py, DMAP, at 0°C), followed by crotonization with DBU then furnished the desired epoxy dienone **6** (95%). Searching for ways to increase oxygenation, a nucleophilic

epoxidation was first tested on dienone **6**, revealing the possibility of differentiating the two conjugated double bonds. Treatment with 30% H_2O_2 and 6N NaOH in methanol converted the dienone **6** to the bis-epoxy-enone intermediate **7** after short reaction times (stirring for less than 4 h at room temperature), along with unreacted starting material and small amounts (<5%) of the tris-epoxy-ketone **8**. Careful experimentation with TLC monitoring brought to light the possibility of selectively directing the reaction to produce either **7** or **8**. Treating **6** under the same conditions but for longer reaction times (15 h) led to the tris-epoxy intermediate **8** being obtained as the major component of the reaction mixture (62%) along with **7** (16%) and some unreacted starting material (5%). In practice the reactions were fast and clean, furthermore allowing for chemo- and stereoselection (**7** and **8** were obtained as single diastereoisomers). We took advantage of the higher reactivity of the C-1–C-2 double bond and carried out a chemoselective epoxidation in the presence of the C-12–C-13 olefin targeting **7** or direct one-pot formation of **8**. Having established conditions for differentiating the double bonds we moved forward. Our next goal was to design an advanced intermediate such as **11a**, that should provide for the synthesis of numerous structural analogues without reworking the entire synthetic approach for each analogue. We therefore prepared **11a** from **4a** and assessed its ability to meet our requirements. After considerable investigation of various alternatives, it was found that conversion of **4a** into **11a** could be carried out in an efficient manner, best results being obtained by sequential use of SeO_2 mediated allylic hydroxylation and subsequent nucleophilic epoxidation, as outlined in Scheme 2. The first operation serves to restore the C-5α oxygen functionality, necessary for ester formation (almost all known taxoids of the C-4(20)-olefin containing group are esterified at C-5) while the second one would provide the necessary oxygenation pattern at C-1 and C-2. Thus, previously obtained precursor aldol **4a** was converted to C-2 acetate **4b** (98%) and crotonized as above to produce the C-1,4(20),12-trienone **9** (96%), which in turn was converted to C-5α-OH **10** by an SeO_2 mediated allylic oxidation. Subjection of **9** to selenium dioxide and *t*-BuOOH (70% in water) in dichloromethane provided, after stirring overnight at room temperature, the desired alcohol **10** necessary for the corresponding ester formation and also for the oxetane D-ring synthesis, in 55% isolated yield. The latter was accompanied by two new compounds, the target intermediate **11a** (6%), the C-4(20)-α-epoxide **32** (10%) and unreacted starting material (24%). Upon subjection of **10** to nucleophilic epoxidation as above (4 h, 0°C to room temperature), a 93% isolated yield of the requisite target was obtained (no other stereoisomer was produced). Preparation of **11a** was thus accomplished in satisfactory overall yield; the synthetic routes to **8** and **11a** are presented in Scheme 2.

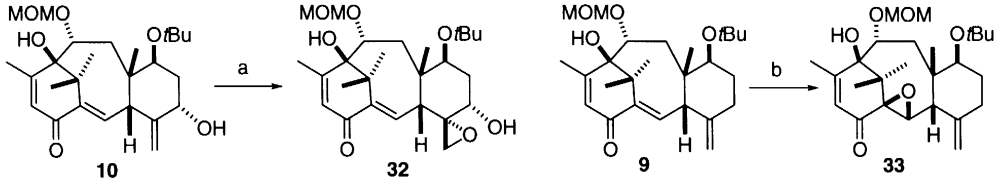
While looking for which sequence to adopt, we found that conversion of **10** to **32** using Sharpless conditions as above gave a 63% isolated yield of the desired compound, which was accompanied by the corresponding C-1–C-2 epoxide **11a** (15%), C-1–C-2, C-4–C-20 bis-epoxide **16a** (7%) and left-over starting material (3%). The formation of a considerable amount of C-1–C-2 epoxide might be due to the folded nature of the taxoid ABC core, which could adopt a conformation bringing the C-5α hydroxyl function close to the C-1–C-2 double bond. Bis-epoxide **16a**, obtained as a by-product, was later synthesized straightforwardly from **11a** using a hydroxyl directed epoxidation as above (Scheme 4).

On the other hand, **9** was converted to **33** as a single diastereoisomer using the chemoselective nucleophilic epoxidation as described above, in a nearly quantitative yield, indicating that the synthetic scheme offers several distinct ways for further elaboration (Scheme 3). Attention was then turned to the preparation of the target D-ring precursors **15**–**19**. A variety of conditions were surveyed to determine the most efficient way for C-4–C-20 oxygenation. The synthesis of a direct oxetane precursor was initially envisioned by the preparation of **15**. To accomplish this, OsO_4-catalyzed dihydroxylation was first tried, though unsuccessfully. However, using standard stoichiometric osmylation procedures conversion of **11a** to a mixture of **12** and **13** was quite clean and rapid (5 h 30 min, at room temperature) and the latter



Scheme 2. (a) $VO(acac)_2$, *t*-BuOOH in dec., PhH, Δ; (b) Ac_2O, py, DMAP then DBU; (c) 30% H_2O_2, 6N NaOH, MeOH, 0°C to rt; (d) SeO_2, *t*-BuOOH 70% in H_2O, CH_2Cl_2, rt

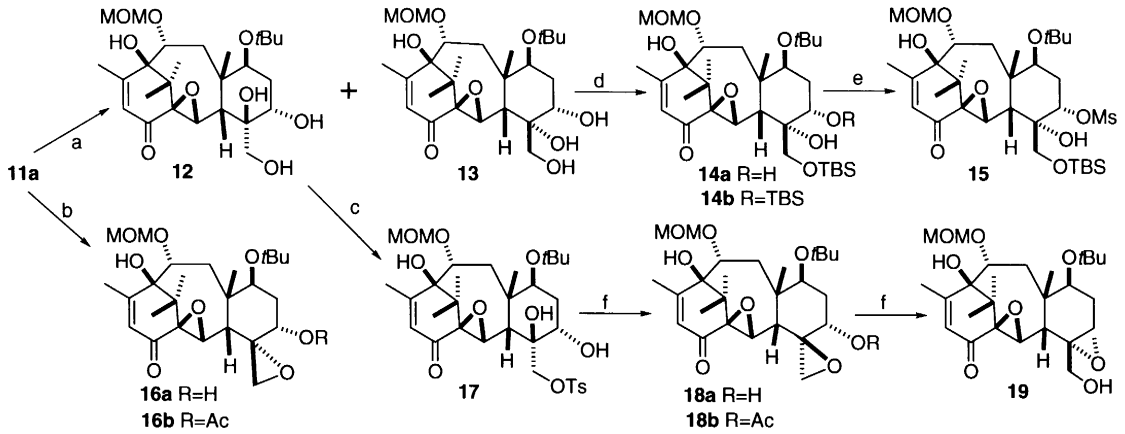
was isolated in 77% combined yield and 1.4:1 ratio, along with unreacted starting material. The origin of π-facial differentiation in oxygenated allylic systems has been debated at length;[13] empirical rules for substrate-controlled delivery of OsO_4 to allylic systems,[14] stereoelectronic arguments and the role of Os-substrate complexation have been advanced.[15]



Scheme 3. (a) $VO(acac)_2$, *t*-BuOOH in dec., PhH, Δ; (b) 30% H_2O_2, 6N NaOH, MeOH, 0°C to rt

Following osmylation, selective protection of the primary C-20 hydroxyl group of **13** as the corresponding mono *tert*-butyldimethylsilylether provided easy access to **14a** (86%). Subsequent mesylation using excess mesyl chloride and a few crystals of DMAP in dry pyridine furnished, after 1 h at 0°C, the desired mesylate **15** (84%), a close precursor of oxetane containing taxoids.[16] During the course of this work an alternative approach was investigated from the major tetraol **12**, which possesses the wrong stereochemistry at the quaternary center C-4. As a result, we established a different route to effect the transformations going from **11a** to either C-4(20)-β-epoxide containing members or the D-ring precursors such as **19**, where the C-4 stereogenic center now possesses the requisite configuration. Starting from **12**, formation of the monotosylate **17** was achieved in 81% isolated yield by treatment of **12** with an excess of *p*-toluenesulfonyl chloride in anhydrous pyridine and a catalytic amount of DMAP. Furthermore, controlled displacement of the tosylate under mild basic conditions proved beneficial. In a preliminary experiment, direct exposure of the resulting crude **17** to a mild base (K_2CO_3) gave **19** directly after stirring overnight at room temperature. However, conversion of **17** to **18a** was quite rapid (1 h) and clean at a temperature below zero and the latter could be easily isolated chromatographically. It is worth noting that taxoids with the C-4(20)-β-epoxy ring system as in **18a** were proposed as possible direct precursors of taxoids containing the oxetane D-ring.[10] Thus, while short exposure to base in anhydrous methanol at a low temperature (1 h at −45°C) produced the expected β-epoxide **18a** (98% isolated yield), prolonged reaction times at room temperature resulted in the Payne rearrangement[17]

leading to **19** (92% isolated yield), as shown in Scheme 4. This allowed a modular construction of the C-4 oxygenated quaternary center providing access to either Baccatin I-type C-4(20)-β-epoxy taxanes or oxetane containing taxanes and, therefore, a better use of the osmylation step. Scheme 4 depicts the synthesis of C-4(20)-α- and β-epoxy substrates, **16** and **18**, respectively, and provides an outline for the modular construction of the C-4 stereogenic center. Major C-4(20) diol **12** was thus elaborated in two steps and 75% overall yield into the C-4 reversed D-ring precursor **19**.



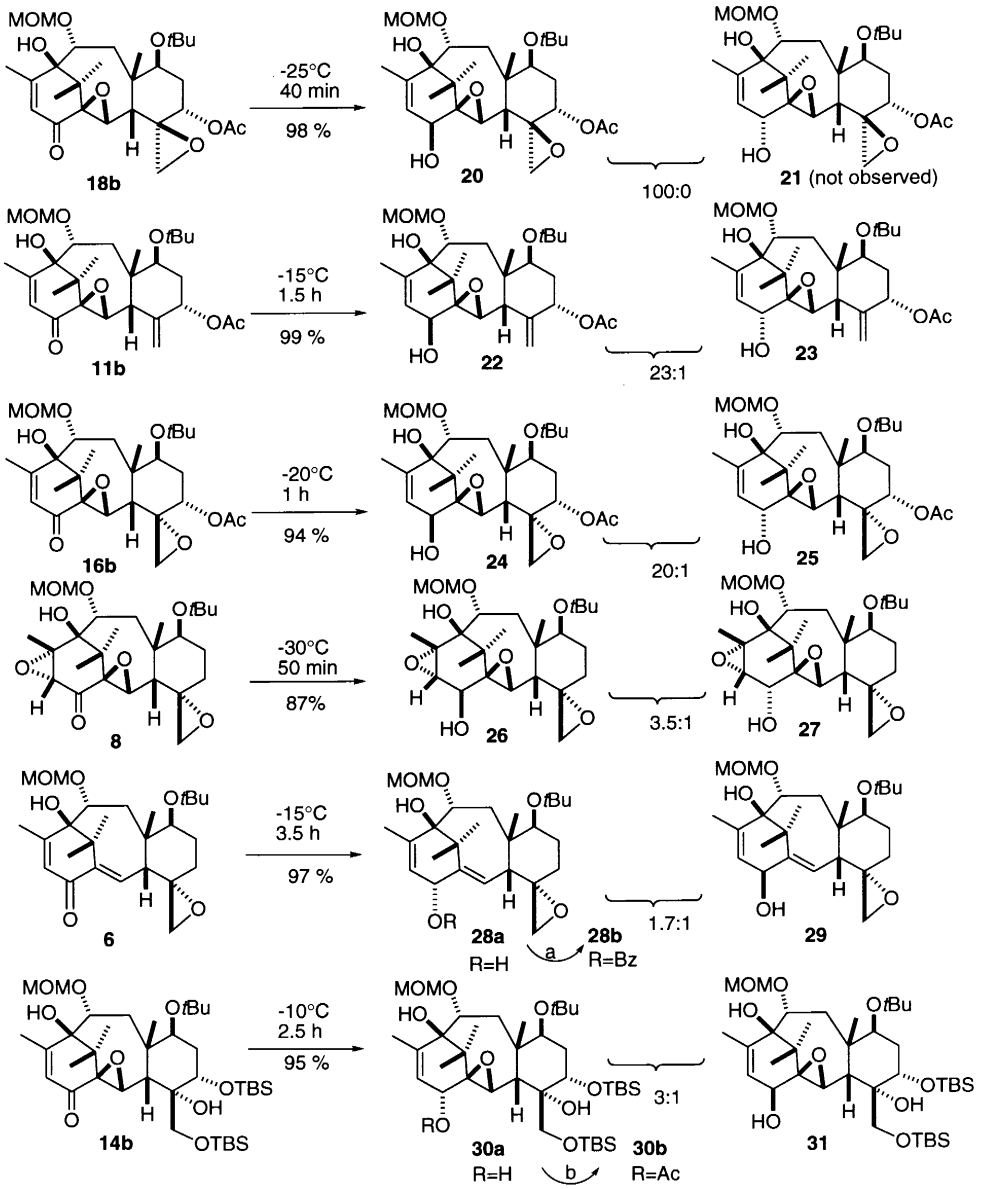
Scheme 4. (a) OsO_4, NMO, *t*-BuOH:H_2O (3:1), py, rt; (b) $VO(acac)_2$, *t*-BuOOH in dec., PhH, Δ; (c) TsCl, py, DMAP, 0°C to rt; (d) TBSCl, Im., DMF, rt; (e) MsCl, py, DMAP, 0°C; (f) K_2CO_3, MeOH

In summary, starting from tricyclic intermediate **11a**, which incorporates all the carbon atoms of the final taxoid skeleton, OH-directed epoxidation led to the α-epoxide at C-4(C-20) **16a**, whereas osmium mediated dihydroxylation provided a modular stereoselectivity for the introduction of the C-4 hydroxyl function.

3. Installation of the C-14 hydroxyl functionality and structure elucidation

The presence of the C-14 carbonyl functionality in all synthesized compounds was suggestive of a way towards taxoids of the Taiwanxan family, possessing an exocyclic olefin at C-4(20) and oxygenation at C-14. Such taxoids, which lack oxygen functionalities at C-1, C-7, C-9 and C-13, have been isolated from the roots and also from cell cultures of *Taxus yunnanensis*,[18] from cell cultures of *Taxus chinensis*[19] or from the bark of *Taxus brevifolia*.[20] A careful reduction was required to install the C-14 hydroxyl group in its β-configuration. This was accomplished using the method reported by Luche et al.[21] which secured complete chemo- and regioselectivity while showing a substrate dependent stereoselectivity. Only carbonyl reduction leading to C-14 allylic alcohols was observed; conjugate reduction which would produce the corresponding saturated alcohol was not detected by high field ^1H NMR spectroscopy and TLC. The first compound tested was the dienone **11b**, a close precursor of taxuyunnanine C **III** (Scheme 1) or Taiwanxan, which was obtained from key intermediate **11a** by acetylation (Ac_2O, pyridine, DMAP, 0°C, 1 h 40 min). Treatment of the former with $NaBH_4$–$CeCl_3$ (−15°C, in CH_2Cl_2:EtOH, 1:1, 1.5 h) provided the desired alcohol **22** along with its C-14α epimer **23** in 99% combined yield and 23:1 diastereoselectivity.

The high chemo-, regio- and stereoselectivity, as well as the excellent chemical yield observed in the reduction of **11b** using the procedure developed by Luche, prompted us to investigate reduction of



Scheme 5. Observed facial selectivity in the C-14 carbonyl reductions, carried out at the indicated temperatures with $NaBH_4$ and $CeCl_3$ in 1:1 EtOH:CH_2Cl_2. (a) BzCl, Et_3N, DMAP, CH_2Cl_2; (b) Ac_2O, py, DMAP

five additional taxoid ABC subunits obtained during this study. The transformations leading to C-14 hydroxylated taxoid precursors **20**–**31** are portrayed in Scheme 5 in order of decreasing β-selectivity. A net preference for C-14-β-hydroxyl selectivity was observed on substrates **18b**, **11b** and **16b**. This selectivity reached its lowest β:α ratio during the reduction of the tris-epoxy-ketone **8**. Finally, a reversal of facial selectivity during hydride reduction occurred with structures **6** and **14b**.The next substrate examined was the bis-β-epoxide **18a**, a precursor of Baccatin I-type taxoids **II** (Scheme 1). The latter was first acetylated (Ac_2O, pyridine, DMAP, 0°C, 94%) at C-5 before reduction. This protection has the added advantage of further reducing the tendency toward formation of the Payne rearrangement

product **19**. Thus, $NaBH_4$–$CeCl_3$ reduction of **18b** (−25°C, in CH_2Cl_2:EtOH, 1:1, 40 min) afforded the C-14β hydroxylated taxoid **20** as a single stereoisomer in 98% isolated yield. The corresponding C-14α-hydroxyl epimer was not observed. The stereochemical course of this reduction established on the strength of NOE experiments, the diagnostic NOEs and preferred conformations of selected examples are illustrated in Fig. 1. Experimental evidence favoring the structures of all investigated compounds came from comprehensive 2D NMR experiments which included COSY, HMQC and HMBC correlations, that allowed all carbons and their respective protons to be assigned with confidence. The relative stereochemistries shown in Scheme 5 were deduced from the magnitudes of coupling constants (vicinal and long range), corroborated by spatial proximity studies using 1D difference NOE experiments, and were in agreement with molecular mechanics calculations. The β-OH stereochemistry at C-14 of **22** was supported by the observation of diagnostic NOEs involving H-14, H-2, H-7 protons, all occupying the α-face of their respective cyclic system. Irradiation of the H-2 epoxidic proton at 3.14 ppm showed strong NOEs to H-14 at 3.74 ppm and H-7 at 3.69 ppm (confirms epoxide stereochemistry). Likewise, when H-14 was irradiated, an NOE was seen to the epoxidic proton H-2. Irradiation of the C-8 angular methyl group, Me-19 singlet at 1.00 ppm, showed an NOE to H-10 at 3.98 ppm as well as to H-3 at 2.60 and H-6βax proton at 1.98 ppm. Irradiation of Me-17 at 1.43 ppm showed an NOE to H-13 at 5.85 ppm while no enhancement was observed for the H-14 proton at 3.74 ppm, confirming the β-OH stereochemistry. Proceeding as above, diagnostic NOEs between H-2 at 3.19 ppm, H-14 at 3.72 ppm and H-7 at 3.68 ppm unambiguously established the C-14-β-hydroxyl disposition for compound **20**. With the remaining four substrates the β-selectivity decreased up to 3.5:1 β:α ratio before reversal to finally reach a 3:1 α:β selectivity, thus making rationalization of the observed selectivity difficult at this stage. Reduction of enone **16b** and tris-epoxy-ketone **8** still furnished C-14β hydroxylated taxoids in high chemical yields, though with a decreasing diastereoselectivity. The bis-epoxy-enone alcohol **16a** was first acetylated at C-5 using standard procedures to afford a 92% yield of **16b**, which was reduced as above (−20°C, 1 h) to the chromatographically separable isomers **24** and **25** in 94% combined yield and 20:1 ratio. The β-OH stereochemistry at C-14, along with β-face disposition of the C-4–C-20 epoxide and the α-face disposition of the C-12–C-13 epoxide of major allylic alcohol **26**, were supported by the observation of diagnostic NOEs involving Me-17, Me-19 and H-14, H-2, H-3, H-7, H-20 protons. Failure to observe an enhancement at the H-14 proton (3.84 ppm) on irradiation of the Me-17 methyl group at 1.60 ppm provides evidence, just as for substrates **20**, **22** and **24**, that they are on opposite faces of the molecule, consistent with an *anti* dipole geometry. The stereochemical outcome of the reduction was first reversed when the C-1–C-2 epoxide was replaced with an olefin as in **6**. Upon subjecting the latter to the above conditions, hydride delivery occurred predominantly from the β-face (convex face) of the molecule, giving the opposite stereochemistry seen for enones **18b**, **16b**, **11b** and tris-epoxy-ketone **8**. This gave a mixture of allylic alcohols in ca. 1.7:1 ratio, with the C-14α-hydroxy derivative **28a** as the main stereoisomer, along with the minor C-14β-hydroxyl isomer **29**. Even though the chemical yield of this transformation was excellent on conversion, only moderate selectivity, favoring the C-14α hydroxylated analogue, was obtained. To obtain the major allylic alcohol pure and furthermore get some insight into the reactivity of this oxygen functionality, pointing towards the concave face of the AB-ring system, the C-14α-hydroxyl of **28a** was benzoylated using BzCl in dry CH_2Cl_2 in the presence of triethylamine and a catalytic amount of DMAP. The stereochemical outcome of enone reduction on **6** was again determined with the aid of 1D NOEDIFF spectra through the configurational assignment of **28b**. This was achieved by simply applying the reasoning used for the above cases. Irradiation of H-14 at 6.30 ppm showed strong NOE to Me-17 at 1.43 ppm (confirms α-hydroxyl configuration) and to the vinylic H-13 proton at 5.71 ppm. Likewise, when Me-17 was irradiated, a strong NOE was seen to the

allylic proton H-14 along with a much weaker one to H-13. These data led to the assignment of the major allylic alcohol to **28a**.

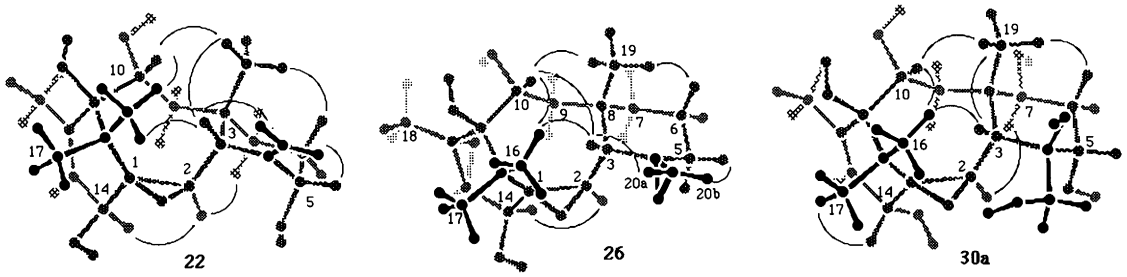


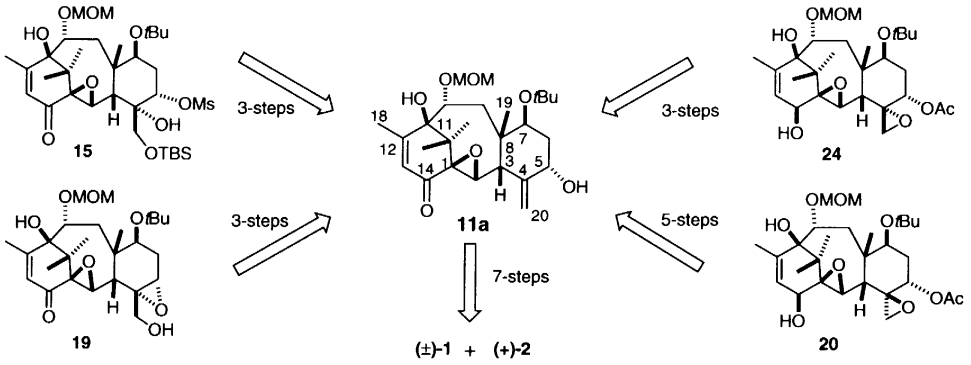
Fig. 1. Lowest energy conformers of **22**, **26** and **30a**, as determined by molecular mechanics calculations using MM3; arcs indicate diagnostic NOEs

Finally, reduction of the enone **14b** (−10°C, 2.5 h) gave the C-14α alcohol **30a** as the major stereoisomer along with **31** in 95% combined isolated yield and 3:1 α:β ratio. The major diastereoisomer **30a** (faster eluting) accounting for 75% of the product mixture was further acetylated using Ac_2O–py–DMAP, in an attempt to check the reactivity of the hydroxyl function, affording **30b** in 90% isolated yield. Diagnostic NOEs (on major isomer **30a**) for H-14 at 4.57, H-2 at 4.01, H-3 at 2.51 and H-7 at 3.86 ppm confirmed the C-14α-hydroxy configuration and validated C-1–C-2 epoxide and C-4 stereochemistry as depicted in Scheme 5. No enhancement was observed for the H-14 proton when H-2 was irradiated, while a strong NOE was observed on H-14 when Me-17 at 1.30 ppm was irradiated, confirming the α-stereochemistry of the C-14-hydroxyl group. Using the above methodology, we have prepared the examples listed in Scheme 5. In all instances, the crude products were obtained with a high degree of purity as assessed by ^{1}H NMR. The stereoselective reduction of the target enone **11b** with $NaBH_4$–$CeCl_3$ produced the desired stereochemistry at C-14 with high stereocontrol and afforded, in excellent chemical yield, an allylic alcohol which can be further elaborated towards the C-14 hydroxylated taxoids. The strategy also allows for access to the hitherto unknown C-14 hydroxylated taxoid derivatives bearing a C-4–C-20 epoxide. In none of the cases investigated was 1,4-reduction or epoxide and/or acetate reduction to an appreciable extent observed, confirming the Luche procedure as a powerful tool for chemoselective transformations.

4. Conclusion

We have shown that close precursors of several members of the taxane family can be accessed through a convergent sequence starting from compounds derived from (*S*)-(+)-Hajos–Parrish ketone and 4-oxoisophorone using a C-10–C-11/C-1–C-2 linking protocol and a further efficient elaboration.

A modular synthesis of advanced taxoids has been presented that allows access to a great variety of structures in this class (Scheme 6). As interest in taxoid diterpenes as possible substitutes for taxol and taxotere in cancer treatment is likely to continue, adaptable synthetic routes to members of this group will play an important role in this area of drug development. The synthetic utility of the current method derives from its applicability to a variety of taxoids and the high stereo-, chemo- and regioselectivities observed for the oxygenation processes; its flexibility to efficiently introduce and further modify various substituents around the core tricyclic intermediate is noteworthy.



Scheme 6. An efficient preparation of advanced enantiopure taxoid subunits

5. Experimental

5.1. General

Solvents and reagents used in this work were purified according to standard literature techniques and stored under argon. Experiments which required an inert atmosphere were carried out under dry argon in a flame dried glass system. 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 plates that were developed by immersion in 5% phosphomolybdic acid in 95% ethanol. '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. NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform at 20°C, unless otherwise noted. ^1H (600 and 800 MHz) and ^{13}C NMR (150 and 200 MHz) experiments were carried out on Bruker Avance DRX-800 and DRX-600 spectrometers, equipped with triple resonance H/C/N probeheads and three-axis pulsed field gradient modules. Gradients were used for the coherence transfer pathway selection in HMBC and HMQC experiments. In the latter, broadband decoupling was performed by using either adiabatic WURST-40 pulses (800 MHz apparatus) or GARP sequence (600 MHz apparatus). Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (1 and 2D experiments), corroborated by spatial proximity studies mainly using the 1D NOEDIFF[22] technique. For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[23] Electron spray mass spectra were obtained in instances where electron impact and chemical ionization failed to produce molecular ions. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^+), using a mobile phase of methanol, will be abbreviated as ESIMS (MeOH). Molecular mechanics calculations were run using Still's Macromodel program version 5.5 operated on a Silicon Graphics work-station. 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).[24]

5.2. Preparation of the further oxygenated models *5*–*8*

Acetic anhydride (0.75 mL, excess) was added to a stirring mixture of aldol **4a** (117 mg, 0.26 mmol) and DMAP (catalytic) in dry pyridine (3.0 ml) under argon. The reaction mixture was stirred for 3 h 45 min at 0°C (TLC monitoring), diluted with EtOAc, washed with saturated sodium bicarbonate then dilute

hydrochloric acid and worked up as usual to give, after silica gel flash column chromatography (eluent: heptane:EtOAc, 4:1), 126 mg of the corresponding acetate (98%), isolated only for characterization purposes. Compound **4b**: mp 131–132°C (heptane–ether); $[\alpha]_D$ −100 (*c* 2.68). IR (film): 3538, 2975, 1740, 1660, 1625, 1445, 1369, 1237, 1190, 1150, 1019, 956, 907, 736 cm^{-1}. ^1H NMR (300 MHz): δ 0.96 (3H, s, Me-19), 1.05 (9H, s, *t*-Bu), 1.15 (3H, s, Me-17), 1.42 (1H, m, H-6), 1.41 (3H, s, Me-16), 1.53 (1H, dd, *J*=6.6, 17.8, H-9α), 1.70 (1H, m, H-6), 1.71 (1H, d, *J*=17.8, H-9β), 1.92 (3H, s, *Me*CO), 2.00 (3H, d, *J*=1.4, Me-18), 2.03 (1H, m, H-5β), 2.36 (1H, tdt, *J*=1.9, 5.6, 14.2, H-5α), 2.49 (1H, d, *J*=1.8, H-1), 2.60 (1H, d, *J*=11.8, H-3), 3.17 (1H, dd, *J*=4.5, 11.1, H-7), 3.44 (3H, s, O*Me*), 3.91 (1H, s, OH), 4.04 (1H, d, *J*=6.1, H-10), 4.60 (1H, d, *J*=6.6, O*CH*$_2$O), 4.61 (1H, t, *J*=1.9, H-20), 4.75 (1H, d, *J*=6.6, O*CH*$_2$O), 4.76 (1H, t, *J*=1.9, H-20), 5.91 (1H, dd, *J*=1.8, 11.8, H-2), 6.14 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3, H-1; {Me-17}: Me-16 (NOE gem), H-1; {Me-19}: H-3, H-10, H-6β, H-9β; {H-2}: H-7, H-5αax. ^{13}C NMR (75 MHz): δ 20.0, 20.4, 20.9, 21.3, 28.7 (3C), 29.1, 30.9, 31.6, 38.7, 39.9, 40.6, 54.7, 55.9, 61.4, 71.8 (2C), 73.3, 76.3, 79.0, 94.1, 113.3, 127.5, 146.0, 163.1, 168.5, 195.5. CIMS: 493 ([MH]$^+$, 100), 461 (20), 437 (16), 433 (41), 377 (14), 371 (12), 359 (10), 315 (17), 297 (9). HRCIMS: calcd for $C_{28}H_{45}O_7$ *m/z*: 493.3165; found: 493.3167.

Hydroxyl-directed epoxidation; preparation of **5**: A mixture of aldol **4a** (140 mg, 0.31 mmol) and $VO(acac)_2$ (1.3 mg, 0.0049 mmol, 0.016 equiv.) in benzene (8.0 mL) was refluxed for 15 min under argon. Addition of 5–6 M *t*-BuOOH in decane (0.1 mL, 0.55 mmol) followed and stirring continued at this temperature for 10 min. After cooling, dilution with EtOAc, washing with saturated aqueous solution of sodium bicarbonate and the usual work-up, the residue was chromatographed on silica gel (heptane:EtOAc, 3:1 to 2:1) to give 136 mg (94%) of the expected epoxide. Compound **5**: $[\alpha]_D$ −87 (*c* 2.31). IR (film): 3517, 2975, 2927, 2876, 2855, 1656, 1628, 1465, 1445, 1400, 1390, 1381, 1364, 1328, 1268, 1244, 1187, 1149, 1120, 1089, 1070, 1047, 1024, 910, 836, 736 cm^{-1}. ^1H NMR (800 MHz): δ 1.09 (9H, s, *t*-Bu), 1.13 (1H, bdd, *J*=5.0, 14.2, H-5β), 1.16 (3H, s, Me-19), 1.22 (3H, s, Me-17), 1.36 (3H, s, Me-16), 1.56 (1H, dd, *J*=6.6, 17.5, H-9α), 1.66 (1H, d, *J*=17.5, H-9β), 1.67 (1H, dd, *J*=2.1, 11.2, H-3), 1.68 (1H, dddd, *J*=5.0, 11.2, 13.8, 14.2, H-6β), 1.92 (1H, dtd, *J*=2.1, 5.0, 14.2, H-6α), 2.04 (3H, d, *J*=1.4, Me-18), 2.37 (1H, ddt, *J*=2.1, 5.0, 14.2, H-5α), 2.73 (1H, bs, H-1), 2.74 (1H, dd, *J*=2.1, 4.5, H-20), 2.80 (1H, d, *J*=4.5, H-20), 3.17 (1H, dd, *J*=5.0, 11.2, H-7), 3.47 (3H, s, O*Me*), 3.84 (1H, s, OH), 4.02 (1H, dd, *J*=1.4, 6.6, H-10), 4.06 (1H, t, *J*=1.4, OH), 4.65 (1H, d, *J*=6.8, O*CH*$_2$O), 4.78 (1H, d, *J*=6.8, O*CH*$_2$O), 4.87 (1H, td, *J*=1.4, 11.2, H-2), 6.14 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-1, H-10, H-3; {Me-17}: Me-16 (NOE gem), H-1; {Me-19}: H-3, H-10; {H-5αax}: H-2, H-7, H-5 (NOE gem); {H-10}: H-3, Me-16, Me-19. ^{13}C NMR (75 MHz): δ 20.1 (Me-16), 20.2 (Me-19), 21.5 (Me-18), 27.6 (C-5), 28.9 (3C, *t*-Bu), 29.6 (C-6), 31.7 (Me-17), 40.8 (Cq-15), 41.2 (Cq-8), 41.2 (C-9), 51.3 (C-3), 56.0 (C-20), 56.2 (O*Me*), 60.8 (C-4), 63.3 (C-1), 71.5 (C-7), 72.8 (C-2), 73.8 (Cq, *t*-Bu), 76.6 (C-10), 79.5 (C-11), 94.4 (O*CH*$_2$O), 128.1 (C-13), 162.9 (C-12), 198.3 (C-14). CIMS: 467 ([MH]$^+$, 100), 449 (67), 435 (16), 417 (14), 411 (17), 405 (19), 393 (19), 349 (14), 331 (29), 313 (8). HRCIMS: calcd for $C_{26}H_{43}O_7$ *m/z*: 467.3008; found: 467.3007.

Proceeding as above, acetylation of **5** (65 mg, 0.14 mmol) was followed by a one-pot crotonization, adding 1.5 mL of DBU. After 22 h stirring at room temperature (TLC monitoring), and washing with 1N HCl, saturated sodium bicarbonate and the usual work-up afforded a crude residue which upon chromatography using heptane:EtOAc, 2:1, as eluent, afforded 60 mg (95%) of **6:** mp 168–170°C (heptane–ether–EtOAc). $[\alpha]_D$ −31 (*c* 1.21). IR (film): 3410, 2976, 1669, 1628, 1462, 1364, 1237, 1196, 1149, 1070, 1014, 911, 853, 806, 732 cm^{-1}. ^1H NMR (300 MHz): δ 1.09 (9H, s, *t*-Bu), 1.18 (1H, m, H-5β), 1.21 (3H, s, Me), 1.30 (3H, s, Me), 1.36 (3H, s, Me), 1.43 (1H, dd, *J*=8.1, 15.9, H-9α), 1.73 (1H, dddd, *J*=3.8, 11.3, 13.6, 14.1, H-6β), 1.81 (1H, d, *J*=15.9, H-9β), 1.89 (1H, dtd, *J*=3.2, 4.4, 13.6, H-6α),

2.01 (3H, d, *J*=1.4, Me-18), 2.27 (1H, ddt, *J*=1.8, 4.3, 14.1, H-5α), 2.52 (1H, d, *J*=12.3, H-3), 2.63 (1H, dd, *J*=1.8, 5.0, H-20), 2.73 (1H, d, *J*=5.0, H-20), 3.16 (1H, dd, *J*=4.4, 11.3, H-7), 3.46 (3H, s, O*Me*), 4.08 (1H, d, *J*=8.1, H-10), 4.65 (1H, d, *J*=6.8, O*CH*$_2$O), 4.74 (1H, d, *J*=6.8, O*CH*$_2$O), 6.08 (1H, d, *J*=12.3, H-2), 6.10 (1H, q, *J*=1.4, H-13). ^{13}C NMR (75 MHz): δ 17.5, 20.3, 22.6, 26.4, 27.4, 28.9 (3C), 29.3, 42.6, 44.3, 47.6, 48.4, 56.1, 56.4, 57.3, 72.7, 73.4, 77.6, 83.1, 94.6, 129.8, 130.7, 149.6, 160.6, 194.3. CIMS: 449 ([MH]$^+$, 100), 431 (17), 417 (8), 393 (23), 387 (11), 375 (16), 331 (13), 313 (11). HRCIMS: calcd for $C_{26}H_{41}O_6$ *m/z*: 449.6131; found: 449.6130.

Nucleophilic epoxidation: To an ice cold magnetically stirred solution of dienone **6** (24.4 mg, 0.054 mmol) in methanol (2 mL) were added 30% H_2O_2 (0.15 mL) and 6N NaOH (0.05 mL). Once addition was complete the cold bath was removed and the reaction mixture was stirred at room temperature for 15 h (TLC monitoring, heptane:EtOAc, 2:1). Following removal of methanol under reduced pressure, the crude reaction mixture was diluted with ethyl acetate and washed with a 5% $NaHSO_3$ solution. Usual work-up and chromatography using heptane:EtOAc, 3:1 to 1:2, as eluent furnished 16.3 mg of **8** (62%), 4.6 mg of **7** (16%) which could be further transformed into **8**, and 5% of unreacted starting material. Compound **8** (faster eluting): $[\alpha]_D$ −83 (*c* 1.22). IR (film): 3514, 2975, 1728, 1458, 1391, 1364, 1324, 1267, 1186, 1148, 1114, 1071, 1022, 914, 883 cm^{-1}. ^{1}H NMR (600 MHz): δ 1.06 (3H, s, Me-16), 1.14 (9H, s, *t*-Bu), 1.15 (3H, s, Me-19), 1.28 (1H, m, H-5), 1.40 (3H, s, Me-17), 1.44 (1H, d, *J*=11.7, H-3), 1.46 (3H, s, Me-18), 1.73 (1H, m, H-6), 1.96 (1H, m, H-6), 1.94 (1H, dd, *J*=6.2, 16.1, H-9), 2.19 (1H, bd, *J*=16.1, H-9), 2.27 (1H, m, H-5), 2.53 (1H, dd, *J*=1.2, 5.1, H-20), 2.68 (1H, d, *J*=5.1, H-20), 2.97 (1H, d, *J*=11.7, H-2), 3.22 (1H, s, H-13), 3.34 (1H, dd, *J*=4.4, 11.4, H-7), 3.44 (3H, s, O*Me*), 4.01 (1H, s, OH), 4.06 (1H, bd, *J*=6.2, H-10), 4.70 (1H, d, *J*=7.0, O*CH*$_2$O), 4.79 (1H, d, *J*=7.0, O*CH*$_2$O). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-19}: H-3, H-10, H-6β; {Me-18}: H-13; {H-2}: H-7, H-5αax; {H-10}: H-3, Me-16, Me-19. ^{13}C NMR (150 MHz): δ 17.2 (Me-19), 19.6 (Me-18), 22.1 (Me-16), 27.4 (Me-17), 27.6 (C-5), 29.0 (3C, *t*-Bu), 29.4 (C-6), 39.8 (Cq-15), 42.7 (C-9), 43.0 (Cq-8), 47.6 (C-3), 55.7 (C-20), 56.2 (O*Me*), 57.5 (Cq-4), 60.8 (C-13), 64.5 (C-2), 64.6 (Cq-12), 67.4 (Cq-1), 72.7 (C-7), 73.8 (Cq, *t*-Bu), 75.2 (C-10), 77.8 (Cq-11), 95.0 (O*CH*$_2$O), 203.1 (C-14). CIMS: 481 ([MH]$^+$, 6), 449 (24), 375 (47), 363 (38), 345 (100), 327 (58), 317 (40), 299 (30), 177 (38), 167 (32), 149 (26), 95 (19). HRCIMS: calcd for $C_{26}H_{41}O_8$ *m/z*: 481.6119; found: 481.6117.

Compound **7** (slower eluting): $[\alpha]_D$ −65 (*c* 0.43). IR (film): 3519, 2974, 1691, 1617, 1461, 1390, 1364, 1268, 1196, 1149, 1073, 1020, 907 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.12 (12H, s, Me-16 and *t*-Bu), 1.20 (1H, m, H-5β), 1.19 (3H, s, Me-19), 1.30 (3H, s, Me-17), 1.49 (1H, d, *J*=11.6, H-3), 1.74 (1H, m, H-6β), 1.75 (1H, dd, *J*=7.0, 16.4, H-9α), 1.92 (1H, dtd, *J*=3.1, 4.5, 13.5, H-6α), 2.00 (1H, bd, *J*=16.4, H-9β), 2.10 (3H, d, *J*=1.4, Me-18), 2.20 (1H, m, H-5α), 2.56 (1H, dd, *J*=1.8, 5.0, H-20a), 2.69 (1H, d, *J*=5.0, H-20b), 2.96 (1H, d, *J*=11.6, H-2), 3.27 (1H, dd, *J*=4.5, 11.3, H-7), 3.47 (3H, s, O*Me*), 4.04 (1H, s, OH), 4.09 (1H, bd, *J*=7.0, H-10), 4.68 (1H, d, *J*=6.8, O*CH*$_2$O), 4.78 (1H, d, *J*=6.8, O*CH*$_2$O), 6.23 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-19}: H-3, H-10, H-6β; {H-3}: H-10, Me-16, Me-19, H-20a; {H-2}: H-7, H-5αax; {H-20a}: H-20b (NOE gem), H-3, Me-19. ^{13}C NMR (75 MHz): δ 17.9, 19.7, 20.8, 25.5, 27.7, 29.0 (3C), 29.4, 41.3, 42.9, 43.0, 47.3, 55.6, 56.2, 57.5, 64.1, 66.1, 72.7, 73.8, 76.0, 81.2, 94.5, 128.1, 163.1, 196.3. ESIMS (MeOH): 951 ([2MNa]$^+$, 100), 503 ([MK]$^+$, 51), 487 ([MNa]$^+$, 30), 465 ([MH]$^+$, 8).

*5.3. Preparation of the key intermediate **11***

Trienone **9** was synthesized by the one-pot acetylation–crotonization procedure as above. Aldol **4a** (243 mg, 0.54 mmol) was first acetylated with excess acetic anhydride in dry pyridine (5 mL) in the

presence of few crystals of DMAP at 0°C, then crotonized in situ by addition of 0.41 mL of DBU at 0°C and stirring at room temperature for 6 h 45 min (TLC monitoring). Washings with 1N HCl then $NaHCO_3$ and the usual work-up, followed by chromatography (heptane:EtOAc, 3:1), furnished 225 mg (96%) of **9**: mp 137–138°C (heptane–ether). $[\alpha]_D$ −21 (*c* 1.97). IR (film): 3529, 3076, 2973, 2935, 2854, 1739, 1629, 1459, 1363, 1332, 1242, 1214, 1189, 1162, 1148, 1093, 1073, 1052, 1019, 913, 894 cm^{-1}. ^1H NMR (800 MHz): δ 1.07 (3H, s, Me-19), 1.09 (9H, s, *t*-Bu), 1.32 (3H, s, Me-17), 1.43 (1H, dd, *J*=8.6, 16.0, H-9α), 1.50 (3H, s, Me-16), 1.54 (1H, dddd, *J*=4.5, 11.5, 13.0, 14.1, H-6β), 1.80 (1H, dtd, *J*=2.5, 4.4, 13.0, H-6α), 1.87 (1H, d, *J*=16.0, H-9β), 2.02 (3H, d, *J*=1.5, Me-18), 2.21 (1H, bd, *J*= 14.1, H-5β), 2.37 (1H, bdt, *J*=4.5, 14.1, H-5α), 3.20 (1H, dd, *J*=4.4, 11.5, H-7), 3.47 (3H, s, O*Me*), 3.47 (1H, d, *J*=12.6, H-3), 3.92 (1H, s, OH), 4.14 (1H, d, *J*=8.1, H-10), 4.66 (1H, d, *J*=6.6, OCH_2O), 4.70 (1H, t, *J*=1.5, H-20), 4.75 (1H, d, *J*=6.6, OCH_2O), 4.79 (1H, t, *J*= 2.0, H-20), 5.95 (1H, d, *J*=12.6, H-2), 6.10 (1H, q, *J*=1.5, H-13). ^{13}C NMR (200 MHz): δ 17.1 (Me-19), 20.5 (Me-18), 22.9 (Me-16), 26.7 (Me-17), 29.1 (3C, *t*-Bu), 29.3 (C-5), 31.2 (C-6), 42.1 (C-9), 44.4 (Cq-15), 47.1 (Cq-8), 50.6 (C-3), 56.2 (O*Me*), 73.1 (C-7), 73.3 (Cq, *t*-Bu), 77.7 (C-10), 83.2 (C-11), 94.6 (OCH_2O), 112.1 (C-20), 129.9 (C-13), 132.8 (C-2), 145.0 (C-4), 147.3 (C-1), 160.9 (C-12), 194.9 (C-14). CIMS: 433 ($[MH]^+$, 7), 253 (4), 211 (5), 146 (9), 113 (11), 77 (7), 73 (100). HRCIMS: calcd for $C_{26}H_{41}O_5$ *m/z*: 433.6137; found: 433.6139.

Trienone **9** (424 mg, 0.98 mmol) was dissolved in dry methylene chloride (20 mL). SeO_2 (109 mg, 0.98 mmol) and 70% *t*-BuOOH (0.49 mL, 5.1 mmol) were added at room temperature under argon. After 8 h stirring, dilution with methylene chloride, usual work-up and chromatography (eluent: heptane:EtOAc, 4:1 to 1:2) afforded 100 mg of starting material (24%), 241 mg (55%) of the expected compound **10**, 27 mg (6%) of **11a** and 22 mg (10%) of **32**.

Compound **10**: $[\alpha]_D$ –6 (*c* 1.35). IR (film): 3450, 2973, 2926, 1733, 1671, 1665, 1656, 1625, 1459, 1390, 1376, 1364, 1247, 1192, 1148, 1091, 1067, 1048, 1021, 920 cm^{-1}. ^1H NMR (800 MHz): δ 1.03 (3H, s, Me-19), 1.12 (9H, s, *t*-Bu), 1.32 (3H, s, Me-17), 1.52 (3H, s, Me-16), 1.55 (1H, dd, *J*=8.0, 15.9, H-9α), 1.75 (1H, ddd, *J*=2.8, 11.5, 14.2, H-6β), 1.88 (1H, d, *J*=15.9, H-9β), 2.03 (3H, d, *J*=1.4, Me-18), 2.07 (1H, ddd, *J*=2.8, 4.1, 14.2, H-6α), 3.48 (3H, s, O*Me*), 3.56 (1H, d, *J*=12.3, H-3), 3.70 (1H, dd, *J*=4.1, 11.5, H-7), 3.91 (1H, s, OH), 4.15 (1H, d, *J*=8.0, H-10), 4.43 (1H, t, *J*=2.8, H-5), 4.67 (1H, d, *J*=6.7, OCH_2O), 4.76 (1H, d, *J*=6.7, OCH_2O), 4.91 (1H, t, *J*=1.8, H-20a), 5.06 (1H, t, *J*=1.8, H-20b), 6.10 (1H, q, *J*=1.4, H-13), 6.45 (1H, d, *J*=12.3, H-2). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-19}: H-3, H-10, H-6β; {H-3}: H-10, Me-16, Me-19, H-20a; {H-6βax}: H-5βeq, Me-19. ^{13}C NMR (200 MHz): δ 16.3 (Me-19), 20.5 (Me-18), 22.8 (Me-16), 26.0 (Me-17), 28.7 (3C, *t*-Bu), 36.1 (C-6), 40.2 (C-9), 44.0 (Cq-15), 46.0 (Cq-8), 49.0 (C-3), 56.5 (O*Me*), 67.1 (C-7), 73.1 (C-5), 73.2 (Cq, *t*-Bu), 77.2 (C-10), 83.0 (C-11), 94.7 (OCH_2O), 116.9 (C-20), 129.8 (C-13), 135.9 (C-2), 146.0 (C-4), 147.0 (C-1), 160.8 (C-12), 194.9 (C-14). CIMS: 449 ($[MH]^+$, 100), 431 (33), 417 (12), 391 (16). HRCIMS: calcd for $C_{26}H_{41}O_6$ *m/z*: 449.2903; found: 449.2908.

Using a similar procedure to that described above, reaction of a solution of **10** (193 mg, 0.43 mmol) in 10 mL of methanol, chilled at 0°C, with 30% H_2O_2 (0.28 mL, 2.7 mmol) and 6N NaOH (0.04 mL, 0.23 mmol), was carried out. After 4 h at room temperature, removal of the solvent without heating, dilution with EtOAc, washing with 5% $NaHSO_3$ and the usual work-up, the residue was chromatographed (silica gel heptane:EtOAc, 2:1 to 1:1) to afford 185 mg (93%) of epoxide **11a**: mp 191–193°C (heptane–ether). $[\alpha]_D$ −69 (*c* 1.11). IR (film): 3469, 2974, 1691, 1616, 1460, 1390, 1364, 1225, 1193, 1150, 1069, 1047, 1021, 915, 886, 872 cm^{-1}. ^1H NMR (300 MHz): δ 0.98 (3H, s, Me-19), 1.13 (9H, s, *t*-Bu), 1.24 (3H, s, Me-16), 1.29 (3H, s, Me-17), 1.72 (1H, ddd, *J*=2.8, 11.3, 14.3, H-6β), 1.80 (1H, dd, *J*=6.4, 16.5, H-9α), 1.89 (1H, bs, OH), 2.05 (1H, d, *J*=16.5, H-9β), 2.07 (1H, ddd, *J*=2.8, 4.4, 14.6, H-6α), 2.09 (3H, d, *J*=1.4, Me-18), 2.46 (1H, d, *J*=11.6, H-3), 3.30 (1H, d, *J*=11.6, H-2), 3.46 (3H, s, O*Me*), 3.76 (1H, dd, *J*=4.4,

11.3, H-7), 4.10 (1H, bs, OH), 4.15 (1H, d, *J*=6.4, H-10), 4.41 (1H, t, *J*=2.8, H-5), 4.68 (1H, d, *J*=6.7, O*CH*$_2$O), 4.79 (1H, d, *J*=6.7, O*CH*$_2$O), 4.91 (1H, d, *J*=1.6, H-20a), 5.10 (1H, d, *J*=1.6, H-20b), 6.18 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: H-10, H-3; {Me-17}: H-13; {Me-19}: H-3, H-10, H-6β; {H-2}: H-7; {H-3}: H-10, Me-16, Me-19, H-20a; {H-5}: H-20b. ^{13}C NMR (75 MHz): δ 17.0, 19.9, 20.8, 25.7, 29.0 (3C), 36.7, 40.5, 41.6, 42.9, 49.2, 56.2, 66.9, 68.1, 69.3, 73.2, 73.8, 76.1, 81.4, 94.4, 118.0, 128.0, 145.0, 162.8, 196.0. CIMS: 465 ([MH]$^+$, 14), 447 (64), 429 (38), 385 (51), 359 (48), 341 (35), 329 (99), 311 (100), 271 (23), 177 (14). HRCIMS: calcd for $C_{26}H_{41}O_7$ *m/z*: 465.2852; found: 465.2857.

Acetic anhydride (4 mL, excess) was added to a stirring mixture of **11a** (182 mg, 0.39 mmol) and DMAP (catalytic) in dry pyridine (10 mL) under argon at 0°C. The reaction mixture was stirred for 1 h 40 min at 0°C (TLC monitoring), diluted with dichloromethane, washed with saturated sodium bicarbonate then 1N hydrochloric acid and worked up as usual to give, after silica gel flash column chromatography (eluent: heptane:EtOAc, 2:1), 182.8 mg (92%) of the corresponding acetate. Compound **11b**: $[\alpha]_D$ −71 (*c* 1.35). IR (film): 3502, 2973, 2928, 1740, 1691, 1617, 1458, 1390, 1373, 1330, 1237, 1192, 1149, 1093, 1074, 1022, 975, 915, 890 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.01 (3H, s, Me), 1.11 (9H, s, *t*-Bu), 1.23 (3H, s, Me), 1.30 (3H, s, Me), 1.80 (1H, dd, *J*=6.5, 15.7, H-9α), 1.81 (1H, ddd, *J*=3.2, 11.6, 14.8, H-6β), 2.03 (1H, ddd, *J*=2.7, 4.2, 14.8, H-6α), 2.04 (3H, s, *Me*CO), 2.06 (1H, d, *J*=15.7, H-9β), 2.11 (3H, d, *J*=1.4, Me-18), 2.47 (1H, d, *J*=11.6, H-3), 3.04 (1H, d, *J*=11.6, H-2), 3.47 (3H, s, O*Me*), 3.61 (1H, dd, *J*=4.2, 11.6, H-7), 4.09 (1H, s, OH), 4.15 (1H, d, *J*=6.5, H-10), 4.69 (1H, d, *J*=6.9, O*CH*$_2$O), 4.79 (1H, d, *J*=6.9, O*CH*$_2$O), 5.06 (1H, d, *J*=2.2, H-20), 5.30 (1H, d, *J*=2.2, H-20), 5.50 (1H, dd, *J*=2.7, 3.2, H-5), 6.20 (1H, q, *J*=1.4, H-13). ^{13}C NMR (75 MHz): δ 17.0, 19.8, 20.8, 21.5, 25.6, 29.0 (3C), 35.2, 40.6, 41.4, 42.9, 49.2, 56.2, 66.4, 68.6, 68.7, 73.9, 74.3, 76.1, 81.4, 94.5, 121.5, 128.0, 139.5, 163.0, 169.8, 196.1. CIMS: 507 ([MH]$^+$, 12), 447 (47), 429 (36), 415 (12), 385 (39), 359 (51), 341 (38), 329 (71), 311 (100), 293 (15), 271 (12). HRCIMS: calcd for $C_{26}H_{41}O_7$ *m/z*: 507.2958; found: 507.2950.

*5.4. Further elaboration of **11a**; preparation of oxetane precursors **12**, **13** and derivatives*

To a magnetically stirred solution of **11a** (162 mg, 0.35 mmol) in *t*-BuOH:H_2O, 3:1 (2.8 mL), in the presence of pyridine (0.03 mL, 0.39 mmol), *N*-methylmorpholine *N*-oxide (41 mg, 0.35 mmol) and then a *t*-BuOH solution of OsO_4 (3.5 mL, 0.35 mmol) were added at room temperature under argon atmosphere. The mixture was stirred at room temperature for 5.5 h and treated with a 20% aqueous solution of $NaHSO_3$. After stirring for 2 h, the products were extracted twice with EtOAc, the combined organic layers were worked up as usual to give a crude residue which was chromatographed (eluent heptane:EtOAc, 1:1 to 1:2, EtOAc and, finally, EtOAc:MeOH, 9:1) to afford 36 mg (22%) of unreacted starting material, 78.3 mg (45%) of faster eluting major isomer 4β-OH **12** and 55.6 mg (32%) of slower eluting minor isomer 4α-OH **13**.

Compound **12**: $[\alpha]_D$ −70 (*c* 2.30). IR (film): 3555, 3477, 2982, 2877, 1722, 1678, 1609, 1466, 1389, 1391, 1362, 1255, 1190, 1150, 1074, 1053, 1021, 917 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.11 (9H, s, *t*-Bu), 1.18 (3H, s, Me), 1.22 (3H, s, Me), 1.35 (3H, s, Me), 1.69 (1H, dd, *J*=7.3, 16.4, H-9α), 1.86 (1H, td, *J*=3.7, 13.9, H-6α), 2.01 (1H, d, *J*=11.9, H-3), 2.02 (1H, d, *J*=16.4, H-9β), 2.11 (3H, d, *J*=1.3, Me-18), 2.19 (1H, ddd, *J*=2.4, 11.7, 13.9, H-6β), 3.17 (1H, bs, OH), 3.20 (1H, d, *J*=11.9, H-2), 3.45 (3H, s, O*Me*), 3.54 (1H, bs, OH), 3.64 (1H, dd, *J*=3.7, 11.7, H-7), 3.74 (1H, d, *J*=11.6, H-20), 3.90 (1H, m, H-5), 3.95 (1H, d, *J*=11.6, H-20), 4.14 (1H, d, *J*=7.3, H-10), 4.16 (1H, s, OH), 4.69 (1H, d, *J*=6.4, O*CH*$_2$O), 4.75 (1H, d, *J*=6.4, O*CH*$_2$O), 6.17 (1H, q, *J*=1.3, H-13). ^{13}C NMR (75 MHz): δ 19.8, 20.1, 21.3, 25.1, 29.1 (3C), 33.3, 41.4, 42.7, 43.2, 47.4, 56.2, 66.0, 66.3, 68.5, 69.3, 71.4, 73.7, 74.7, 78.5, 81.0, 95.4, 127.5, 165.1, 197.1. CIMS: 499 ([MH]$^+$, 66), 481 (24), 419 (26), 393 (30), 363 (100), 345 (70), 327 (45), 305

(23), 287 (17), 211 (32), 193 (24), 177 (17), 151 (19). HRCIMS: calcd for $C_{26}H_{43}O_9$ *m/z*: 499.2907; found: 499.2901.

Compound **13**: $[\alpha]_D$ −61 (*c* 1.17). IR (film): 3460, 2978, 1733, 1682, 1616, 1464, 1391, 1267, 1193, 1148, 1059, 1021, 918, 871 cm^{-1}. ^1H NMR (300 MHz): δ 1.12 (9H, s), 1.17 (3H, s), 1.20 (3H, s), 1.23 (3H, s), 1.76 (1H, m), 1.77 (1H, dd, *J*=6.4, 16.6), 2.07 (1H, m), 2.05 (1H, d, *J*=16.6), 2.12 (3H, d, *J*=1.4), 2.33 (1H, d, *J*=11.6), 3.10 (1H, bs, OH), 3.30 (1H, d, *J*=11.6), 3.46 (3H, s), 3.50 (1H, bs), 3.55–3.67 (2H, m), 3.69 (1H, dd, *J*=4.4, 11.2), 3.90–3.92 (2H, m), 4.12 (1H, d, *J*=6.4), 4.13 (1H, s, OH), 4.72 (1H, d, *J*=6.6), 4.75 (1H, d, *J*=6.6), 6.20 (1H, q, *J*=1.4). ^{13}C NMR (75 MHz): δ 20.0, 20.2, 21.4, 25.0, 29.0 (3C), 34.1, 41.0, 42.9, 43.1, 45.1, 56.3, 67.0, 67.1, 68.3, 68.5, 70.8, 73.9, 75.8, 79.3, 80.9, 95.8, 127.7, 164.3, 196.4. CIMS: 499 ($[MH]^+$, 38), 481 (47), 463 (22), 437 (32), 423 (100), 401 (21), 381 (21), 363 (68), 345 (75), 327 (67), 309 (34), 211 (20), 193 (37), 175 (23), 151 (21), 137 (15). HRCIMS: calcd for $C_{26}H_{43}O_9$ *m/z*: 499.2907; found: 499.2917.

TBDMS monoprotection at C-20 of the major isomer **12**: To a magnetically stirred solution of **12** (72 mg, 0.144 mmol) in dry DMF (2 mL) chilled at 0°C and under argon, imidazol (81 mg, 1.19 mmol) and 10 min later *tert*-butyldimethylsilyl chloride (79 mg, 0.52 mmol) were added and the reaction mixture was allowed to warm to room temperature. After 2.5 h, quenching with a saturated NH_4Cl solution, extraction with EtOAc and the usual work-up furnished upon chromatography (heptane:EtOAc, 4:1) 76.2 mg, 86% of the monoTBS protected compound **12**-C-20-OTBS: $[\alpha]_D$ −52 (*c* 1.34). IR (film): 3522, 2956, 2858, 1686, 1617, 1472, 1390, 1363, 1266, 1192, 1148, 1068, 1022, 915, 869, 838, 781, 740 cm^{-1}. ^1H NMR (300 MHz): δ 0.11 (3H, s, *Me*-TBS), 0.12 (3H, s, *Me*-TBS), 0.90 (9H, s, *t-Bu*-TBS), 1.14 (9H, s, *t*-Bu), 1.20 (3H, s, Me-16), 1.26 (3H, s, Me-17), 1.37 (3H, s, Me-19), 1.56 (1H, d, *J*=3.9, OH), 1.77 (1H, dd, *J*=6.8, 15.9, H-9α), 1.84 (1H, td, *J*=3.9, 14.2, H-6αeq), 2.01 (1H, d, *J*=15.9, H-9β), 2.02 (1H, d, *J*=12.1, H-3), 2.11 (3H, d, *J*=1.3, Me-18), 2.27 (1H, ddd, *J*=2.4, 11.7, 14.2, H-6βax), 3.04 (1H, s, OH), 3.16 (1H, d, *J*=12.1, H-2), 3.47 (3H, s, O*Me*), 3.53 (1H, d, *J*=10.3, H-20), 3.66 (1H, dd, *J*=3.9, 11.7, H-7), 3.92 (1H, m, H-5), 4.13 (1H, s, OH), 4.15 (1H, d, *J*=10.3, H-20), 4.17 (1H, d, *J*=6.8, H-10), 4.70 (1H, d, *J*=6.4, O*CH*$_2$O), 4.77 (1H, d, *J*=6.4, O*CH*$_2$O), 6.18 (1H, q, *J*=1.4, H-13). ^{13}C NMR (62.9 MHz): δ −5.4 (2*Me*-TBS), 18.1 (Cq), 19.9 (Me-16), 20.0 (Me-19), 21.2 (Me-18), 25.2 (Me-17), 25.8 (*t-Bu*-TBS), 29.0 (*t*-Bu), 33.7 (C-6), 41.6 (Cq), 42.7 (C-9), 43.1 (Cq), 47.3 (C-3), 56.2 (O*Me*), 65.1 (C-2), 65.3 (C-20), 67.5 (Cq), 69.1 (C-7), 71.4 (C-5), 73.7 (Cq), 74.2 (Cq), 78.5 (C-10), 81.0 (Cq), 95.3 (O*CH*$_2$O), 127.8 (C-13), 163.8 (C-12), 196.6 (C-14).

TBDMS monoprotection at C-20 of the minor isomer **13**: A solution of **13** (72 mg, 0.144 mmol), imidazole (81 mg, 1.19 mmol) and *tert*-butyldimethylsilyl chloride (22 mg, 0.15 mmol), in dry DMF (2.0 mL), was stirred under argon at 0°C to room temperature for 2.5 h. After washing with a saturated solution of NH_4Cl, extraction with ethyl acetate and the usual work-up the resulting crude was purified by chromatography (heptane:EtOAc, 4:1) to give 76.2 mg (86%) of **14a** along with recovered starting material. Compound **14a**: $[\alpha]_D$ −50 (*c* 0.84). IR (film): 3436, 2929, 1682, 1620, 1470, 1362, 1249, 1194, 1072, 1024, 916, 839, 780, 734 cm^{-1}. ^1H NMR (300 MHz): δ 0.08 (6H, s, *Me*–TBS), 0.90 (9H, s, *t-Bu*–TBS), 1.14 (9H, s, *t*-Bu), 1.16 (3H, s, Me), 1.21 (3H, s, Me), 1.27 (3H, s, Me), 1.70 (1H, tdd, *J*=2.8, 12.0, 14.3, H-6β), 1.81 (1H, dd, *J*=7.0, 16.0, H-9α), 2.04 (1H, d, *J*=16.0, H-9β), 2.12 (3H, d, *J*=1.6, Me-18), 2.14 (1H, td, *J*=4.2, 14.3, H-6α), 2.51 (1H, d, *J*=11.8, H-3), 3.06 (1H, bs, OH), 3.22 (1H, s, OH), 3.26 (1H, d, *J*=11.8, H-2), 3.48 (3H, s, O*Me*), 3.49 (1H, d, *J*=9.8, H-20), 3.67–3.72 (2H, m, H-5, H-7), 3.69 (1H, d, *J*=9.8, H-20), 4.09 (1H, s, OH), 4.13 (1H, d, *J*=7.0, H-10), 4.73 (1H, d, *J*=6.7, O*CH*$_2$O), 4.77 (1H, d, *J*=6.7, O*CH*$_2$O), 6.22 (1H, q, *J*=1.6, H-13). ^{13}C NMR (75 MHz): δ −5.4 (2C), 18.3, 19.6, 20.3, 21.3, 25.1, 25.9 (3C), 29.1 (3C), 33.8, 41.0, 42.8, 43.1, 43.8, 56.3, 66.9, 67.1, 68.6, 69.1, 71.1, 74.0, 75.5, 79.1, 81.0, 95.7, 128.0, 163.3, 196.1. ESIMS (MeOH): 635 ($[MNa]^+$, 100).

TBS-protection at both primary (C-20) and secondary (C-5) hydroxyl groups: Proceeding as above, **13** (38 mg, 0.076 mmol) was dissolved in 1.0 mL of dry DMF; imidazol (83 mg, 1.22 mmol) and TBSCl (64 mg, 0.42 mmol) were added at 0°C and the reaction mixture was stirred at room temperatue for 4 h. After the usual work-up, the crude was chromatographed (heptane:EtOAc, 8:1 to 1:1) to afford 36 mg (65%) of bis-TBS protected **14b** and 9 mg (18%) of monoTBS protected **14a**. Compound **14b**: $[\alpha]_D$ −34 (*c* 1.80). IR (film): 3600, 3535, 2954, 2858, 1693, 1620, 1472, 1389, 1362, 1255, 1193, 1149, 1072, 1022, 911, 835, 778, 734, 673 cm^{-1}. ^1H NMR (300 MHz): δ 0.05 (3H, s, *Me*-TBS), 0.06 (3H, s, *Me*-TBS), 0.07 (3H, s, *Me*-TBS), 0.13 (3H, s, *Me*-TBS), 0.88 (9H, s, *t-Bu*-TBS), 0.90 (9H, s, *t-Bu*-TBS), 1.10 (9H, s, *t*-Bu), 1.13 (3H, s, Me-19), 1.17 (3H, s, Me-16), 1.25 (3H, s, Me-17), 1.76 (1H, dd, *J*=6.8, 16.3, H-9α), 1.81 (1H, ddd, *J*=4.4, 10.2, 14.2, H-6β), 1.93 (1H, ddd, *J*=4.4, 5.5, 14.2, H-6α), 2.00 (1H, d, *J*=16.3, H-9β), 2.10 (3H, d, *J*=1.4, Me-18), 2.38 (1H, d, *J*=11.6, H-3), 2.78 (1H, s, OH), 3.24 (1H, d, *J*=11.6, H-2), 3.46 (3H, s, O*Me*), 3.49 (1H, d, *J*=9.8, H-20), 3.56 (1H, d, *J*=9.8, H-20), 3.69 (1H, dd, *J*=5.5, 10.2, H-7), 3.87 (1H, t, *J*=4.4, H-5), 4.02 (1H, s, OH), 4.12 (1H, d, *J*=6.8, H-10), 4.71 (1H, d, *J*=6.6, O*CH*$_2$O), 4.75 (1H, d, *J*=6.6, O*CH*$_2$O), 6.18 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-17}: Me-16 (NOE gem), H-13; {Me-19}: H-3, H-10, H-6β, H-9β, H-20; {H-3}: H-10, Me-16, Me-19, H-20; {H-2}: H-7, H-9α. ^{13}C NMR (62.9 MHz): δ −5.5 (2C), −4.8 (2C), 18.0, 18.1, 20.0 (2C), 21.3, 24.9, 25.8 (6C), 29.0 (3C), 37.0, 40.9, 42.0, 43.0, 43.7, 56.2, 66.3, 66.5, 67.1, 69.2, 70.9, 73.7, 75.3, 79.4, 80.9, 95.5, 128.0, 162.8, 196.2. ESIMS (MeOH): 749 ($[MNa]^+$, 100), 727 ($[MH]^+$, 3).

Mesylation at C-5: To an ice cooled, magnetically stirred solution of the secondary alcohol **14a** (6.0 mg, 0.01 mmol) in dry pyridine (0.5 mL), a few crystals of DMAP were added. The mixture was stirred for 5–10 min at 0°C under argon, MsCl (0.05 mL, 0.65 mmol) was added and the reaction mixture was stirred at 0°C for 1 h. Addition of a saturated sodium bicarbonate solution followed and stirring continued for 15 min at 0°C. Extraction with methylene chloride, washing with 1N HCl, $NaHCO_3$ and the usual work-up furnished, after chromatography (heptane:EtOAc, 2:1 to 1:1), 5.7 mg (84%) of the desired mesylate **15**: $[\alpha]_D$ −33 (*c* 0.57). IR (film): 3501, 2931, 2858, 1688, 1619, 1471, 1391, 1360, 1259, 1176, 1078, 1022, 969, 914, 839 cm^{-1}. ^1H NMR (600 MHz): δ 0.09 (3H, s, *Me*-TBS), 0.10 (3H, s, *Me*-TBS), 0.91 (9H, s, Si-*t*-Bu), 1.14 (9H, s, O-*t*-Bu), 1.17 (3H, s, Me-19), 1.19 (3H, s, Me), 1.27 (3H, s, Me), 1.79 (1H, dd, *J*=6.9, 16.2, H-9α), 1.93 (1H, ddd, *J*=3.5, 11.0, 15.0, H-6β), 2.07 (1H, d, *J*=16.2, H-9β), 2.13 (3H, d, *J*=1.3, Me-18), 2.27 (1H, td, *J*=4.6, 15.0, H-6α), 2.44 (1H, d, *J*=11.6, H-3), 3.04 (1H, bs, OH), 3.05 (1H, d, *J*=11.6, H-2), 3.20 (3H, s, O*Ms*), 3.48 (3H, s, O*Me*), 3.60 (1H, d, *J*=9.8, H-20), 3.63 (1H, d, *J*=9.8, H-20), 3.64 (1H, dd, *J*=4.6, 11.0, H-7), 4.05 (1H, s, OH), 4.13 (1H, d, *J*=6.9, H-10), 4.74 (1H, d, *J*=6.7, O*CH*$_2$O), 4.77 (1H, d, *J*=6.7, O*CH*$_2$O), 4.92 (1H, t, *J*=3.5, H-5), 6.23 (1H, q, *J*=1.3, H-13). ^{13}C NMR (150 MHz): δ −5.4 (2C, *Me*-TBS), 18.2 (Cq, TBS), 20.1 (Me), 20.3 (Me-19), 21.4 (Me-18), 25.0 (Me), 25.8 (3C, Si-*t*-Bu), 29.0 (3C, O-*t*-Bu), 34.5 (C-6), 38.9 (O*Ms*), 41.1 (Cq-8), 42.3 (C-9), 43.0 (Cq-15), 44.9 (C-3), 56.4 (O*Me*), 66.3 (C-2), 66.5 (C-1), 68.0 (C-20), 68.8 (C-7), 74.5 (Cq, *t*-Bu), 74.7 (C-4), 79.4 (C-10), 80.9 (C-11), 81.7 (C-5), 95.8 (O*CH*$_2$O), 128.1 (C-13), 163.4 (C-12), 195.8 (C-14). CIMS: 691 ($[MH]^+$, 1), 595 (16), 579 (2), 537 (12), 481 (26), 401 (30), 193 (32), 173 (40), 153 (100), 75 (92).

Proceeding as for **5**, to a magnetically stirred solution of **11a** (45 mg, 0.097 mmol) in 4.0 mL of dry benzene was added $VO(acac)_2$ (0.4 mg, 0.0015 mmol) and the reaction mixture was heated at reflux for 15 min, whereupon 5–6 M *t*-BuOOH/decane (0.02 mL, 0.107 mmol) was added and stirring at reflux continued for 1 h 50 min. Cooling to room temperature, dilution with EtOAc, washing with a saturated $NaHCO_3$ solution and work-up as usual afforded after chromatography (heptane:EtOAc, 1:1 to 1:2) 24.1 mg (52%) of bisepoxide **16a** and 18 mg (40%) of starting material. Compound **16a**: $[\alpha]_D$ −66 (*c* 1.10). IR (film): 3469, 2975, 2927, 1686, 1615, 1466, 1447, 1422, 1391, 1364, 1224, 1192, 1149, 1066, 1020,

941, 914, 875, 810 cm^{-1}. ^1H NMR (300 MHz): δ 1.12 (3H, s, Me-16), 1.14 (9H, s, *t*-Bu), 1.16 (3H, s, Me-19), 1.27 (3H, s, Me-17), 1.58 (1H, dd, *J*=1.2, 11.5, H−3), 1.83 (1H, dd, *J*=6.9, 16.1, H-9α), 1.88 (1H, ddd, *J*=3.2, 11.4, 14.4, H-6β), 2.03 (1H, d, *J*=16.1, H-9β), 2.09 (3H, d, *J*=1.4, Me-18), 2.16 (1H, ddd, *J*=3.2, 4.3, 14.4, H-6α), 2.65 (1H, d, *J*=4.8, H-20a), 2.79 (1H, d, *J*=4.8, H-20b), 3.47 (3H, s, O*Me*), 3.52 (1H, bt, *J*=3.2, H-5), 3.54 (1H, d, *J*=11.5, H-2), 3.75 (1H, dd, *J*=4.3, 11.4, H-7), 4.04 (1H, s, OH), 4.11 (1H, d, *J*=6.9, H-10), 4.69 (1H, d, *J*=6.8, O*CH*$_2$O), 4.79 (1H, d, *J*=6.8, O*CH*$_2$O), 6.21 (1H, q, *J*=1.4, H-13). ^{13}C NMR (75 MHz): δ 17.5, 19.8, 20.8, 25.5, 29.0 (3C), 35.6, 41.0, 42.6, 42.8, 47.0, 55.5, 56.2, 59.5, 65.4, 66.5, 67.9, 73.5, 74.0, 76.0, 81.2, 94.5, 128.1, 162.7, 196.2. CIMS: 481 ($[MH]^+$, 15), 407 (8), 363 (21), 345 (100), 327 (46), 309 (13), 287 (18), 211 (52), 193 (26), 151 (37). HRCIMS: calcd for $C_{26}H_{41}O_8$ *m/z*: 481.2801; found: 481.2806.

Using the standard protocol **16a** (13.8 mg, 0.029 mmol) was dissolved in dry pyridine (1 mL), DMAP (catalytic) was added and the solution was chilled at 0°C. Ac_2O (0.4 mL) was added and the reaction mixture was stirred at this temperature for 2 h. Extraction with methylene chloride, washing with 1N HCl solution and a saturated sodium bicarbonate followed by usual work-up and chromatography (heptane:EtOAc, 1:1 to 1:2) afforded 14.4 mg (92%) of the C-5α-acetylated compound. Compound **16b**: $[\alpha]_D$ −38 (*c* 1.28). IR (film): 3468, 2974, 1739, 1688, 1442, 1372, 1237, 1190, 1148, 1075, 1037, 1023, 910, 884 cm^{-1}. ^1H NMR (300 MHz): δ 1.10 (9H, s, *t*-Bu), 1.11 (3H, s, Me), 1.18 (3H, s, Me), 1.28 (3H, s, Me), 1.57 (1H, dd, *J*=1.3, 11.5, H-3), 1.82 (1H, dd, *J*=6.3, 16.3, H-9α), 1.94 (1H, ddd, *J*=3.2, 11.7, 15.0, H-6β), 2.02 (1H, d, *J*=16.3, H-9β), 2.13 (1H, ddd, *J*=3.2, 4.4, 15.0, H-6α), 2.10 (3H, d, *J*=1.4, Me-18), 2.12 (3H, s, *Me*CO), 2.61 (1H, d, *J*=5.0, H-20), 2.81 (1H, d, *J*=5.0, H-20), 3.31 (1H, d, *J*=11.5, H-2), 3.45 (3H, s, O*Me*), 3.56 (1H, dd, *J*=4.4, 11.7, H-7), 4.01 (1H, s, OH), 4.10 (1H, d, *J*=6.3, H-10), 4.69 (1H, dt, *J*=1.3, 3.2, H-5), 4.70 (1H, d, *J*=6.8, O*CH*$_2$O), 4.78 (1H, d, *J*=6.8, O*CH*$_2$O), 6.22 (1H, q, *J*=1.4, H-13). ^{13}C NMR (75 MHz): δ 17.5, 19.7, 20.8, 21.2, 25.5, 28.9 (3C), 34.3, 41.0, 42.6, 42.8, 47.2, 54.7, 56.2, 56.6, 65.2, 66.1, 68.4, 74.1, 75.2, 76.1, 81.2, 94.5, 128.1, 162.9, 169.8, 196.3. CIMS: 523 ($[MH]^+$, 100), 463 (8), 387 (16), 357 (16), 345 (40), 327 (52), 309 (20), 211 (10), 193 (20), 165 (24), 121 (14), 95 (20). HRCIMS: calcd for $C_{28}H_{43}O_9$ *m/z*: 523.2907; found: 523.2910.

Selective tosylation at C-20: The alcohol **12** (36.0 mg, 0.072 mmol) was dissolved in 1.5 mL of dry pyridine, DMAP (cat.) and *p*-toluenesulfonyl chloride (62 mg, 0.33 mmol) were added and the mixture was stirred from 0°C to room temperature for 30 h (TLC monitoring; excess of TsCl was added several times). The mixture was cooled to 0°C, diluted with methylene chloride, quenched with a saturated aqueous solution of sodium bicarbonate and worked up as usual. Chromatography (heptane:EtOAc, 1:1 to EtOAc) afforded 37.9 mg (81%) of the required tosylate **17** and 6.4 mg (18%) of recovered starting material. Compound **17**: mp 124–126°C (heptane–ether). $[\alpha]_D$ −64 (*c* 1.43). IR (film): 3502, 2975, 1682, 1616, 1462, 1361, 1176, 1058, 1021, 977, 913, 869, 839, 814, 736 cm^{-1}. ^1H NMR (300 MHz): δ 1.11 (3H, s, Me), 1.12 (9H, s, *t*-Bu), 1.20 (3H, s, Me), 1.33 (3H, s, Me), 1.73 (1H, dd, *J*=7.0, 16.3, H-9α), 1.90 (1H, td, *J*=3.7, 14.1, H-6α), 2.00 (1H, d, *J*=16.3, H-9β), 2.01 (1H, d, *J*=11.9, H-3), 2.09 (3H, d, *J*=1.3, Me-18), 2.20 (1H, ddd, *J*=2.5, 11.7, 14.1, H-6β), 2.45 (3H, s, *Me*-Ar), 2.86 (1H, d, *J*=4.8, OH), 3.17 (1H, d, *J*=11.9, H-2), 3.45 (3H, s, O*Me*), 3.65 (1H, dd, *J*=3.7, 11.7, H-7), 3.97 (1H, d, *J*=10.7, H-20), 3.98 (1H, m, H-5), 4.11 (1H, s, OH), 4.12 (1H, d, *J*=7.0, H-10), 4.69 (1H, d, *J*=6.5, O*CH*$_2$O), 4.75 (1H, d, *J*=6.5, O*CH*$_2$O), 4.76 (1H, d, *J*=10.7, H-20), 6.17 (1H, q, *J*=1.3, H-13), 7.36 (2H, d, *J*=8.3, *Ar*), 7.82 (2H, d, *J*=8.3, *Ar*). ^{13}C NMR (75 MHz): δ 19.8, 20.2, 21.2, 21.6, 25.2, 29.0 (3C), 33.0, 41.5, 42.7, 43.1, 47.3, 56.2, 64.6, 67.9, 68.8, 70.8, 73.9, 74.0, 74.5, 78.6, 80.9, 95.4, 127.7, 127.8 (2C), 130.0 (2C), 132.6, 145.2, 163.9, 196.1. ESIMS (MeOH): 675 ($[MNa]^+$, 100).

Tosylate displacement and Payne rearrangement: To a flask containing tosylate **17** (28 mg, 0.043 mmol) and K_2CO_3 (45 mg, 0.32 mmol), vacuumed and flashed with argon several times, cooled at

−45°C, anhydrous MeOH (1 mL) was added and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was then cooled to −70°C, diluted with ether and washed with water (twice) and brine until pH 7. Chromatography (heptane:EtOAc, 1.5:1 to 1:1.5) afforded 20.1 mg (98%) of bisepoxide **18a:** mp decomposition at 228–230°C (heptane–THF). $[\alpha]_D$ −73 (*c* 0.99). IR (film): 3509, 2968, 1686, 1615, 1466, 1441, 1391, 1362, 1266, 1225, 1189, 1149, 1117, 1068, cm^{-1}. ^1H NMR (600 MHz): δ 1.09 (3H, s, Me-16), 1.13 (9H, s, *t*-Bu), 1.20 (3H, s, Me-19), 1.25 (3H, s, Me-17), 1.46 (1H, dd, *J*=1.3, 12.0, H-3), 1.74 (1H, dd, *J*=7.3, 16.2, H-9α), 2.02–2.07 (3H, m, 2H-6, H-9β), 2.08 (3H, d, *J*=1.4, Me-18), 2.67 (1H, d, *J*=4.5, H-20b), 2.75 (1H, d, *J*=4.5, H-20a), 3.34 (1H, d, *J*=12.0, H-2), 3.41 (1H, bs, H-5), 3.44 (3H, s, O*Me*), 3.73 (1H, dd, *J*=5.3, 10.5, H-7), 4.09 (1H, s, OH), 4.10 (1H, d, *J*=7.3, H-10), 4.67 (1H, d, *J*=6.7, OCH_2O), 4.76 (1H, d, *J*=6.7, OCH_2O), 6.17 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-19}: H-3, H-10, H-6β, H-9β; {H-3}: H-10, Me-16, Me-19, H-20a; {H-6βax}: H-5βeq, Me-19; {H-2}: H-7, H-9α; {H-5βeq}: H-20b. ^{13}C NMR (150 MHz): δ 17.6 (Me-19), 19.8 (Me-16), 20.9 (Me-18), 25.6 (Me-17), 29.1 (3C, *t*-Bu), 34.9 (C-6), 40.9 (C-9), 41.5 (Cq-8), 42.8 (Cq-15), 48.2 (C-3), 49.4 (C-20), 56.4 (O*Me*), 57.2 (Cq-4), 65.0 (C-2), 68.1 (2C, C-7, Cq-1), 73.9 (Cq, *t*-Bu), 74.0 (C-5), 76.5 (C-10), 81.2 (Cq-11), 94.7 (OCH_2O), 127.8 (C-13), 163.4 (C-12), 196.1 (C-14). CIMS: 481 ($[MH]^+$, 48), 463 (16), 419 (20), 393 (19), 375 (30), 363 (61), 345 (100), 327 (50), 211 (89), 197 (40), 165 (34), 151 (40), 95 (22). HRCIMS: calcd for $C_{26}H_{41}O_8$ *m/z*: 481.2801; found: 481.2812.

Compound **18a** (15.5 mg, 0.032 mmol) thus obtained was carefully acetylated at C-5, in 1 mL of pyridine, in the presence of DMAP (cat.) and acetic anhydride (0.12 mL) at 0°C for 30 min (TLC monitoring). Following dilution with dichloromethane and washing with 1N HCl, then a saturated sodium bicarbonate solution, the reaction mixture was worked up as usual. Chromatography (heptane:EtOAc, 2:1) afforded 15.8 mg (94%) of the corresponding acetate. Compound **18b**: $[\alpha]_D$ −58 (*c* 1.35). IR (film): 3523, 2976, 1744, 1691, 1617, 1460, 1374, 1233, 1149, 1076, 1023, 950, 738 cm^{-1}. ^1H NMR (300 MHz): δ 1.11 (3H, s, Me), 1.13 (9H, s, *t*-Bu), 1.25 (3H, s, Me), 1.29 (3H, s, Me), 1.50 (1H, bd, *J*=12.0, H-3), 1.77 (1H, dd, *J*=7.1, 16.4, H-9α), 1.98 (1H, ddd, *J*=3.2, 3.9, 14.8, H-6α), 2.07 (1H, d, *J*=16.4, H-9β), 2.10 (3H, s, *Me*CO), 2.12 (3H, d, *J*=1.4, Me-18), 2.15 (1H, ddd, *J*=3.2, 11.6, 14.8, H-6β), 2.73 (1H, d, *J*=4.6, H-20), 2.83 (1H, d, *J*=4.6, H-20), 3.09 (1H, d, *J*=12.0, H-2), 3.47 (3H, s, O*Me*), 3.60 (1H, dd, *J*=3.9, 11.6, H-7), 4.11 (1H, s, OH), 4.13 (1H, d, *J*=7.1, H-10), 4.62 (1H, bt, *J*=3.2, H-5), 4.71 (1H, d, *J*=6.7, OCH_2O), 4.78 (1H, d, *J*=6.7, OCH_2O), 6.21 (1H, q, *J*=1.4, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-19}: H-3, H-10, H-6β, H-9β; {H-3}: H-10, Me-16, Me-19, H-20a; {H-6βax}: H-5βeq, Me-19; {H-2}: H-7, H-9α; {H-5βeq}: H-20b. ^{13}C NMR (75 MHz): δ 17.5, 19.6, 20.9, 21.2, 25.5, 28.9 (3C), 33.1, 40.9, 41.4, 42.8, 48.0, 49.6, 55.2, 56.2, 64.5, 67.7, 68.5, 74.0, 75.2, 76.5, 81.2, 94.7, 127.8, 163.6, 169.5, 196.0. CIMS: 523 ($[MH]^+$, 48), 491 (12), 461 (18), 435 (24), 404 (66), 387 (36), 327 (75), 317 (15), 287 (15), 253 (100), 197 (66), 177 (33), 151 (39), 133 (21), 95 (27). HRCIMS: calcd for $C_{28}H_{43}O_9$ *m/z*: 523.2907; found: 523.2912.

When tosylate displacement on **17** (6.5 mg, 0.01 mmol) with excess K_2CO_3 in 0.5 mL of dry methanol was performed at room temperature, the Payne rearrangement product **19** (4.4 mg) was obtained in 92% isolated yield after chromatography (heptane:EtOAc, 1.5:1). Compound **19**: $[\alpha]_D$ −90 (*c* 0.44). IR (film): 3495, 2976, 1689, 1616, 1459, 1390, 1364, 1270, 1194, 1149, 1073, 1020, 924, 886, 738 cm^{-1}. ^1H NMR (800 MHz): δ 1.06 (3H, s, Me-19), 1.08 (9H, s, *t*-Bu), 1.21 (3H, s, Me-16), 1.31 (3H, s, Me-17), 1.58 (1H, dd, *J*=7.2, 16.4, H-9α), 1.85 (1H, ddd, *J*=1.9, 10.0, 15.4, H-6β), 1.98 (1H, d, *J*=16.4, H-9β), 2.05 (1H, d, *J*=10.9, H-3), 2.10 (3H, d, *J*=1.3, Me-18), 2.36 (1H, ddd, *J*=1.9, 5.4, 15.4, H-6α), 2.82 (1H, d, *J*=10.9, H-2), 3.31 (1H, dd, *J*=5.4, 10.0, H-7), 3.44 (1H, t, *J*=1.9, H-5), 3.47 (3H, s, O*Me*), 3.59 (1H, bdd, *J*=6.5, 12.1, H-20), 3.77 (1H, d, *J*=12.1, H-20), 4.05 (1H, s, OH), 4.17 (1H, d, *J*=7.2, H-10), 4.67

(1H, d, *J*=6.7, O*CH*$_2$O), 4.76 (1H, d, *J*=6.7, O*CH*$_2$O), 6.18 (1H, q, *J*=1.3, H-13). ^{13}C NMR (200 MHz): δ 17.5 (Me-19), 19.6 (Me-16), 20.9 (Me-18), 25.3 (Me-17), 28.8 (3C, *t*-Bu), 30.7 (C-6), 38.5 (2C, C-9 and Cq-8), 40.5 (C-3), 42.9 (Cq-15), 56.2 (O*Me*), 57.3 (C-5), 59.9 (Cq-4), 63.9 (C-20), 64.0 (C-2), 67.3 (Cq-1), 67.9 (C-7), 73.8 (Cq, *t*-Bu), 76.1 (C-10), 81.1 (Cq-11), 94.2 (O*CH*$_2$O), 127.8 (C-13), 163.0 (C-12), 195.6 (C-14). CIMS: 481 ([MH]$^+$, 6), 463 (18), 431 (13), 401 (42), 389 (16), 375 (50), 363 (37), 345 (100), 327 (80), 309 (23), 299 (12), 211 (12), 120 (4). HRCIMS: calcd for $C_{26}H_{41}O_8$ *m/z*: 481.2801; found: 481.2812.

5.5. Reduction of the carbonyl group at C-14

Cerium chloride heptahydrate (10.9 mg, 0.029 mmol) was added to a solution of **18b** (12.8 mg, 0.023 mmol) in methylene chloride (1 ml) and ethanol (1 ml) at −25 °C. After 5 min, sodium borohydride (3.8 mg, 0.1 mmol) was added, the mixture was stirred for 40 min at −25°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 worked up as usual to afford after chromatography (heptane:EtOAc, 2:1 to 1:1) 12.6 mg (98%) of **20**: $[\alpha]_D$ −3 (*c* 1.21). IR (film): 3493, 2974, 1739, 1462, 1372, 1234, 1190, 1078, 1031, 949, 916, 866, 738, 702, 675 cm^{-1}. ^{1}H NMR (800 MHz): δ 1.02 (3H, s, Me-16), 1.16 (9H, s, *t*-Bu), 1.22 (3H, s, Me-19), 1.41 (3H, s, Me-17), 1.61 (1H, d, *J*=12.4, H-3), 1.74 (1H, dd, *J*=7.2, 16.0, H-9α), 1.88 (3H, d, *J*=1.3, Me-18), 1.95 (1H, d, *J*=16.0, H-9β), 1.99 (1H, td, *J*=3.4, 14.9, H-6α), 2.08 (3H, s, *Me*CO), 2.16 (1H, ddd, *J*=3.3, 11.7, 14.9, H-6β), 2.71 (1H, d, *J*=4.8, H-20), 2.81 (1H, d, *J*=4.8, H-20), 3.19 (1H, d, *J*=12.4, H-2), 3.43 (3H, s, O*Me*), 3.68 (1H, dd, *J*=3.4, 11.7, H-7), 3.72 (1H, d, *J*=3.8, H-14), 3.84 (1H, s, OH), 3.94 (1H, d, *J*=7.2, H-10), 4.63 (1H, bs, H-5), 4.65 (1H, d, *J*=6.9, O*CH*$_2$O), 4.75 (1H, d, *J*=6.9, O*CH*$_2$O), 5.85 (1H, m, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-19}: H-3, H-10, H-6β, H-9β; {H-3}: H-10, Me-16, Me-19, H-20a; {H-6βax}: H-5βeq, Me-19; {H-2}: H-7, H-14, H-9α. ^{13}C NMR (200 MHz): δ 17.4 (Me-19), 19.6 (Me-18), 19.7 (Me-16), 21.3 (*Me*CO), 27.1 (Me-17), 28.8 (3C, *t*-Bu), 33.0 (C-6), 40.0 (Cq-15), 40.5 (C-9), 40.8 (Cq-8), 47.2 (C-3), 49.4 (C-20), 55.2 (Cq-4), 55.9 (O*Me*), 64.8 (Cq-1), 67.0 (C-2), 68.3 (C-7), 73.8 (Cq, *t*-Bu), 74.7 (C-14), 75.6 (C-5), 76.7 (C-10), 80.8 (Cq-11), 94.3 (O*CH*$_2$O), 124.2 (C-13), 141.4 (Cq-12), 169.2 (Me*CO*). CIMS: 525 ([MH]$^+$, 6), 449 (3), 435 (16), 405 (19), 389 (79), 271 (38), 253 (48), 153 (100), 135 (69), 121 (37), 95 (50). HRCIMS: calcd for $C_{28}H_{45}O_9$ *m/z*: 525.3063; found: 525.3069.

Proceeding as above, **11b** (13.4 mg, 0.028 mmol) in 1.0 mL of 1:1 DCM:EtOH, $CeCl_3 \cdot 7H_2O$ (12.7 mg, 0.034 mmol) and $NaBH_4$ (3.2 mg, 0.085 mmol) at −15°C for 1.5 h afforded 13.4 mg of allylic alcohols in 99% combined yield and a 23:1 β:α ratio. Chromatography (heptane:EtOAc, 1:2 to 1:5) gave the major isomer **22**: $[\alpha]_D$ −12 (*c* 1.33). IR (film): 3436, 2971, 2928, 1737, 1649, 1460, 1372, 1237, 1191, 1156, 1075, 1022, 981, 912, 888 cm^{-1}. ^{1}H NMR (600 MHz): δ 1.00 (3H, s, Me-19), 1.14 (9H, s, *t*-Bu), 1.16 (3H, s, Me-16), 1.43 (3H, s, Me-17), 1.77 (1H, dd, *J*=7.0, 16.1, H-9α), 1.82 (1H, m, H-6α), 1.88 (3H, d, *J*=1.2, Me-18), 1.96 (1H, d, *J*=16.1, H-9β), 2.02 (3H, s, *Me*CO), 2.05 (1H, m, H-6β), 2.22 (1H, bs, OH), 2.60 (1H, d, *J*=11.9, H-3), 3.14 (1H, d, *J*=11.9, H-2), 3.44 (3H, s, O*Me*), 3.69 (1H, dd, *J*=4.3, 11.7, H-7), 3.74 (1H, bd, *J*=4.1, H-14), 3.84 (1H, s, OH), 3.98 (1H, d, *J*=7.0, H-10), 4.65 (1H, d, *J*=6.8, O*CH*$_2$O), 4.76 (1H, d, *J*=6.8, O*CH*$_2$O), 5.05 (1H, d, *J*=1.6, H-20a), 5.28 (1H, d, *J*=1.6, H-20b), 5.53 (1H, t, *J*=3.1, H-5), 5.85 (1H, dq, *J*=1.2, 4.1, H-13). Diagnostic NOEs: {Me-16}: H-10, H-3; {Me-17}: H-13; {Me-19}: H-3, H-10, H-6β; {H-2}: H-7, H-14; {H-3}: H-10, Me-16, Me-19, H-20a; {H-5}: H-20b. ^{13}C NMR (150 MHz): δ 17.0 (Me-19), 19.7 (Me-18), 20.0 (Me-16), 21.6 (*Me*CO), 27.3 (Me-17), 29.0 (3C, *t*-Bu), 35.2 (C-6), 40.2 (C-9), 40.3 (Cq-8), 40.9 (Cq-15), 48.4 (C-3), 56.1 (O*Me*), 66.1

(Cq-1), 68.6 (C-7), 69.0 (C-2), 73.8 (Cq, *t*-Bu), 74.8 (C-5), 74.9 (C-14), 76.4 (C-10), 81.2 (Cq-11), 94.2 (O*CH*$_2$O), 121.3 (C-20), 124.5 (C-13), 140.2 (Cq-4), 141.5 (Cq-12), 169.5 (Me*CO*). ESIMS (MeOH): 531 ([MNa]$^+$, 100). The minor isomer was only present in minute quantities and could only be quantified by proton integration; no further characterization was accomplished.

Proceeding as above, **16b** (12 mg, 0.023 mmol) in 1.0 mL of 1:1 DCM:EtOH, $CeCl_3 \cdot 7H_2O$ (10.3 mg, 0.028 mmol) and $NaBH_4$ (2.6 mg, 0.069 mmol) at −20°C for 1 h afforded after chromatography (heptane:EtOAc, 1:1 to 1:7) 11.3 mg (94%) of a faster eluting major isomer and nearly 0.25 mg of a slower eluting minor isomer, obtained impure, not allowing for characterization. Compound **24** (faster eluting): $[\alpha]_D$ +19 (*c* 0.95). IR (film): 3469, 2972, 1738, 1632, 1462, 1372, 1238, 1190, 1156, 1076, 1030, 987, 966, 908, 864 cm^{-1}. ^{1}H NMR (800 MHz): δ 1.02 (3H, s, Me-16), 1.14 (9H, s, *t*-Bu), 1.17 (3H, s, Me-19), 1.41 (3H, s, Me-17), 1.70 (1H, d, *J*=11.9, H-3), 1.81 (1H, dd, *J*=7.2, 16.1, H-9α), 1.89 (3H, d, *J*=1.4, Me-18), 1.94 (1H, d, *J*=16.1, H-9β), 1.98 (1H, ddd, *J*=3.0, 11.7, 14.9, H-6β), 2.11 (3H, s, *Me*CO), 2.15 (1H, td, *J*=3.9, 14.9, H-6α), 2.25 (1H, bs, OH), 2.62 (1H, d, *J*=5.1, H-20a), 2.81 (1H, d, *J*=5.1, H-20b), 3.41 (1H, d, *J*=11.9, H-2), 3.44 (3H, s, O*Me*), 3.66 (1H, dd, *J*=3.9, 11.7, H-7), 3.75 (1H, s, OH), 3.77 (1H, d, *J*=4.0, H-14), 3.94 (1H, d, *J*=7.2, H-10), 4.65 (1H, d, *J*=7.1, O*CH*$_2$O), 4.71 (1H, m, H-5), 4.76 (1H, d, *J*=7.1, O*CH*$_2$O), 5.87 (1H, dq, *J*=1.4, 4.0, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-17}: Me-16 (NOE gem), H-13; {Me-19}: H-3, H-10, H20a, H-6β; {H-2}: H-7, H-14; {H-3}: H-10, Me-16, Me-19, H-20a; {H-14}: H-2, H-13; {H-5}: H-20b. ^{13}C NMR (200 MHz): δ 17.4 (Me-19), 19.7 (Me-18), 19.9 (Me-16), 21.2 (*Me*CO), 27.1 (Me-17), 28.8 (3C, *t*-Bu), 34.3 (C-6), 40.0 (Cq-15), 40.7 (C-9), 42.1 (Cq-8), 46.4 (C-3), 54.9 (C-20), 56.0 (O*Me*), 56.5 (Cq-4), 63.3 (Cq-1), 67.7 (C-2), 68.4 (C-7), 74.0 (Cq, *t*-Bu), 74.7 (C-14), 75.7 (C-5), 76.4 (C-10), 81.0 (Cq-11), 94.4 (O*CH*$_2$O), 124.6 (C-13), 141.2 (C-12), 169.6 (Me*CO*). CIMS: 525 ([MH]$^+$, 2), 507 (6), 405 (12), 389 (26), 329 (27), 271 (56), 211 (42), 193 (46), 153 (100), 135 (69), 95 (57).

Proceeding as above, **8** (12 mg, 0.025 mmol) in 1.0 mL of 1:1 DCM:EtOH, $CeCl_3 \cdot 7H_2O$ (10.3 mg, 0.028 mmol) and $NaBH_4$ (2.6 mg, 0.069 mmol) at −30°C for 50 min afforded 10.5 mg (87%) of a 3.5:1 mixture of allylic alcohols, which after chromatography (heptane:EtOAc, 1:1 to 1:2), gave a faster eluting minor isomer **27** (2.3 mg) and a slower eluting major isomer **26** (8.2 mg): $[\alpha]_D$ –9 (*c* 0.77). IR (film): 3501, 2977, 1727, 1462, 1390, 1364, 1266, 1185, 1154, 1119, 1072, 1024, 894, 738 cm^{-1}. ^{1}H NMR (800 MHz): δ 1.00 (3H, s, Me-16), 1.17 (3H, s, Me-19), 1.20 (9H, s, *t*-Bu), 1.23 (1H, td, *J*=4.2, 13.9, H-5β), 1.42 (3H, s, Me-18), 1.60 (3H, s, Me-17), 1.61 (1H, d, *J*=11.8, H-3), 1.79 (1H, ddt, *J*=4.2, 10.7, 13.9, H-6β), 1.92 (1H, dd, *J*=6.6, 15.7, H-9α), 1.96 (1H, qd, *J*=4.2, 13.9, H-6α), 2.14 (1H, dd, *J*=1.0, 15.7, H-9β), 2.28 (1H, ddt, *J*=1.6, 4.2, 13.9, H-5α), 2.30 (1H, bs, OH), 2.56 (1H, dd, *J*=1.6, 5.1, H-20a), 2.70 (1H, d, *J*=5.1, H-20b), 3.04 (1H, d, *J*=11.8, H-2), 3.35 (1H, d, *J*=5.0, H-13), 3.38 (1H, dd, *J*=4.2, 10.7, H-7), 3.44 (3H, s, O*Me*), 3.81 (1H, s, OH), 3.84 (1H, d, *J*=5.0, H-14), 3.99 (1H, d, *J*=6.6, H-10), 4.70 (1H, d, *J*=6.9, O*CH*$_2$O), 4.78 (1H, d, *J*=6.9, O*CH*$_2$O). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-17}: Me-16 (NOE gem); {Me-18}: H-13; {Me-19}: H-3, H-10, H20a, H-6β; {H-2}: H-7, H-14, H-9α; {H-3}: H-10, Me-16, Me-19, H-20a; {H-14}: H-2, H-13; {H-20b}: H-5β. ^{13}C NMR (200 MHz): δ 17.0 (Me-19), 20.1 (Me-18), 22.4 (Me-16), 26.0 (Me-17), 27.6 (C-5), 28.9 (3C, *t*-Bu), 29.2 (C-6), 41.0 (Cq-15), 42.6 (2C, C-9, Cq-8), 46.6 (C-3), 55.6 (C-20), 55.8 (O*Me*), 57.4 (Cq-4), 61.0 (C-13), 62.4 (Cq-1), 64.3 (Cq-12), 66.1 (C-2), 73.1 (C-7), 73.6 (Cq, *t*-Bu), 74.5 (C-14), 74.8 (C-10), 77.8 (Cq-11), 94.6 (O*CH*$_2$O). CIMS: 483 ([MH]$^+$, 4), 465 (2), 433 (4), 377 (22), 363 (10), 359 (20), 347 (72), 329 (78), 271 (26), 243 (38), 195 (50), 179 (66), 135 (100), 109 (84), 95 (92). HRCIMS: calcd for $C_{26}H_{43}O_8$ *m/z*: 483.2958; found: 483.2957.

Compound **27**: IR (film): 3459, 2976, 1461, 1389, 1364, 1266, 1186, 1152, 1072, 1021, 982, 910 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.06 (3H, s), 1.16 (3H, s), 1.20 (9H, s), 1.28 (1H, m), 1.37 (3H, s), 1.42

(3H, s), 1.61 (1H, bd, *J*=11.6), 1.79 (1H, m), 1.97 (1H, m), 2.02–2.14 (2H, m), 2.24 (1H, d, *J*=3.7, OH), 2.36 (1H, m), 2.59 (1H, dd, *J*=1.8, 4.8), 2.71 (1H, d, *J*=4.8), 3.12 (1H, s), 3.45 (3H, s), 3.47 (1H, dd, *J*=4.6, 11.6), 3.80 (1H, s, OH), 3.83 (1H, d, *J*=12.0), 4.00 (1H, dd, *J*=2.3, 5.1), 4.62 (1H, d, *J*=3.7), 4.70 (1H, d, *J*=6.9), 4.81 (1H, d, *J*=6.9). ^{13}C NMR (50.3 MHz): δ 17.3, 20.3, 23.0, 24.7, 27.9, 29.1 (3C), 29.5, 41.2, 42.6, 43.1, 47.0, 55.9, 56.1, 56.5, 58.1, 63.3, 63.4, 65.0, 65.1, 73.0, 73.8, 74.9, 78.0, 94.8. ESIMS (MeOH): 505 ([MNa]$^+$, 100).

Proceeding as above, reduction of **6** (61 mg, 0.13 mmol) in 6 mL of Cl_2CH_2:EtOH, 1:1, with $CeCl_3\cdot 7H_2O$ (60 mg, 0.16 mmol) and $NaBH_4$ (15 mg, 0.40 mmol) at −15°C (3.5 h) led to a residue, which was chromatographed on silica gel (heptane:ether, 1:2) to give 40 mg (67%) of an inseparable 3:1 mixture of **28a** (faster eluting, major isomer), starting material **6** and 18 mg (30%) of **29** (slower eluting) that was unstable on standing. The inseparable mixture of **28a** and **6** (40 mg) was then benzoylated by treatment with BzCl (0.1 mL, 0.9 mmol) in 2 mL of methylene chloride in the presence of NEt_3 (0.5 mL, 3.6 mmol) and DMAP (catalytic) for 6 h (0°C to room temperature). After quenching with ice, extraction with methylene chloride, washings with 1N HCl, a saturated aqueous solution of $NaHCO_3$, water and the usual work-up the crude was chromatographed (heptane:EtOAc, 3:1) to yield 31.4 mg (85%) of **28b** along with 8.5 mg (14.6%) of starting material **6**. Compound **28b**: $[\alpha]_D$ −82 (*c* 1.57). IR (film): 3531, 2973, 1721, 1602, 1452, 1364, 1314, 1268, 1193, 1153, 1071, 1026, 908, 739, 711 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.18 (9H, s, *t*-Bu), 1.20 (3H, s, Me-19), 1.17 (1H, m, H-5β), 1.41 (3H, s, Me-16), 1.43 (3H, s, Me-17), 1.69–2.01 (3H, m, H-6α, H-6β, H-9α), 1.71 (1H, d, *J*=15.4, H-9β), 1.78 (3H, t, *J*=1.7, Me-18), 2.19 (1H, ddt, *J*=1.7, 4.7, 13.8, H-5α), 2.55 (1H, d, *J*=12.6, H-3), 2.66 (1H, dd, *J*=1.7, 5.0, H-20a), 2.72 (1H, d, *J*=5.0, H-20b), 3.45 (3H, s, O*Me*), 3.46 (1H, dd, *J*=4.5, 10.6, H-7), 3.79 (1H, bs, OH), 3.98 (1H, d, *J*=6.8, H-10), 4.64 (1H, d, *J*=6.7, O*CH*$_2$O), 4.77 (1H, d, *J*=6.7, O*CH*$_2$O), 5.71 (1H, quintet, *J*=1.7, H-13), 5.92 (1H, dd, *J*=1.7, 12.6, H-2), 6.30 (1H, sextet, *J*=1.7, H-14), 7.45–7.50 (2H, m, *Ar*), 7.60 (1H, m, *Ar*), 8.13–8.16 (2H, m, *Ar*). ^{13}C NMR (75 MHz): δ 17.5, 18.7, 23.4, 26.2, 27.8, 29.0 (3C), 29.5, 42.8, 44.0, 46.3, 48.3, 56.0, 57.2, 57.8, 73.0, 73.1, 73.4, 76.6, 82.9, 94.3, 120.0, 126.6, 128.4 (3C), 129.4 (2C), 133.1, 140.3, 141.4, 165.1. ESIMS (MeOH)**:** 577 ([MNa]$^+$, 100), 593 ([MK]$^+$, 11), 1131 ([2MNa]$^+$, 13).

Proceeding as above, **14b** (32 mg, 0.044 mmol) in 2.0 mL of 1:1 DCM:EtOH, $CeCl_3\cdot 7H_2O$ (25.0 mg, 0.066 mmol) and $NaBH_4$ (21 mg, 0.56 mmol) at −10°C for 2.5 h afforded a crude residue which after chromatography (heptane:ether, 3:1 to 1:1) gave a faster eluting major isomer **30a** (23.1 mg, 72%), a slower eluting minor isomer **31** (7.4 mg, 23%) along with 1.0 mg (3%) of recovered starting material. Compound **30a**: $[\alpha]_D$ −22 (*c* 0.94). IR (film): 3513, 2930, 2858, 1472, 1389, 1362, 1255, 1193, 1151, 1080, 966, 940, 836 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.06 (3H, s, *Me*-TBS), 0.07 (3H, s, *Me*-TBS), 0.09 (3H, s, *Me*-TBS), 0.11 (3H, s, *Me*-TBS), 0.90 (9H, s, *t-Bu*-TBS), 0.91 (9H, s, *t-Bu*-TBS), 1.13 (3H, s, Me-19), 1.16 (9H, s, *t*-Bu), 1.19 (3H, s, Me-16), 1.30 (3H, s, Me-17), 1.62 (1H, d, *J*=3.7, OH), 1.84 (1H, m, H-6β), 1.83 (3H, t, *J*=1.8, Me-18), 1.84 (1H, d, *J*=16.0, H-9β), 1.95 (1H, ddd, *J*=4.6, 5.1, 14.3, H-6α), 2.05 (1H, dd, *J*=6.0, 16.0, H-9α), 2.51 (1H, d, *J*=12.0, H-3), 3.02 (1H, s, OH), 3.43 (3H, s, O*Me*), 3.49 (d, 1H, *J*=10.0, H-20), 3.58 (1H, dd, *J*=0.8, 10.0, H-20), 3.83 (1H, t, *J*=4.6, H-5), 3.86 (1H, dd, *J*=5.1, 10.6, H-7), 3.85 (1H, s, OH), 3.95 (1H, d, *J*=6.0, H-10), 4.01 (1H, d, *J*=12.0, H-2), 4.57 (1H, quintet, *J*=1.8, H-14), 4.68 (1H, d, *J*=6.7, O*CH*$_2$O), 4.75 (1H, d, *J*=6.7, O*CH*$_2$O), 5.66 (1H, quintet, *J*=1.8, H-13). Diagnostic NOEs: {Me-16}: Me-17 (NOE gem), H-10, H-3; {Me-17}: Me-16 (NOE gem), H-14; {Me-19}: H-3, H-10, H-6β; {H-2}: H-7, H-9α; {H-3}: H-10, Me-16, Me-19; {H-14}: Me-17. ^{13}C NMR (75 MHz): δ −5.6, −5.4, −4.9 (2C), 18.0, 18.1, 19.3, 19.9, 20.6, 25.0, 25.7 (3C), 25.8 (3C), 29.0 (3C), 37.0, 40.5, 42.4, 42.7, 43.2, 56.0, 60.1, 64.1, 67.8, 68.1, 69.0, 71.7, 73.7, 75.7, 78.5, 80.8, 95.3, 125.8, 139.6. ESIMS (MeOH): 751 ([MNa]$^+$, 100).

Compound **31**: $[\alpha]_D$ +11 (*c* 0.60). IR (film): 3535, 2930, 2858, 1692, 1472, 1389, 1362, 1255, 1193,

1149, 1069, 967, 941, 922, 837, 777, 740, 672 cm^{-1}. ^1H NMR (300 MHz): δ 0.06 (3H, s, *Me*-TBS), 0.08 (3H, s, *Me*-TBS), 0.10 (3H, s, *Me*-TBS), 0.12 (3H, s, *Me*-TBS), 0.89 (9H, s, Si-*t*-Bu), 0.91 (9H, s, Si-*t*-Bu), 1.11 (3H, s, Me), 1.12 (3H, s, Me), 1.15 (9H, s, *t*-Bu), 1.37 (3H, s, Me), 1.71 (1H, dd, *J*=7.2, 16.0, H-9α), 1.84 (1H, ddd, *J*=4.6, 10.2, 14.5, H-6β), 1.91 (3H, t, *J*=1.2, Me-18), 1.92 (1H, d, *J*=16.0, H-9β), 1.94 (1H, ddd, *J*=4.6, 5.6, 14.5, H-6α), 2.12 (1H, bs, OH), 2.48 (1H, d, *J*=12.0, H-3), 2.90 (1H, s, OH), 3.44 (3H, s, O*Me*), 3.44 (d, 1H, *J*=12.0, H-2), 3.49 (1H, d, *J*=9.5, H-20), 3.56 (1H, d, *J*=9.5, H-20), 3.69 (1H, m, H-14), 3.72 (1H, s, OH), 3.77 (1H, dd, *J*=5.6, 10.2, H-7), 3.92 (1H, t, *J*=4.6, H-5), 3.97 (1H, d, *J*=7.2, H-10), 4.68 (1H, d, *J*=6.5, OCH_2O), 4.80 (1H, d, *J*=6.5, OCH_2O), 5.85 (1H, qd, *J*=1.2, 5.9, H-13). ^{13}C NMR (75 MHz): δ −5.4 (2C), −4.9, −4.7, 18.1 (2C), 20.1, 20.2, 20.3, 25.8 (3C), 25.9 (3C), 26.3, 29.1 (3C), 37.2, 39.8, 40.7, 41.9, 43.1, 56.2, 63.6, 67.4, 69.4, 69.6, 71.1, 73.6, 74.6, 75.3, 80.0, 80.8, 95.5, 124.6, 141.0. ESIMS (MeOH): 751 ([MNa]$^+$, 100).

The major allylic alcohol **30a** thus obtained (18.8 mg, 0.026 mmol) was acetylated with Ac_2O (0.1 mL, excess) in dry pyridine (0.5 mL), in the presence of DMAP (catalytic) at 0°C. After 30 min (TLC monitoring), work-up as above and chromatography (heptane:EtOAc, 4:1) afforded 18.1 mg (90%) of acetylated compound **30b**: $[\alpha]_D$ −51 (*c* 1.70). IR (film): 3585, 2930, 1745, 1473, 1362, 1235, 1086, 1022, 966, 834, 777 cm^{-1}. ^1H NMR (300 MHz): δ 0.05 (3H, s), 0.06 (3H, s), 0.09 (3H, s), 0.13 (3H, s), 0.89 (9H, s), 0.90 (9H, s), 1.11 (3H, s), 1.17 (12H, s), 1.35 (3H, s), 1.83 (3H, s), 1.84–2.06 (4H, m), 2.08 (3H, s), 2.45 (1H, d, *J*=11.8), 2.91 (1H, s, OH), 3.43 (1H, d, *J*=9.6), 3.43 (3H, s), 3.56 (1H, d, *J*=9.6), 3.82 (1H, d, *J*=11.8), 3.82 (1H, s, OH), 3.86 (1H, dd, *J*=6.2, 9.6), 3.95–4.00 (2H, m), 4.68 (1H, d, *J*=6.8), 4.74 (1H, d, *J*=6.8), 5.55 (1H, bs), 5.67 (1H, bs). ^{13}C NMR (75 MHz): δ −5.5 (2C), −4.7, −4.5, 18.0, 18.3, 19.4, 20.0, 20.8, 21.5, 24.9, 25.8 (3C), 25.9 (3C), 29.0 (3C), 37.8, 40.4, 41.8, 42.5, 43.1, 56.1, 60.4, 62.0, 66.9, 68.9, 70.0, 70.4, 73.5, 75.7, 79.4, 80.4, 95.5, 123.0, 141.0, 170.2. ESIMS (MeOH): 793 ([MNa]$^+$, 100).

5.6. Preparation of *32* and *33*

Proceeding as for **5**, hydroxyl directed epoxidation of **10** (48 mg, 0.11 mmol) in dry benzene (4.0 mL) with $VO(acac)_2$ (0.5 mg, 0.0019 mmol), reflux for 15 min then 5–6 M *t*-BuOOH in decane (0.02 mL, 0.107 mmol) and an additional 10 min reflux afforded after work-up and chromatography (heptane:EtOAc, 1:1 to 1:3) 32 mg of epoxide **32** (63%), along with 8.3 mg of 1,2-epoxide **11a** (15%), 1.3 mg of unreacted starting material (3%) and 4.1 mg bisepoxide **16a** (7%). Compound **32**: mp 196–198°C (heptane–ether–EtOAc). $[\alpha]_D$ −25 (*c* 1.18). IR (film): 3466, 2977, 1669, 1630, 1469, 1390, 1266, 1190, 1149, 1064, 1019, 919, 808, 740 cm^{-1}. ^1H NMR (300 MHz): δ 1.11 (9H, s, *t*-Bu), 1.18 (3H, s, Me), 1.27 (3H, s, Me), 1.34 (3H, s, Me), 1.52 (1H, dd, *J*=8.0, 15.9, H-9α), 1.82 (1H, d, *J*=15.9, H-9β), 1.88 (1H, ddd, *J*=3.0, 11.5, 14.5, H-6β), 2.00 (3H, d, *J*=1.4, Me-18), 2.12 (1H, ddd, *J*=3.6, 4.1, 14.5, H-6α), 2.49 (1H, bs, OH), 2.62 (1H, d, *J*=12.0, H-3), 2.70 (1H, d, *J*=4.8, H-20), 2.82 (1H, d, *J*=4.8, H-20), 3.45 (3H, s, O*Me*), 3.51 (1H, m, H-5), 3.67 (1H, dd, *J*=4.1, 11.5, H-7), 3.86 (1H, s, OH), 4.08 (1H, d, *J*=8.0, H-10), 4.65 (1H, d, *J*=6.7, OCH_2O), 4.74 (1H, d, *J*=6.7, OCH_2O), 6.07 (1H, q, *J*=1.4, H-13), 6.64 (1H, d, *J*=12.0, H-2). ^{13}C NMR (75 MHz): δ 17.4, 20.4, 22.8, 26.6, 29.0 (3C), 35.7, 42.4, 44.3, 47.2, 47.8, 56.2, 56.6, 59.0, 67.9, 73.7, 73.8, 77.8, 83.1, 94.7, 130.0, 133.4, 149.6, 160.2, 194.6. CIMS: 465 ([MH]$^+$, 32), 447 (26), 433 (27), 403 (44), 391 (18), 373 (41), 359 (23), 347 (62), 329 (100), 311 (65), 299 (40), 213 (32), 189 (31), 165 (40), 135 (12), 99 (14). HRCIMS: calcd for $C_{26}H_{41}O_7$ *m/z*: 465.2852; found: 465.2849.

Proceeding as for **11a**, nucleophilic epoxidation of trienone **9** (18 mg, 0.042 mmol) in 1.0 mL of methanol with 30% H_2O_2 (0.03 mL, 0.25 mmol) and 6N NaOH (0.003 mL, 0.021 mmol) at 0°C to

room temperature for 3.5 h furnished after dilution with EtOAc, usual work-up and chromatography (heptane:EtOAc, 5:1 to 2:1) 19 mg (99%) of **33**: $[\alpha]_D$ −90 (*c* 1.04). IR (film): 3522, 2971, 2928, 1694, 1651, 1463, 1390, 1361, 1259, 1225, 1193, 1151, 1072, 1022, 918 cm^{-1}. ^1H NMR (300 MHz): δ 1.03 (3H, s, Me-19), 1.11 (9H, s, *t*-Bu), 1.24 (3H, s, Me-16), 1.31 (3H, s, Me-17), 1.57 (1H, ddd, *J*=5.0, 11.4, 16.0, H-6β), 1.65 (1H, m, H-5), 1.72 (1H, dd, *J*=7.4, 16.5, H-9α), 1.81 (1H, m, H-6α), 2.03 (1H, d, *J*=16.5, H-9β), 2.10 (3H, d, *J*=1.4, Me-18), 2.27 (1H, m, H-5), 2.42 (1H, d, *J*=11.6, H-3), 2.82 (1H, d, *J*=11.6, H-2), 3.29 (1H, dd, *J*=4.4, 11.4, H-7), 3.47 (3H, s, O*Me*), 4.11 (1H, s, OH), 4.14 (1H, d, *J*=7.4, H-10), 4.68 (1H, d, *J*=6.6, OCH_2O), 4.74 (1H, t, *J*=1.8, H-20a), 4.78 (1H, d, *J*=6.6, OCH_2O), 4.87 (1H, t, *J*=1.8, H-20b), 6.20 (1H, q, *J*=1.4, H-13). ^{13}C NMR (75 MHz): δ 17.4, 19.8, 20.8, 25.7, 29.1 (3C), 29.3, 31.0, 40.8, 41.9, 42.9, 49.9, 56.2, 64.9, 68.6, 72.9, 73.5, 76.0, 81.4, 94.4, 113.5, 128.0, 143.3, 163.3, 196.3. CIMS: 449 ($[MH]^+$, 10), 433 (4), 393 (19), 375 (13), 361 (30), 343 (31), 331 (60), 313 (67), 295 (16), 213 (46), 197 (50), 179 (100), 161 (24), 151 (53), 125 (22), 107 (24), 95 (23). HRCIMS: calcd for $C_{26}H_{41}O_6$ *m/z*: 449.2902; found: 449.2905.

Acknowledgements

The authors thank the Ministerio de Educacion y Cultura (Spain) for a fellowship to Dr. J. I. Martín Hernando, the European Commission for a Research Training Grant to Dr. J. I. Candela Lena, and Professor P. Potier for his kind interest and constant encouragement.

References

1. For review articles, see: Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemporary Organic Synthesis* **1994**, *1*, 47–75; Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 15–44; total syntheses: Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634; Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc*. **1994**, *116*, 1597–1600; Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1723–1726; Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreansic, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. J.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc*. **1997**, *119*, 2757–2758; Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Japan Acad., Ser. B* **1997**, *73*, 95–100; Morihara, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc*. **1998**, *120*, 12 980–12 981.
2. Arseniyadis, S.; Martín Hernando, J. I.; Quílez del Moral, J.; Yashunsky, D. V.; Potier, P. *Tetrahedron Lett*. **1998**, *39*, 3489–3492; Arseniyadis, S.; Martín Hernando, J. I.; Quílez del Moral, J.; Yashunsky, D. V.; Potier, P. *Synlett* **1998**, 1010–1012; Martín Hernando, J. I.; Quílez del Moral, J.; del Rosario Rico Ferreira, M; Candela Lena, J. I.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 783–797; 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.; Yashunsky, D. V.; Pereira de Freitas, R.; Muñoz-Dorado M.; Potier, P.; Toupet, L. *Tetrahedron* **1996**, *52*, 12 443–12 458; Arseniyadis, S.; Rodriguez, R.; Muñoz Dorado, M.; Brondi Alves, R.; Ouazzani, J.; Ourisson, G. *Tetrahedron* **1994**, *50*, 8399–8426.
3. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615–1621.
4. Still, W. C. *J. Am. Chem. Soc*. **1978**, *100*, 1481–1486.
5. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666; Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13–19.
6. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, 1984; Vol. 3, 111.
7. Gueritte-Voegelein, F.; Guenard, D.; Potier, P. *J. Nat. Prod*. **1987**, *50*, 9–18; Potier, P. *Chem. Soc. Rev.* **1992**, 113–119; Appendino, G. *Nat. Prod. Rep*. **1995**, 349–360.
8. Shigemori, H.; Sakurai, C. A.; Hosoyama, H.; Kobayashi, A.; Kajiyama, S.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 2553–2558.

9. Menhard, B.; Eisenreich, W.; Hylands, P. J.; Bacher, A.; Zenk, M. H. *Phytochemistry* **1998**, *49*, 113–125.
10. Della Casa de Marcano, D. P.; Halsall, T. G. *J. Chem. Soc., Chem. Commun*. **1970**, 1381–1382.
11. Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc*. **1986**, *108*, 3513–3515.
12. Sharpless, K. B.; Michaelson, R. C. *J. Org. Chem*. **1973**, *95*, 6136–6137.
13. Cha, J. K.; Kim, N. S. *Chem Rev*. **1995**, *95*, 1761–1795.
14. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett*. **1983**, *24*, 3943–3946 and 3947–3950.
15. Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett*. **1997**, *38*, 5027–5030; Vedejs, E.; Kruger, A. W. *J. Org. Chem*. **1999**, *64*, 4790–4797, and references cited therein.
16. Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823–9838.
17. Payne, G. B. *J. Org. Chem*. **1962**, *27*, 3819–3822; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.
18. Zhang, H.; Takeda, Y.; Minami, Y.; Yoshida, K.; Matsumoto, T.; Xiang, W.; Mu, O.; Sun, H. *Chem. Lett*. **1994**, 957–960; Cheng, K.; Fang, W.; Yang, Y.; Xu, H.; Meng, C.; Kong, M.; He, W.; Fang, Q. *Phytochemistry* **1996**, *42*, 73–75.
19. Ma, W.; Stahlhut, R. W.; Adams, T. L.; Park, G. L.; Evans, W. A.; Blumenthal, S. G.; Gomez, G. A.; Nieder, M. H.; Highlands, P. J. *J. Nat. Prod*. **1994**, *57*, 1320–1324.
20. Rao, K. V.; Juchum, J. *Phytochemistry* **1998**, *47*, 1315–1324.
21. Luche, J.-L; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun*. **1978**, 601–602; Luche, J.-L. *J. Am. Chem. Soc*. **1978**, *100*, 2226–2227.
22. Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. S*oc. **1980**, *102*, 5703–5711.
23. LeCocq, C.; Lallemand, J. Y. *J. Chem. Soc., Chem. Commun*. **1981**, 150–152.
24. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem*. **1990**, *11*, 440–467.