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Influence of the substitution pattern on the $Pb(OAc)_4$ mediated oxidative cleavage of steroidal 1,2-diols

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Abstract

A rapid increase in molecular complexity, modulated by the substitution pattern, upon treatment of steroidal unsaturated diols with lead tetraacetate is presented. The steric and electronic factors involved in these cascade type transformations are investigated, the products serving as useful mechanistic probes.

1. Introduction

Previously, we have demonstrated that bicyclic unsaturated 1,2-diols react with lead tetraacetate in a cascade fashion with high yields.[1] Extension of the chemistry to involve steroidal unsaturated 1,2-diols of type **1a** was successful and products **2** were obtained in high yields, which were improved by conducting the reaction in acetic acid.[2] As illustrated in Scheme 1, subjection of testosterone based 2,3-diol **1a** to $Pb(OAc)_4$ mediated oxidative cleavage led to a B-ring-enlarged-A-nor-steroid of type **2**, deriving from C10–C5 bond migration. The resultant ring-expanded compounds were readily transformed to a bicyclo[3.2.2]ring system of type **3** via a mild fused to bridged ring system interchange. To explore further the scope of these one-pot multistage transformations, nor-testosterone derived unsaturated 1,2-diol **1b** leading to **4** was examined. Finally, in order to better assess the role of substitution during these cascade transformations, **1c** leading to type **5c** compounds was targeted for study. This paper describes a series of experiments addressed to probe the influence of the substitution pattern; options **1b** and **1c** were selected, in attempts to understand the factors involved in the three related processes (they all proceed via the same half-cascade intermediate of type **5**). In Scheme 1, 'P' at C-17 stands for *t*Bu or TBS protection

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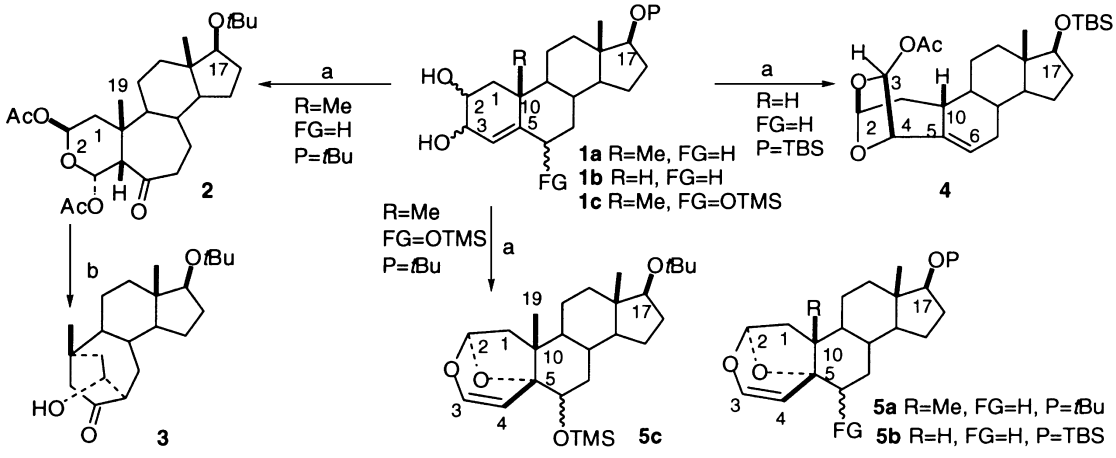
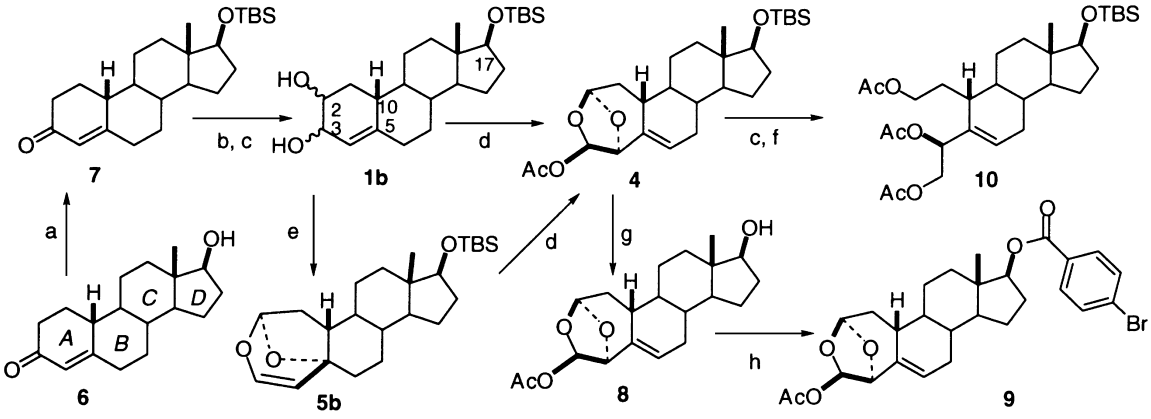
but with a carbonyl group at C-17, protected as a ketal, the same cascade transformations were also carried out.



Scheme 1. (a) $Pb(OAc)_4$, in CH_3CN or CH_3CO_2H. (b) K_2CO_3–MeOH–H_2O

2. Results and discussion

The required 1,2-unsaturated steroidal-diol derivatives were prepared according to a general synthetic protocol involving conversion of an enone to the corresponding α-acetoxy derivative, followed by lithium aluminum hydride reduction. The preparation of **1b**, lacking the angular methyl group at C-10 (Me-19, steroid numbering), which was considered to be a challenging substrate for the cascade transformations,[3] was achieved straightforwardly starting from the commercially available 19-nor-testosterone **6**. As before,[4] the synthesis began with α-acetoxylation and subsequent reduction of the known[5] steroidal enone **7** (Scheme 2). Thus, 17β-(*tert*-butyldimethylsilyloxy)ester-4-ene-3-one **7** was reacted with lead tetraacetate in refluxing benzene under argon to give a mixture of two isomeric diacetates in about 80% yield, which were reduced without separation using lithium aluminum hydride. Exposure of the resulting unsaturated diol **1b** (diastereomeric mixture) to $Pb(OAc)_4$ (1.1 equiv.) at 0°C in acetonitrile effected a smooth conversion into the cyclic ene-acetal **5b** in 40% yield, along with the corresponding C2–C3 dialdehyde (30%). Use of excess (2.2 equiv.) of $Pb(OAc)_4$ was found to initiate further rearrangement affording the acetoxy bis-acetal ring system **4** (35%) together with 17% of **5b** and dialdehyde resulting from the oxidative cleavage (28%), which did not undergo further rearrangement but rather showed some tendency to isomerize (*Z*/*E* enal geometry). Treatment of **1b** or cyclic acetal **5b**, the result of initial 'half-cascade' transformations, with $Pb(OAc)_4$ in acetic acid gave **4** (47%) after 15 h of stirring at room temperature, along with dialdehyde. Extensive NMR studies (COSY, HMQC, HMBC) established the A-nor-steroidal structure **4** and permitted the assignment of all the proton and carbon resonances. The relative configuration of the bis-acetal portion was secured by 1D NOEDIFF experiments. Lithium aluminum hydride reduction of **4** in dry THF (0°C to rt, 5 h) and subsequent acetylation of the crude triol thus obtained with Ac_2O in pyridine, in the presence of 4-DMAP, gave the corresponding triacetylated A-seco derivative **10** (95%, two steps). Lastly, deprotection of the TBS ether **4** was accomplished utilizing standard conditions (40% aqueous HF in acetonitrile, 1 h at 0°C) which provided the alcohol **8** in 85% yield.



Scheme 2. (a) TBSCl–Im, rt. (b) $Pb(OAc)_4$, PhH, Δ. (c) $LiAlH_4$. (d) 3 equiv. $Pb(OAc)_4$, MeCN, 50 h, rt or in AcOH, 15 h, rt. (e) 1.1 equiv. $Pb(OAc)_4$, MeCN, −20°C to rt. (f) Ac_2O, Py, DMAP, 0°C. (g) HF–MeCN, 0°C. (h) *p*-BrBzCl, Py–DMAP, 0°C to rt

Single-crystal X-ray diffraction analysis of the crystalline 17-*p*-bromobenzoate derivative **9** (Scheme 2) enabled unequivocal stereochemical assignment and further confirmed the accuracy of previous assignments by NMR techniques. The latter was obtained upon treatment of **8** with *p*-bromobenzoyl chloride in dry pyridine in the presence of DMAP (0°C to room temperature, 12 h). The desired *p*-bromobenzoate **9** thus obtained crystallized, allowing for an X-ray crystallographic study, the computer generated drawing of which is shown in Fig. 1 (left), along with an MM3 minimized structure of the hypothetical precursor organolead intermediate (right).

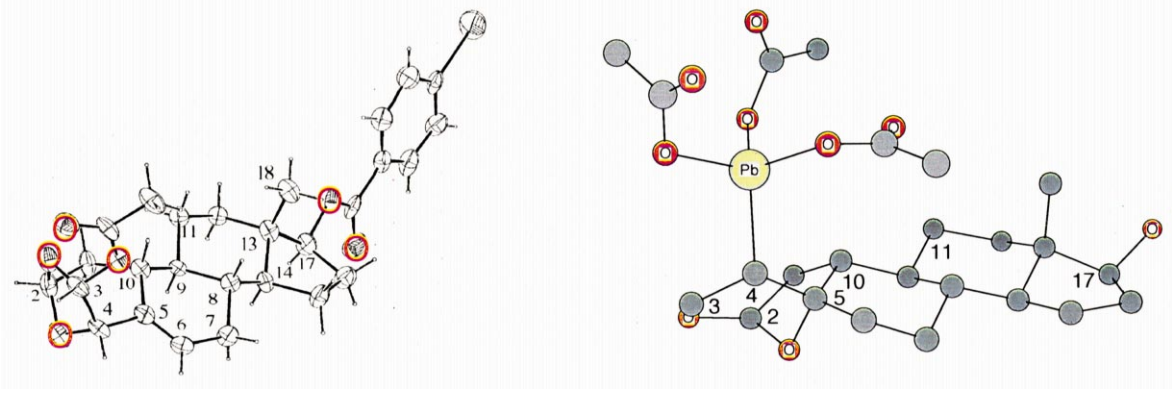
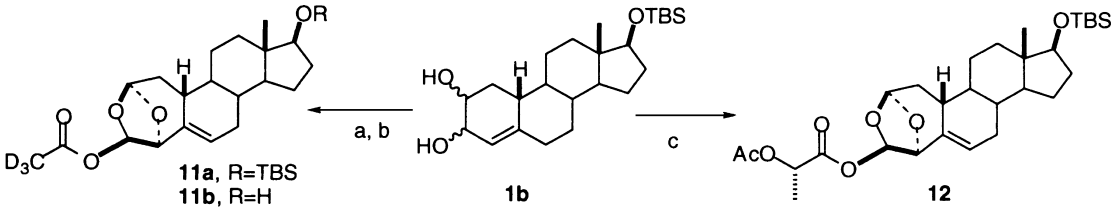


Figure 1. Perspective drawing of the X-ray structure of **9** (left), and a hypothetical precursor structure (right)

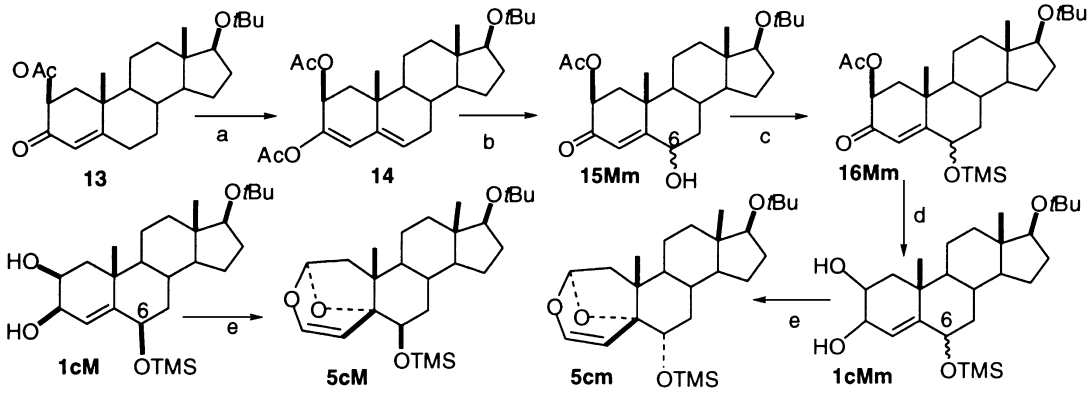
In an effort to elucidate a reaction mechanism, we examined the effect of changing several reaction parameters. To this end, the effect of solvent was briefly investigated in the reaction of **1b** with lead tetraacetate. Replacing acetonitrile with other solvents, such as acetic acid or (*S*)-*O*-acetyllactic acid, led to an increase of rate but no significant improvement in yield was observed. Use of deuterium labeled acetic acid led to the formation of **11a** (39%), accompanied by the corresponding dialdehyde. Removal of the TBS protective group as above afforded cleanly the deuterium labeled C-17 free hydroxy derivative **11b**. On the other hand, using (*S*)-*O*-acetyllactic acid as solvent led to **12** (40%) together with 3% of **4** and dialdehyde as above (Scheme 3). It is noteworthy that there was no sign of the alternative ring-enlarged type **2** product, arising from C10–C5 bond migration, in any of these reactions.

The conclusion of the current phase of our investigation involved the allylically substituted **1c** as a



Scheme 3. (a) $Pb(OAc)_4$, CD_3COOD, rt. (b) HF–MeCN, 0°C. (c) $Pb(OAc)_4$, $CH_3CH(OAc)COOH$, rt

substrate. To this end, we generated the allylic alcohols **15** from the corresponding acetoxy enone **13** by way of the intermediate dienol acetate species, using known procedures (Scheme 4). The dienol acetate, obtained by heating **13** in pyridine in the presence of acetic anhydride and 4-DMAP, was then subjected to epoxidation using methyltrioxorhenium (MTO)[6] as catalyst and aqueous hydrogen peroxide as terminal oxidant. A clean reaction ensued and the product had ^1H and ^{13}C NMR spectra concordant with structure **15Mm** (in a roughly 4:1 β-OH/α-OH ratio; M stands for major, m for minor). The resulting mixture was protected at C-6 by treatment with TMSOTf (trimethylsilyltrifluoromethane sulfonate) in the presence of collidine in dry toluene (10 mL/mmol), at −40°C under argon, affording cleanly the desired TMS–ether **16Mm**, in quantitative yield. Lithium aluminum hydride reduction of the crude thus obtained in ether at 0°C furnished the target diols in quantitative yield. In order to facilitate characterization, a small part of the initial mixture (**1cMm**) was chromatographically separated on silica gel. In line with our expectations were the results obtained from lead tetraacetate mediated cleavage of allylically substituted steroidal diols of type **1c**.

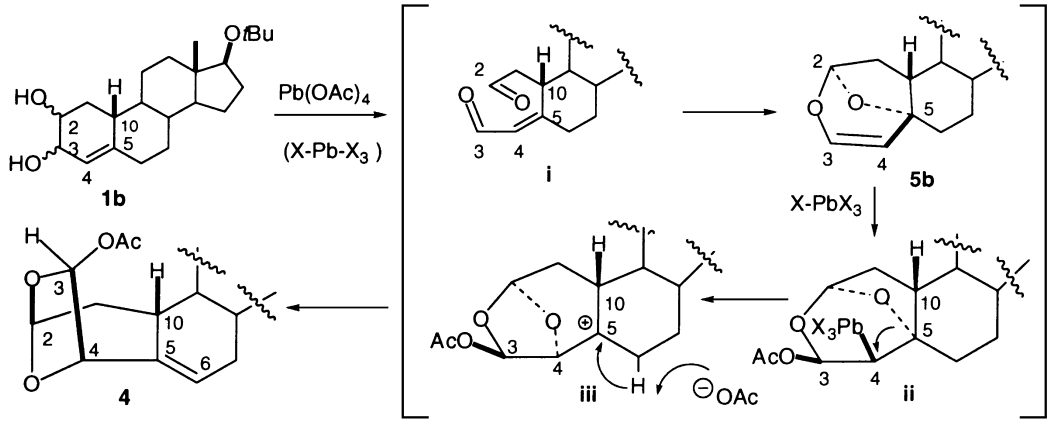


Scheme 4. (a) Ac_2O, Py, DMAP, 80–100°C. (b) MTO, 30% H_2O_2, py, CH_2Cl_2, rt. (c) TMSOTF, collidine, PhMe, −40°C. (d) $LiAlH_4$, Et_2O, 0°C. (e) $Pb(OAc)_4$ in MeCN or in AcOH

Chromatographically purified **1cM** (β-OTMS) and the mixture of α,β-OTMS derivative **1cMm** were tested separately, both of which afforded the corresponding cyclic ene-acetal, derived from oxidative cleavage and subsequent intramolecular 4+2 cycloaddition (half-cascade cursus).[7] Thus, subjection of either **1cM** or **1cMm** to lead tetraacetate, as above, afforded **5cM** for the former and a separable mixture of **5cM**+**5cm** for the latter, in high isolated yields. The configurational assignments of **13**, **14**, **1cM**, **5cM**, and **5cm** were determined with the aid of NMR techniques, especially by studying spatial proximities using the 1D NOEDIFF spectra.

We next examined the reactivity of the half-cascade intermediates **5cM** or **5cm**, formed on cleavage and IMDA (**1c→i→5c**, by analogy to **1b→i→5b** in Scheme 5), to see if they would undergo ring-expansion onto the corresponding A-nor-B-homosteroid in analogy with the fragmentation of the related diol **1a**. All efforts to induce **5cM** or **5cm** to undergo a full-cascade transformation failed to generate

even a trace of a ring-expanded product. Prolonged room temperature stirring or heating, as well as changing the solvent and the stoichiometry, did not produce the ring-expanded product of type **2**. Instead, work up provided recovered starting material and extensive decomposition products, which could not be characterized. It is noteworthy that there was no sign of the alternative full-cascade product, arising from C10–C5 bond migration. The result is presumably due to steric hindrance.



Scheme 5. A mechanistic rationale for the one-pot multistage transformations in the 19-nor-steroidal unsaturated diol series

3. Prediction and interpretation of skeletal changes

The mechanistic pathway of the cascade for **1b** is portrayed in Scheme 5. Thus, upon lead tetraacetate treatment,[8] **1b** initially undergoes an oxidative cleavage to the dialdehyde **i** followed by a 4+2 cycloaddition leading to the isolable **5b**. Upon further treatment with $Pb(OAc)_4$, formation of an inisolable organolead intermediate of type **ii** (X=OAc) occurs, which in turn undergoes rearrangement, involving 1,2-oxygen shift of the best aligned C5–O bond. In Scheme 5, it is proposed that the intermediate bridgehead cation **iii** is not acylated at C-5 by the acetate ions resulting from the organolead intermediate. Instead, it suffers a proton abstraction presumably by the acetate ions generated from the reagent acting as a base, as illustrated, leading to the rearranged compound **4**.

In the cases investigated, the outcome of the lead tetraacetate mediated one-pot multistage transformations depends originally on steric factors, which in turn control the effectiveness of orbital overlap depending on the initial alignment of relevant bonds.[9] In the above observed rearrangements, the migrating bond was antiperiplanar to the leaving group ('sp^3 alignment factor'). To determine the likely conformation of type **5** common intermediates (**5a**, **5b**, **5cM** and **5cM**) a molecular mechanics study was performed using Allinger's MM3 force field and Still's Macromodel program[10] (since the effective bulk of lead triacetate is not easy to assess, consideration of the torsional and steric factors involved is done on its silicon analog). Examination of the results realized in examples **1a**, **1b** and **1c** provides insight into the operation of an apparent stereoelectronic control in product distribution and is supportive of the mechanistic reasoning advanced above. The outcome of the influence of the substitution pattern is rationalized in terms of the pre-transition state structures (before electrophilic attack of the metal on the C3–C4 double bond) depicted in Fig. 2.

With regard to the proposed mechanism,[11] the key transformation, which is triggered by an electrophilic attack of the metal on the electron rich double bond C3–C4 (the 1,3-dioxene part of the molecule), should set up the ring expansion process from **5a**. As a result of the configuration-control originating from

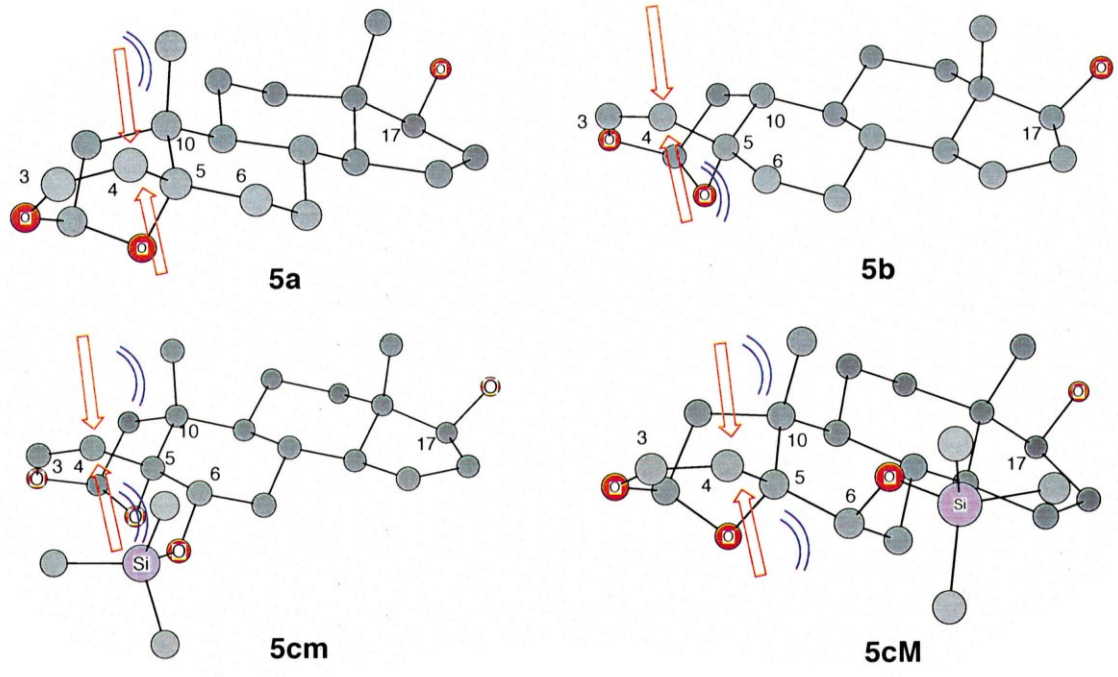


Figure 2. Lowest energy conformers of **5a**, **5b**, **5cm** and **5cM**, as determined by molecular mechanics calculations, used to rationalize the steric course of the electrophilic attack of Pb^{4+} on the C3–C4 olefin

the angular methyl group Me-19, the organolead intermediate has the C10–C5 bond in a *trans* coplanar arrangement to the carbon–lead bond, which is most likely to migrate. The formation of **4** in the 19-nor-steroid series, via **5b**, could be rationalized by the generation of an organolead intermediate on the more accessible β-face of the C3–C4 olefin. The C5–oxygen bond is perfectly aligned for a backside colinear displacement on such an intermediate while the C5–C10 bond cannot assume geometry favorable to the migration. The results are consistent with the above mechanistic rationale. That is, depending on the substitution pattern at C-10, which controls the stereochemistry of the key step, the rearrangement products arise via backside attack of the migrating bond on the C-4 carbon, bearing the lead triacetate group. Furthermore, either top or bottom face substitution at C-6 inhibits electrophilic attack by the metal on the C3–C4 olefin (the key step), thus stopping the transformations on the 'half-cascade' level.

4. Conclusion

Lack of an angular methyl substitution at C-10 led to a different cascade transformation, in complete agreement with the influence of the bond alignment of the migrating and leaving groups (bond C10–C5 migration versus bond C5–O migration). The path is predictably determined by geometry in the reactant (bond alignment factor), which in turn depends on the substitution pattern of the substrates investigated. Allylic substitution at C-6, either α- or β-, led to an incomplete cascade transformation due to steric interactions between both the α- or β-trimethylsyliloxy substituents and the attacking metal. We are currently in the process of further investigation of this reaction sequence and its extension to other systems.

5. Experimental

5.1. General

Experimental details were as previously described.[12] NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform, unless otherwise noted. NMR experiments (800 MHz) were carried out on a Bruker Avance DRX-800 spectrometer, equipped with a triple resonance H/C/N probehead and a three-axis pulsed field gradient module. Gradients were used for the coherence transfer pathway selection in HMBC and HMQC experiments. In the latter, broadband decoupling was performed by using adiabatic WURST-40 pulses. For the proof of stereochemistry of investigated products we carried out an elaborate series of nuclear Overhauser enhancement (NOE) experiments using difference spectra, in order to establish the configuration of the key centers in the target products. 'Usual work up' means washing of the organic layer with brine, drying over anhydrous magnesium sulfate, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Flash chromatographies were run on silica gel (230–400 mesh).

5.2. Preparation of the 19-nor substrates: the *1b* series and the interrupted cascade

The procedure previously described by us[2] was used to convert the known **7** to the C-2 acetoxy derivatives, obtained as an epimeric mixture (80%, ca. 1:1) which was directly reduced with lithium aluminum hydride in ether to give the desired unsaturated 1,2-diol **1b**. Placed in a flame dried flask, the target diol **1b** (630 mg, 1.5 mmol) and $Pb(OAc)_4$ (820 mg, 1.9 mmol) were vacuumed and flashed with argon, cooled to −20°C and 10 mL of acetonitrile were added. TLC control during 24 h room temperature stirring indicated total consumption of the starting diol and appearance of a higher spot corresponding to the product of the half-cascade **5b** together with another one of lower R_f corresponding to the dialdehyde. The A-nor-steroid thus obtained was purified by chromatography (heptane:EtOAc, 10:1 to 3:1) to afford 250 mg (40%) of **5b** along with the dialdehyde resulting from the oxidative cleavage, which does not give cycloaddition but rather tends to isomerize and decompose on standing. Compound **5b**: $[\alpha]_D$ +56.5 (*c* 1.45, $CHCl_3$). IR (film): 2954, 2928, 2857, 1637, 1471, 1248, 1214, 1139, 1089, 1073, 1022, 944, 898, 876, 836, 776 cm^{-1}. ^1H NMR (250 MHz): 0.01 (6H, s), 0.73 (3H, s), 0.88 (9H, s), 0.62–1.74 (13H, m), 1.85–1.98 (3H, m), 2.14–2.23 (1H, m), 2.45 (1H, dd, *J*=7.6, 14.0), 3.55 (1H, dd, *J*=7.8, 8.6), 4.84 (1H, d, *J*=6.0), 5.69 (1H, d, *J*=5.5), 6.17 (1H, d, *J*=6.0). ^{13}C NMR (62.9 MHz): −4.8, −4.5, 11.3, 18.1, 23.3, 25.2, 25.8 (3C), 26.2, 30.9, 31.5, 37.0, 39.2, 41.2, 43.7, 46.3, 49.2, 53.8, 80.3, 81.7, 100.1, 111.7, 139.9. CIMS: 405 ($[MH]^+$, 100), 361 (13), 273 (8), 146 (10), 117 (6), 73 (27). HRCIMS: calcd for $C_{24}H_{41}O_3Si$ m/z 405.2825, found 405.2829.

5.3. One-pot preparation of nor-steroidal acetoxy acetals *4*, *11* and *12* from *1b*: the C-10 modulated full-cascade transformations

Using acetic acid as solvent: to a flame dried flask containing 1.22 g (3.0 mmol) of diol **1b** and 4.00 g (9.0 mmol, 3 molar equiv.) of $Pb(OAc)_4$, evacuated and flashed with argon, were added 15 mL of dry and degassed acetic acid at room temperature. After 15 h of stirring, the reaction mixture was diluted with ethyl acetate, washed with aqueous saturated $NaHCO_3$ and worked up as usual. Chromatography (heptane:ethyl acetate, 6:1) afforded 652 mg (47%) of the rearranged compound **4** together with 25% of dialdehyde.

Using acetonitrile as solvent: to a flame dried flask containing 350 mg (0.86 mmol) of diol **1b** and 840 mg (1.89 mmol, 2.2 molar equiv.) of $Pb(OAc)_4$, vacuumed and flashed with argon, were added 5 mL of dry acetonitrile at 0°C. The mixture was stirred at room temperature for 30 h, diluted with ether and filtered through Celite. The residue was purified on silica gel (heptane:EtOAc, 6:1) to yield 59 mg (17%) of **5b** along with 139 mg (35%) of **4** and 98 mg (28%) of dialdehyde resulting from the oxidative cleavage. Compound **4**: mp 119–121°C (CH_2Cl_2–EtOH). $[\alpha]_D$ −41.7 (*c* 1.99, $CHCl_3$). IR (film): 2953, 2928, 2857, 1747, 1675, 1366, 1238, 1139, 1126, 1091, 1039, 1025, 985, 877, 835, 775 cm^{-1}. ^1H NMR (300 MHz): 0.01 (6H, s), 0.73 (3H, s), 0.87 (9H, s), 0.80–1.80 (13H, m), 1.82–1.94 (1H, m), 2.04–2.18 (1H, m), 2.10 (3H, s), 2.38–2.52 (1H, m), 3.57 (1H, t, *J*=7.8), 4.60 (1H, d, *J*=3.7), 5.57 (2H, bs), 6.03 (1H, d, *J*=3.7). ^{13}C NMR (75 MHz): −4.8, −4.5, 11.2, 18.1, 21.1, 23.2, 25.5, 25.8 (3C), 30.4, 30.7, 35.6, 36.7 (2C), 37.0, 43.3, 45.0, 50.0, 79.5, 81.7, 96.0, 103.0, 126.0, 132.4, 169.9. CIMS: 403 ($[MH]^+$–AcOH, 100), 359 (13), 289 (6), 271 (12), 133 (5), 73 (10).

Using acetic $acid_{D4}$ as solvent (deuterium labeling experiment): to a flask charged with **1b** (167 mg, 0.41 mmol) and $Pb(OAc)_4$ (546 mg, 1.20 mmol, 3 molar equiv.), vacuumed and flashed with argon, was added 4 mL of CD_3CO_2D and the mixture was stirred under argon for 14 h at room temperature. Purification by chromatography (heptane:EtOAc, from 10:1 to 3:1) afforded 74 mg (39%) of the deuterium labeled A-nor-steroid **11a**. Similarly, the half-cascade intermediate **5b** (292 mg, 0.70 mmol) when treated with $Pb(OAc)_4$ (960 mg, 2.2 mmol, 3 molar equiv.) in 5 mL of CD_3CO_2D afforded 168 mg (50% isolated yield) of **11a**: $[\alpha]_D$ −39.3 (*c* 1.95, $CHCl_3$). IR (film): 3058, 2954, 1754, 1472, 1434, 1387, 1360, 1332, 1251, 1138, 1089, 1034, 1007, 987, 968, 878, 836, 774, 739, 704, 668 cm^{-1}. ^1H NMR (300 MHz): 0.00 (3H, s), 0.01 (3H, s), 0.73 (3H, s), 0.88 (9H, s), 0.62–1.78 (12H, m), 1.83–1.93 (1H, m), 2.03–2.17 (2H, m), 2.39–2.45 (1H, m), 3.58 (1H, dd, *J*=8.0, 8.4), 4.60 (1H, d, *J*=4.0), 5.59 (2H, bs), 6.03 (1H, d, *J*=4.0). ^{13}C NMR (75 MHz): −4.9, −4.5, 11.2, 18.1, 23.2, 25.6, 25.8 (3C), 30.4, 30.7, 35.6, 36.7, 36.8, 37.0, 43.4, 45.1, 50.0, 79.5, 81.7, 96.0, 103.0, 126.0, 132.4, 169.9. CIMS: 466 ($[MH]^+$, 11), 403 (100), 391 (8), 374 (10), 146 (13), 117 (11), 73 (30). TBS removal at C-17 was then carried out as follows. To a magnetically stirred solution of **11a** (35 mg, 0.075 mmol) in 3 mL of acetonitrile at 0°C was added 0.1 mL of aqueous 40% HF. Stirring was continued at 0°C for 1 h, then quenching with a saturated solution of sodium bicarbonate, extraction with ethyl acetate and usual work up furnished 25 mg (95%) of **11b**: mp 128–130°C (ether–heptane). $[\alpha]_D$ −49.0 (*c* 0.93, $CHCl_3$). IR (film): 3255, 2924, 2854, 1759, 1678, 1461, 1364, 1230, 1132, 1070, 1031, 1004, 992, 964, 951, 882, 851, 816 cm^{-1}. ^1H NMR (800 MHz): 0.69 (3H, s, Me-13), 0.87 (1H, dc, *J*=4.6, 10.6, H-9), 0.93 (1H, dt, *J*=7.2, 11.8, H-14), 1.03 (1H, dt, *J*=3.9, 12.9, H-12ax), 1.10 (1H, dc, *J*=3.9, 13.0, H-11ax), 1.21 (1H, dc, *J*=6.0, 12.3, H-15ax), 1.26–1.31 (2H, m, H-8, H-1ax), 1.35–1.40 (1H, m, H-16ax), 1.50–1.54 (1H, m, H-15eq), 1.57–1.61 (1H, m, H-7ax), 1.65 (1H, ddd, *J*=3.9, 7.3, 13.3, H-11eq), 1.73 (1H, td, *J*=3.4, 12.5, H-12eq), 1.95–2.03 (2H, m, H-7eq, H-16eq), 2.01 (3H, s, OCOMe), 2.05 (1H, dd, *J*=1.8, 7.1, H-1eq), 2.34–2.40 (1H, m, H-10), 3.58 (1H, t, *J*=8.7, H-17), 4.52 (1H, d, *J*=4.2, H-4), 5.50–5.52 (2H, bs, H-2, H-6), 5.96 (1H, d, *J*=4.2, H-3). ^{13}C NMR (75 MHz): 10.9, 23.1, 25.5, 30.3 (2C), 35.6, 36.2, 36.7, 36.9, 43.0, 44.9, 50.3, 79.5, 81.7, 95.9, 103.0, 125.9, 132.4, 187.7. CIMS: 369 ($[MNH_4]^+$, 100), 184 (6), 152 (14), 118 (13), 105 (9), 88 (17), 52 (99), 35 (99).

Using (*S*)-*O*-acetyllactic acid as solvent: proceeding as above, 745 mg (1.83 mmol) of **1b** were treated with 2.44 g (5.5 mmol, 3 molar equiv.) of $Pb(OAc)_4$, in 10 mL of (*S*)-*O*-acetyllactic acid. After stirring at room temperature for 13 h the reaction mixture was worked up as above and purified by chromatography using heptane:ethyl acetate, 6:1 to 1:1, as eluent. The crude residue afforded 28 mg (3%) of **4** and 393 mg (40%) of **12**: $[\alpha]_D$ −61.4 (*c* 1.14, $CHCl_3$). IR (film): 2954, 1749, 1472, 1372, 1249, 1103, 1046, 1027, 1008, 985, 905, 879, 836, 758 cm^{-1}. ^1H NMR (300 MHz): 0.00 (3H, s), 0.01 (3H, s), 0.71 (3H, s), 0.78–1.63 (8H, m), 0.87 (9H, s), 1.45 (3H, d, *J*=7.1), 1.64–1.78 (3H, m), 1.82–1.95 (1H, m), 1.97–2.20

(1H, m), 2.06–2.19 (2H, m), 2.11 (3H, s), 2.35–2.47 (1H, m), 3.56 (1H, t, *J*=8.1), 4.65 (1H, d, *J*=3.9), 5.14 (1H, q, *J*=7.1), 5.55–5.63 (2H, m), 6.03 (1H, d, *J*=3.9). ^{13}C NMR (75 MHz): −4.9, −4.6, 11.1, 16.6, 18.0, 20.5, 23.2, 25.6, 25.8 (3C), 30.3, 30.7, 35.5, 36.6 (2C), 36.7, 43.3, 44.9, 49.9, 67.9, 79.6, 81.6, 97.1, 103.2, 126.4, 132.0, 169.5, 169.9. CIMS: 535 ([MH]$^+$, 6), 403 (100), 385 (9), 375 (10), 361 (11), 349 (8), 133 (99).

*5.4. Preparation of the X-ray sample **9***

This compound was obtained by desilylation–esterification of the corresponding A-nor-steroid framework **4**. The deprotection was effected as follows. To a stirred solution of **4** (303 mg, 0.65 mmol) in acetonitrile (16 mL) was added 0.3 mL of aqueous 40% HF. The resulting solution was stirred at 0°C for 1 h (TLC monitoring). It was then poured into a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. Usual work up afforded a crude residue which was purified on silica eluting with heptane:EtOAc, 2:1. This afforded 194 mg (85%) of **8** as a white solid: mp 129–131°C (ether–heptane–EtOAc). $[\alpha]_D$ −53.1 (*c* 0.89, $CHCl_3$). IR (nujol): 3259, 2925, 1765, 1434, 1365, 1217, 1129, 991, 880, 853, 812, 758 cm^{-1}. ^{1}H NMR (800 MHz): 0.69 (3H, s, Me-13), 0.87 (1H, dq, *J*=4.6, 10.6, H-9), 0.93 (1H, dt, *J*=7.2, 11.8, H-14), 1.03 (1H, dt, *J*=3.9, 12.9, H-12ax), 1.10 (1H, dq, *J*=3.9, 13.0, H-11ax), 1.21 (1H, dq, *J*=6.0, 12.3, H-15ax), 1.26–1.31 (2H, m, H-8, H-1ax), 1.35–1.40 (1H, m, H-16ax), 1.50–1.54 (1H, m, H-15eq), 1.57–1.61 (1H, m, H-7ax), 1.65 (1H, ddd, *J*=3.9, 7.3, 13.3, H-11eq), 1.73 (1H, td, *J*=3.4, 12.5, H-12eq), 1.95–2.03 (2H, m, H-7eq, H-16eq), 2.01 (3H, s, OCOMe), 2.05 (1H, dd, *J*=1.8, 7.1, H-1eq), 2.34–2.40 (1H, m, H-10), 3.58 (1H, t, *J*=8.7, H-17), 4.52 (1H, d, *J*=4.2, H-4), 5.50–5.52 (2H, bs, H-2, H-6), 5.96 (1H, d, *J*=4.2, H-3). ^{13}C NMR (200 MHz): 10.9 (Me-13), 21.0 (OCO*Me*), 23.0 (C-15), 25.4 (C-11), 30.2 (C-7), 30.3 (C-16), 35.5 (C-10), 36.1 (C-12), 36.6 (C-8), 36.9 (C-1), 43.0 (C-13), 44.8 (C-9), 50.3 (C-14), 79.4 (C-4), 81.6 (C-17), 95.9 (C-3), 103.0 (C-2), 125.9 (C-6), 132.3 (C-5), 169.9 (O*CO*Me). CIMS: 289 ([MH]$^+$–AcOH, 100), 271 (17), 245 (13), 146 (8), 100 (16), 73 (26). Anal. calcd for $C_{20}H_{28}O_5 \cdot 0.55H_2O$: C, 67.04; H, 8.19; found: C, 67.06; H, 7.97.

To a stirred solution of **8** (53 mg, 0.15 mmol) in dry pyridine (2 mL) at 0°C was added a catalytic amount of DMAP. After 10 min of stirring, addition of an excess of *p*-BrBzCl (66 mg, 0.30 mmol) followed and stirring continued overnight at room temperature. The reaction mixture was then poured into an equal volume of ice cooled water and extracted with DCM. The combined organic extracts were washed with 1N HCl, saturated aqueous solution of sodium hydrogen carbonate and brine, dried (magnesium sulfate) and concentrated in vacuo. The residue was then purified on silica eluting with 3:1 to 1:1 heptane:EtOAc. This afforded **9**, as a white solid (92% yield based on recovered starting material). Compound **9**: mp 136–138°C (ether–heptane). $[\alpha]_D$ −10.8 (*c* 1.57, $CHCl_3$). IR (film): 2922, 1740, 1717, 1591, 1484, 1397, 1274, 1173, 1126, 1070, 1042, 1012, 986, 881, 851, 812, 759, 737, 704 cm^{-1}. ^{1}H NMR (800 MHz): 0.97 (3H, s), 1.02 (1H, dq, *J*=4.5, 10.6), 1.17–1.23 (2H, m), 1.30 (1H, dt, *J*=4.1, 13.4), 1.38–1.47 (3H, m), 1.65–1.69 (1H, m), 1.71–1.77 (3H, m), 1.84 (1H, td, *J*=3.3, 12.9), 2.12 (3H, s), 2.11–2.16 (2H, m), 2.30–2.35 (1H, m), 2.46–2.51 (1H, m), 4.63 (1H, d, *J*=4.0), 4.86 (1H, dd, *J*=7.9, 9.2), 5.60 (1H, t, *J*=1.7), 5.62 (1H, dd, *J*=2.3, 5.1), 6.06 (1H, d, *J*=4.0), 7.58 (2H, d, *J*=8.6), 7.90 (2H, d, *J*=8.6). ^{13}C NMR (75 MHz): 12.2, 21.1, 23.3, 25.3, 27.5, 30.3, 35.5, 36.4, 36.5, 36.9, 43.1, 44.7, 50.1, 79.4, 83.4, 95.9, 103.0, 125.7, 127.8, 129.6, 131.0 (2C), 131.6 (2C), 132.4, 165.7, 169.8. CIMS: 533 ([MH]$^+$, 5), 531 ([MH]$^+$, 5), 474 (9), 473 (33), 472 (9), 471 (32), 453 (12), 393 (84), 271 (100), 243 (29), 181 (17), 146 (13), 139 (17), 123 (91).

X-Ray structure determination of **9**: $BrC_{27}H_{31}O_6$, Mr=531.43, monoclinic, $P2_1$, *a*=8.596(2), *b*=7.809(2), *c*=37.848(9) Å, β=90.80(2)°, *V*=2541(1) Å^{-3}, *Z*=4, D_x=1.657 Mg m^{-3}, λ(MoKα)=0.71073 Å, μ=16.57 cm^{-1}, *F*(000)=1104, *T*=293 K. The sample (0.28×0.20×0.15 mm) was studied on an

automatic diffractometer CAD4 NONIUS with graphite monochromated MoKα radiation.[13] The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$=54°, scan ω/2θ=1, t_{max}=60 s, range HKL: H 0,10 K 0,9 L −45,45, intensity controls without appreciable decay (1.2%) gave 6268 reflections of which 5886 were independent (2524 with $I>2.0\sigma(I)$). After Lorenz and polarization corrections[14] the structure was solved with SIR-97[15] which reveals the non-hydrogen atoms of the structure. After anisotropic refinement, all the hydrogen atoms were found with a Fourier difference. The whole structure was refined with SHELXL97[16] by the full-matrix least-square techniques (use of F magnitude; x, y, z, β_{ij} for Br, C, and O atoms, x, y, z in riding mode for H atoms; 614 variables and 5886 observations; calcd $w=1/[\sigma^2(Fo^2)+(0.1499P)^2 +0.0040P]$ where $P=(Fo^2+2Fc^2)/3$ with the resulting R=0.077, R_w=0.194 and S_w=1.001 (residual $\Delta\rho$=0.93 eÅ^{-3})). Absolute configuration verified with the Flack parameter[17] 0(2). Atomic scattering factors from the *International Tables for X-ray Crystallography*.[18] Ortep views realized with PLATON98.[19] All the calculations were performed on a Silicon Graphics Indy computer.

5.5. Preparation of the A-seco-steroid **10**

Compound **4** (162.5 mg, 0.35 mmol) was reduced with excess of $LiAlH_4$ (70 mg) in 7 mL of THF (5 h, from 0°C to room temperature). Proceeding as above, after quenching and filtration on SiO_2 (eluent: EtOAc) the crude was directly acetylated under usual conditions as follows. To a stirred solution of the crude triol in 2 mL of pyridine and 0.05 molar equiv. of DMAP was added 5 molar equiv. of acetic anhydride. The reaction mixture was stirred at 0°C for 2 h. After completion (TLC monitoring) saturated aqueous sodium bicarbonate was added and the reaction mixture was extracted with dichloromethane. Washings with 1N HCl, then $NaHCO_3$, usual work up and chromatography, using heptane:EtOAc, 4:1, as eluent, furnished 156 mg (95%) of **10**: $[\alpha]_D$ +45.0 (*c* 1.81, $CHCl_3$). IR (film): 2956, 2857, 1743, 1658, 1471, 1368, 1243, 1142, 1098, 1044, 943, 904, 873, 837, 776 cm^{-1}. ^{1}H NMR (800 MHz): −0.01 (3H, s), 0.00 (3H, s), 0.72 (3H, s, Me-18), 0.88 (9H, s, *t*-Bu), 0.92–0.96 (1H, m, H-14), 1.02–1.07 (2H, m, H-9, H-12), 1.17–1.29 (3H, m, H-8, H-11, H-15), 1.42–1.47 (1H, m, H-16), 1.49–1.56 (2H, m, H-7, H-15), 1.76 (1H, td, *J*=3.2, 12.6, H-12), 1.85–1.91 (2H, m, H-11, H-16), 1.98–2.03 (3H, m, 2 H-1, H-7), 2.03 (3H, s, *Me*CO), 2.05 (3H, s, *Me*CO), 2.06 (3H, s, *Me*CO), 2.16–2.18 (1H, m, H-10), 3.56 (1H, t, *J*=8.4, H-17), 3.92–3.96 (1H, m, H-2), 4.03–4.07 (1H, m, H-2), 4.19 (1H, dd, *J*=8.6, 11.8, H-3), 4.31 (1H, dd, *J*=3.7, 11.8, H-3), 5.51 (1H, dd, *J*=3.7, 8.6, H-4), 5.97 (1H, dd, *J*=1.8, 6.8, H-6). ^{13}C NMR (200 MHz): −4.9 (Me), −4.6 (Me), 11.2 (Me-18), 18.0 (Cq, TBS), 20.7 (*Me*CO), 20.9 (*Me*CO), 21.1 (*Me*CO), 23.2 (C-15), 25.8 (3C, *t*-Bu), 26.9 (C-11), 27.9 (C-1), 30.0 (C-7), 30.8 (C-16), 36.7 (C-8), 36.8 (C-12), 40.5 (C-10), 43.0 (C-9), 43.3 (C-13), 49.9 (C-14), 61.6 (C-2), 64.4 (C-3), 72.5 (C-4), 81.6 (C-17), 130.0 (C-6), 135.2 (C-5), 170.3 (Me*CO*), 170.6 (Me*CO*), 171.0 (Me*CO*). CIMS: 568 ($[MNH_4]^+$, 100), 510 (36), 452 (9), 241 (7), 192 (23), 184 (9), 152 (11), 132 (5), 118 (16), 88 (10), 77 (9). Anal. calcd for $C_{30}H_{50}O_7Si$: C, 65.42; H, 9.15; found: C, 65.72; H, 9.11.

5.6. Preparation and cascade type reactions of the allylically substituted substrates: the **1c** series

Starting from the known C-2β acetoxy enone **13**, obtained as previously described by us,[2] the required C-6 hydroxylated diol **1c** was synthesized in four straightforward steps as follows. To a magnetically stirred solution of acetoxy enone **13** (3.145 g, 7.82 mmol) and DMAP (521 mg, 4.26 mmol) in pyridine (12 mL), acetic anhydride (12 mL, 108 mmol) was added at 0°C. The reaction mixture was allowed to reach room temperature, then heated at 100°C for 27 h, after which solvent was removed under reduced pressure. Usual work up gave after silica gel chromatography (using heptane:EtOAc, 8:1 to 3:1, as eluent)

2.39 g (69%) of the desired dienol acetate **14** along with unreacted starting material (21%). Compound **14**: mp: 146–149°C (heptane–ether). $[\alpha]_D$ −194 (*c* 0.83, $CHCl_3$). IR (film): 2973, 2935, 2908, 2838, 1756, 1736, 1633, 1457, 1432, 1369, 1238, 1209, 1199, 1131, 1072, 1040, 1009, 987, 923 cm^{-1}. ^1H NMR (300 MHz): 0.74 (3H, s), 0.71–2.23 (15H, m), 1.13 (9H, s), 1.16 (3H, s), 2.06 (3H, s), 2.12 (3H, s), 3.38 (1H, t, *J*=8.2), 5.55–5.56 (2H, m), 5.93 (1H, s). ^{13}C NMR (75 MHz): 11.6, 20.8, 20.9, 21.2 (2C), 23.7, 28.7 (3C), 31.1, 31.4, 31.5, 34.4, 36.9, 39.8, 42.4, 48.4, 51.3, 67.2, 72.2, 80.7, 122.7, 127.5, 138.7, 142.0, 169.4, 170.8. CIMS: 462 ($[MNH_4]^+$, 12), 436 (9), 402 (21), 385 (100), 343 (36).

Installation of the C-6 hydroxy group was then carried out using methyltrioxorhenium developed by the Herrmann group.[6] To a stirred solution of dienol acetate **14** (1.815 g, 4.09 mmol) in 4.0 mL of CH_2Cl_2, pyridine (0.04 mL, 0.49 mmol), 30% H_2O_2 (0.63 mL, 6.14 mmol) and $MeReO_3$ (5.0 mg, 0.02 mmol) were added and the reaction mixture stirred under argon at room temperature for 26 h. Upon dilution with CH_2Cl_2, and washings with $Na_2S_2O_3$ and brine, the organic layers were dried, concentrated and chromatographed (SiO_2, heptane:EtOAc, 6:1 to 1:1) to afford 1.214 g (71% yield) of **15Mm** as an epimeric mixture at C-6 (approximately 4:1, major:minor, β/α ratio), along with unreacted starting material. Compound **15M**: IR (film): 3468, 2968, 2938, 2869, 1747, 1695, 1614, 1450, 1363, 1232, 1198, 1078, 895 cm^{-1}. ^1H NMR (300 MHz): 0.78 (3H, s), 0.72–2.34 (16H, m), 1.14 (9H, s), 1.40 (3H, s), 2.13 (3H, s), 3.36 (1H, dd, *J*=7.5, 8.7), 4.47 (1H, t, *J*=2.8), 5.24 (1H, dd, *J*=5.0, 11.2), 5.85 (1H, s). ^{13}C NMR (75 MHz): 11.7, 20.9, 21.8, 23.7, 24.0, 28.7 (3C), 30.4, 31.1, 36.8, 37.7, 38.5, 40.5, 42.6, 50.2, 51.5, 70.4, 72.3, 74.1, 80.5, 122.3, 170.2 (2C), 194.2. CIMS: 419 ($[MH]^+$, 100), 401 (21), 377 (16), 359 (64), 341 (11). It should be pointed out that, if the reaction is quenched after only 1 h, the 5,6-epoxide is isolated in 45% yield along with an equal amount of recovered starting material.

Protection of the C-6 hydroxy group was performed without separation of the major and minor isomers as follows. To a stirring solution of the epimeric mixture **15Mm** (1.214 g, 2.90 mmol) in dry toluene (30 mL) were added collidine (7.7 mL, 58.1 mmol) and TMSOTf (trimethylsilyl trifluoromethane sulfonate, 4 mL, 21.80 mmol) at −40°C. Stirring at this temperature continued for 30 min, after which time the reaction mixture was diluted by addition of heptane (250 mL). Washing with 1N HCl, then a saturated aqueous solution of $NaHCO_3$ and usual work up, afforded upon purification on silica gel, using heptane:EtOAc, 1:6, as eluent, 1.335 g (94%) of **16Mm** (only the major isomer is described): IR (film): 2970, 2873, 2852, 1751, 1700, 1618, 1457, 1252, 1086, 1064, 944, 908, 843, 736 cm^{-1}. ^1H NMR (300 MHz): 0.10 (9H, s), 0.79 (3H, s), 0.80–2.10 (15H, m), 1.13 (9H, s), 1.33 (3H, s), 2.15 (3H, s), 3.37 (1H, t, *J*=8.1), 4.38 (1H, t, *J*=2.8), 5.26 (1H, dd, *J*=5.1, 12.4), 5.80 (1H, s). ^{13}C NMR (50 MHz): 0.04 (3C), 11.7, 20.9, 21.9, 23.7, 24.1, 28.7 (3C), 30.5, 31.0, 36.8, 38.1, 41.1, 42.1, 42.7, 50.2, 51.2, 70.4, 72.2, 74.4, 80.5, 121.2, 170.2, 170.5, 194.3. CIMS: 491 ($[MH]^+$, 100), 431 (83), 413 (71), 341 (65), 91 (20).

The key intermediate **1cMm** was then obtained straightforwardly by reducing the C-6 epimeric mixture **16Mm**, via standard literature procedures. Lithium aluminum hydride (380 mg, 10 mmol) was suspended in dry ether (120 mL) and the mixture cooled to 0°C. The diastereomeric mixture of **16Mm** (1.162 g, 2.37 mmol) in dry ether (100 mL) was added slowly, and stirring continued for 30 min at 0°C. The reaction mixture was then diluted with technical ether, a few drops of water were added and the mixture stirred at room temperature for 30 min. The crude reaction mixture was filtered through silica (some washings of the silica with ethyl acetate may be necessary for maximum recovery) and the filtrate concentrated under reduced pressure to give the target diol **1cMm**, nearly quantitatively (1.16 g), as an epimeric mixture at C-6, which was taken as such for the next step. For characterization purposes only, a small quantity of the above mixture was purified on silica gel affording pure **1cM** (6-β-OTMS): mp: 169–171°C (heptane–ether). $[\alpha]_D$ −44.7 (*c* 1.04, $CHCl_3$). IR (film): 3381, 2957, 2933, 2873, 2848, 1458, 1389, 1361, 1250, 1198, 1165, 1122, 1083, 1056, 951, 864, 840, 744 cm^{-1}. ^1H NMR (300 MHz): 0.05 (9H, s), 0.74 (3H, s), 0.71–1.86 (17H, m), 1.10 (9H, s), 1.24 (3H, s), 3.32 (1H, dd, *J*=7.8, 8.5), 3.81 (1H, bs), 4.02

(1H, bs), 4.17 (1H, t, *J*=2.7), 5.37 (1H, d, *J*=3.8). ^{13}C NMR (75 MHz): 0.3 (3C), 11.8, 21.0, 23.7, 23.8, 28.7 (3C), 30.3, 31.1, 37.1, 38.0, 40.1, 41.3, 42.6, 50.6, 54.1, 67.1, 67.3, 72.1, 74.6, 80.8, 121.4, 149.7. CIMS: 451 ([MH]$^+$, 4), 433 (100), 415 (16), 361 (38), 343 (87), 287 (18), 269 (8), 91 (14).

To a flask charged with **1c** (246 mg, 0.55 mmol) and $Pb(OAc)_4$ (484 mg, 1.10 mmol, 2 molar equiv.), vacuumed and flashed with argon, was added 5.0 mL of dry acetonitrile and the mixture was stirred under argon for 4 h at −30°C then 24 h at room temperature. Dilution with acetonitrile, filtration through a pad of Celite and $MgSO_4$ using heptane:ether, 1:1, evaporation to dryness and filtration through silica (heptane:EtOAc, 12:1) afforded, by order of elution, 186 mg (76%) of **5cM**, 6-β-OTMS containing major isomer, along with 47 mg (19%) of **5cm** (6-α-OTMS). Increasing the reaction temperature resulted in a slight decrease in chemical yield with no evidence of significant alteration in the product composition. Thus, the same reaction, repeated in refluxing acetonitrile for 24 h, afforded a similar result although the reaction crude was somewhat sluggish. Changing the solvent showed only marginal effects on the reaction rate and chemical yield. When the reaction was carried out in acetic acid at room temperature for 24 h and then heating at 40°C for 4.5 h, 64% of **5cM** (only major) was obtained, the minor stereoisomer being destroyed. Compound **5cM**: mp 113–114°C (heptane–ether). $[\alpha]_D$ +1.8 (*c* 1.61, THF). IR (film): 3074, 2972, 2872, 1631, 1444, 1389, 1361, 1251, 1201, 1149, 1109, 1067, 953, 940, 860, 842, 734 cm^{-1}. ^{1}H NMR (300 MHz): 0.12 (9H, s), 0.75 (3H, s), 0.87–1.67 (11H, m), 1.11 (3H, s), 1.13 (9H, s), 1.77 (1H, td, *J*=3.3, 12.3), 1.82–1.95 (1H, m), 1.86 (1H, dd, *J*=0.9, 13.9), 2.17 (1H, dd, *J*=5.8, 13.9), 3.36 (1H, dd, *J*=7.9, 8.5), 3.99 (1H, t, *J*=2.7), 5.27 (1H, d, *J*=6.2), 5.55 (1H, d, *J*=5.6), 6.24 (1H, d, *J*=6.2). ^{13}C NMR (75 MHz): 0.2 (3C), 11.6, 14.9, 21.3, 23.7, 28.7 (3C), 29.1, 31.2, 34.1, 37.4, 42.8, 47.8, 48.2, 50.1, 53.5, 69.2, 72.1, 80.8, 83.0, 99.4, 108.7, 139.2. CIMS: 449 ([MH]$^+$, 100), 431 (16), 377 (20), 375 (20), 146 (27). Anal. calcd for $C_{26}H_{44}O_4Si$: C, 69.59; H, 9.88; found: C, 69.84; H, 10.03. Compound **5cm**: $[\alpha]_D$ +11.3 (*c* 0.67). IR (film): 3077, 2970, 2873, 1735, 1634, 1450, 1390, 1361, 1251, 1202, 1108, 1095, 1069, 1032, 974, 878, 841, 734 cm^{-1}. ^{1}H NMR (300 MHz): 0.13 (9H, s), 0.72 (3H, s), 0.75–1.65 (11H, m), 1.07 (3H, s), 1.13 (9H, s), 1.76 (1H, td, *J*=3.3, 12.3), 1.84–1.94 (1H, m), 1.90 (1H, dd, *J*=1.2, 13.9), 2.17 (1H, dd, *J*=5.8, 13.8), 3.37 (1H, dd, *J*=7.7, 8.7), 3.59 (1H, dd, *J*=4.7, 11.3), 4.82 (1H, d, *J*=6.2), 5.60 (1H, d, *J*=5.4), 6.25 (1H, d, *J*=6.2). ^{13}C NMR (75 MHz): 0.5 (3C), 11.7, 14.1, 21.4, 23.7, 28.7 (3C), 31.2, 34.9, 35.2, 37.1, 42.6, 47.2, 47.6, 50.2, 56.0, 71.1, 72.2, 80.6, 85.4, 99.4, 109.1, 139.9. CIMS: 449 ([MH]$^+$, 100), 391 (11), 377 (11), 359 (10), 315 (8). HRCIMS: calcd for $C_{26}H_{45}O_4Si$ m/z 449.3087, found 449.3091.

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