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Modified steroids: $Pb(OAc)_4$ mediated one-pot multistage transformations of steroidal unsaturated 1,2-diols

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Abstract

Lead tetraacetate treatment of steroidal 1,2-unsaturated diols provided a convenient route to molecules possessing functionalities that are appropriate for the synthesis of a great variety of skeleton modified steroids, such as A-nor or A-nor-B-homosteroids, which could present interesting biological activities. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Investigations into the relationship of structural changes to biological activity in the steroid series, started over 50 years ago, and numerous reports have described syntheses and structure–activity studies on A- and B-ring modified steroids.[1] Dihydrotestosterone, produced by the reduction of testosterone via a process catalyzed by the enzyme 5α-reductase, is believed to be involved in the progression of benign prostatic hyperplasia and to be a causative factor in acne and male-pattern baldness.[2] In search for agents that could lower levels of dihydrotestosterone, a number of modified steroids were synthesized, some of them exhibiting high antiandrogenic activity. Work targeting the inhibition of 5α-reductase, which is believed to be involved in several androgen dependent diseases, gave rise to useful drugs such as Proscar[3] (developed by Merck Sharp & Dohme) and Episteride[4] (developed by Smith Kline Beecham), both modified steroids with changes localized on the A-ring and on segments attached at the C-17 position of the steroid nucleus.

Earlier work from this laboratory has focused on one-pot multistage transformations[5] by treating selected unsaturated 1,2-diols with lead tetraacetate[6] in acetonitrile. This was found to initiate a ring expansion, giving rise to a new ring expansion/rearrangement methodology. The reaction involves an oxidative cleavage yielding the corresponding dialdehyde, which then undergoes a series of transformations affording, in one synthetic operation, ring-enlarged intermediates possessing functionalities that

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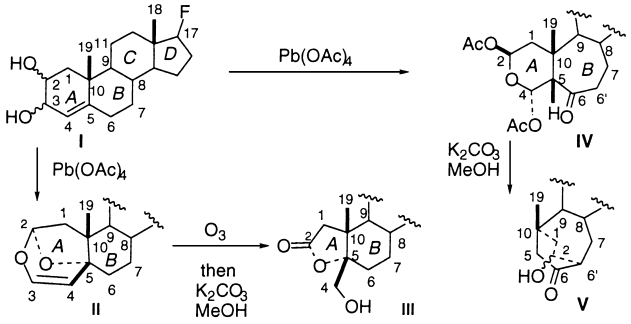
are appropriate for chemoselective elaboration. To examine further this new ring expansion process, first investigated with the unsaturated diols obtained from Hajos–Parrish[7] and Wieland–Miescher[8] ketones, the reaction of steroidal unsaturated 1,2-diols with $Pb(OAc)_4$ has been undertaken.[9] This should produce A-ring modified steroids (A-nor steroids of types **II** and **III**) via the interrupted cascade[10] and A-nor-B-homosteroids (of types **IV** and **V**) by way of ring-expanded intermediates based on the trend established in our previous work. The process was thus extended to type **I** steroidal diols (F stands for various functional groups) obtained from common steroids such as cholesterol, progesterone, testosterone and others.

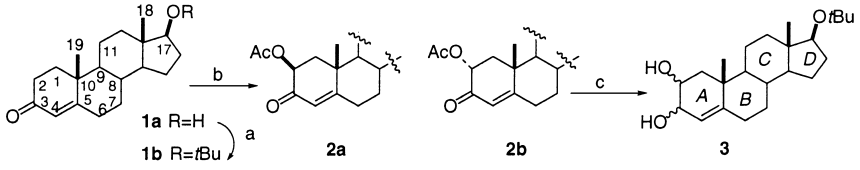
To illustrate its applicability we will present the results with testosterone as the starting material and describe in detail the preparation of A-nor and A-nor-B-homosteroids, **4**–**8**, **10** and **9**, and **11**–**14**, respectively. The modified steroids thus obtained (for the sake of comparison, the steroid numbering is retained in A-nor-steroids **II** and **III**, while an arbitrary, steroid-based numbering is used for the AB-ring modified steroids **IV** and **V**) allow scope for easy incorporation of oxygen or nitrogen atoms into the steroid A-ring for the synthesis of several substrates that could affect metabolism. Scheme 1 shows in concept the proposed studies.



Scheme 1. Cascade transformations on steroidal unsaturated diols; a concise route towards the A- (**II**, **III**) and AB-ring (**IV**, **V**) modified steroids

2. Results and discussion

The preparation of the requisite steroidal diol **3** was achieved straightforwardly from 17-O*t*Bu-protected testosterone **1b**, via its corresponding C-2 acetoxy derivative **2** according to the synthetic protocol in Scheme 2. Thus, **1b** was first converted to the corresponding acetoxyenone **2** using an improved lead tetraacetate oxidation protocol (excess of $Pb(OAc)_4$ in refluxing benzene),[11] which, on reaction with lithium aluminum hydride in ether, was reduced to the corresponding diol **3**, obtained as a diastereomeric mixture. Even though unnecessary for the following operation, acetoxyenones **2α** and **2β** were readily separated by silica gel flash chromatography for characterization purposes. Following reduction of **2** to **3**, the scope of the methodology was investigated as illustrated in Scheme 1.

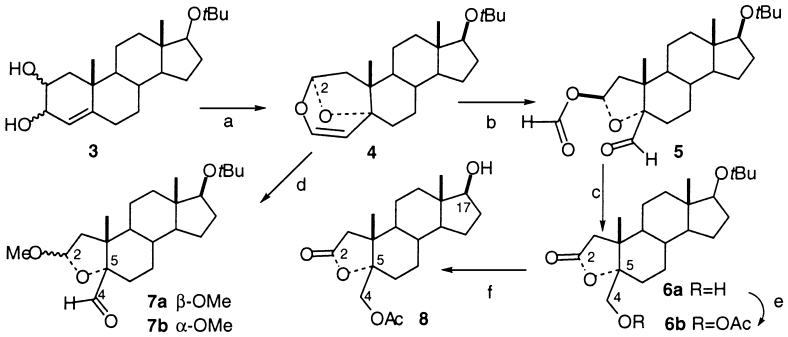


Scheme 2. (a) H^+, $CH_2{=}CMe_2$, CH_2Cl_2. (b) $Pb(OAc)_4$, PhH, reflux, 4 days. (c) $LiAlH_4$, Et_2O, 0°C, 30 min

First, the synthesis of A-homo steroid **4** was accomplished through a controlled (by limiting the amount of $Pb(OAc)_4$ to 1.1 equiv.) lead tetraacetate mediated oxidative cleavage. When 1 mmol of steroidal

unsaturated diol **3** was subjected to the glycol cleavage conditions[12] with 1.1 mmol of $Pb(OAc)_4$, in 5 ml of dry acetonitrile after 30 min stirring, a 98% isolated yield of the A-ring modified testosterone derivative **4** was obtained. The latter serves for the preparation of steroidal lactone **6**, obtained, in two steps, by direct analogy to our previous work on Wieland–Miescher ketone derived unsaturated diols.[10] Thus, introduction of ozone into a solution of the A-ring modified steroidal enol ether **4** in dry methylene chloride, followed by Me_2S mediated reductive workup, gave dicarbonyl species **5** in high yield. Formylacetal-aldehyde **5** thus obtained was then converted to steroidal lactone **6a**, upon mild base treatment (K_2CO_3–MeOH–H_2O, room temperature) via an intramolecular Cannizzaro type oxidoreduction.[13]

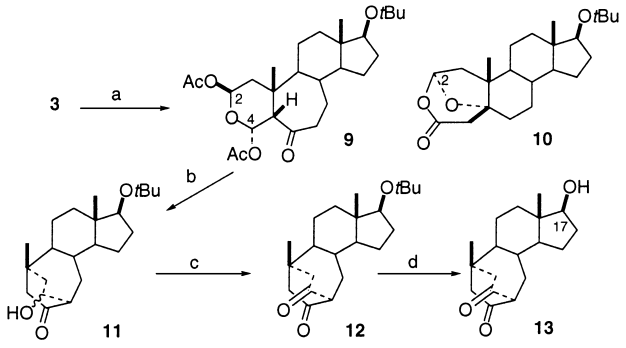
Lactone **6a** was acetylated using standard conditions to yield the corresponding acetate **6b** as the sole product. In our previous work on the Wieland–Miescher ketone derived analogues we proved that the γ-lactone, formed initially, rapidly converts to its corresponding δ-lactone product, by an intramolecular transesterification. It is noteworthy that, unlike the Wieland–Miescher ketone derived analogues, neither during acetylation nor upon acidic or basic treatments of **6a** was translactonization towards the 6-membered ring lactone with an angular hydroxy group (instead of the hydroxymethyl one) detected. Acetylation was useful in differentiating between the structure depicted in Scheme 3 and its translactonized form (not observed in these series).



Scheme 3. (a) 1.1 Equiv. $Pb(OAc)_4$, CH_3CN, −20°C to rt, 30 min. (b) O_3/CH_2Cl_2, −78°C, then Me_2S, −78°C to rt, 30 min. (c) K_2CO_3–MeOH–H_2O, rt. (d) O_3/MeOH, −78°C, Me_2S, −78°C to rt, 30 min, then MeOH. (e) Ac_2O, Py, DMAP, 0°C to rt. (f) $BF_3 \cdot OEt_2$, $PhCH_3$, 0°C to rt

Chemoselective deprotection of the *t*Bu protected C-17 hydroxy group by treatment of **6b** with $BF_3 \cdot OEt_2$ in toluene[14] secured access to the steroidal lactone **8** (98% isolated yield), offering possibilities for C-17 elaboration. On the other hand, carrying out ozonolysis in MeOH, at −78°C and stirring the crude product thus obtained with technical methanol (transacetalization) overnight, afforded a diastereomeric mixture of steroidal methyl furanosides **7a** (faster eluting isomer, 17%) and **7b** (slower eluting isomer, 75%) in a ca 1:4.4 ratio. Next, the one-pot **3** to **9** transformation was examined (Scheme 4). Steroidal diol **3** was treated with 2 equiv. of lead tetraacetate in acetonitrile (5 mL per mmol) for 50 h at room temperature. Workup provided the full-cascade product **9** (60% isolated yield) together with the interrupted-cascade product, the A-ring modified steroidal enol ether **4** (25% isolated yield). Conclusion of the current phase of our investigation involved the 1,3-dicarbonyl compound **13**, a structural subunit for a retro-Claisen transformation, a substrate obtained via a mild fused- to bridged-ring system interchange.[8] Thus, basic treatment of the steroidal bis-acetoxy acetal **9** afforded an unseparable 1:1 epimeric mixture of bicyclic aldols **11**. Tetrapropylammonium perruthenate (TPAP)-catalyzed oxidation[15] proved efficient in the oxidation of the secondary alcohol. Thus, treatment of **11** with NMO and catalytic TPAP in dry CH_3CN at room temperature furnished the 1,3-diketone **12**, in 85% yield. The resultant B-homosteroid

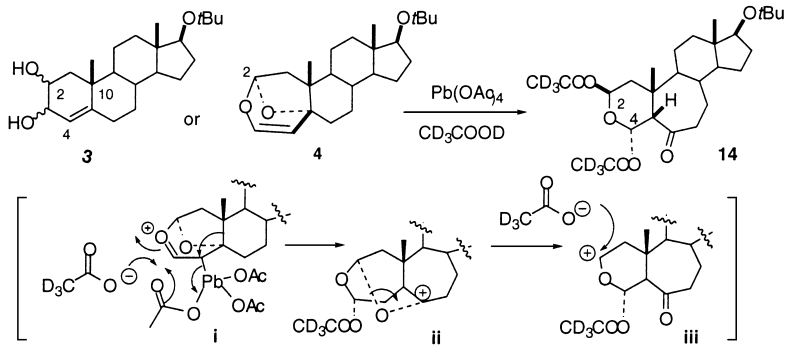
12 was readily transformed to its C-17 free hydroxy compound **13** by treatment with $BF_3 \cdot OEt_2$ as above, in 97% isolated yield.



Scheme 4. (a) 2 Equiv. $Pb(OAc)_4$, CH_3CN, 50 h, rt or 2.2 equiv. $Pb(OAc)_4$, CH_3CO_2H, 20 h, rt. (b) K_2CO_3–MeOH–H_2O, rt. (c) TPAP–NMO, MeCN, 4Å MS, rt. (d) $BF_3 \cdot OEt_2$, $PhCH_3$, 0°C to rt

At this stage, the effect of solvent was briefly investigated in the reaction of **3** and **4** with $Pb(OAc)_4$. We thus examined the possibility of replacing acetonitrile with other, polar and nonpolar, solvents in the hope of improving the yield and the rate of the one-pot multistage transformations. Replacement of acetonitrile with acetic acid dramatically increased the rate to give the full cascade product, bis-acetoxy acetal **9**, in 72% isolated yield within 20 h of room temperature stirring, instead of 50 h (60%) with acetonitrile as solvent. The new minor product, formed alongside **9**, obtained in 5–10% yield, was assigned as the A-ring modified steroidal lactone **10**. Neither cyclic acetal **4** nor any other side product was detected. The reaction sequence could also be carried out in other solvents, such as benzene, trifluorotoluene, methylene chloride, chloroform, acetone, DME, THF, or *O*-acetyl lactic acid with significant changes in the rate, yield and product distribution of cascade transformations depending on the solvent's nature. It was also found that the use of dry acetic acid, distilled over P_2O_5 and kept under argon, in the conversions **3** to **9** and **4** to **9** resulted in reactions that were faster, cleaner and more efficient than those carried out in the absence of this additional drying. The polar nature of the postulated intermediates (**i**, **ii** and **iii**, Scheme 5)[16] favors a rate increase when polar solvents are used, as experimentally observed. On the other hand, the use of more than 4 equiv. of lead tetraacetate gave a much faster and equally clean reaction. The dramatic reduction in reaction time using carboxylic acids as solvent is noteworthy. Running the cascade transformations in *O*-acetyl lactic acid furnished, after less than 6 h room temperature stirring, the ring expanded steroidal bis-acetoxy acetals as a mixture of isomers containing acetyl and lactyl groups at C-2, C-4. No attempt was made to identify them at this stage. Rather, subjection to a mild base treatment as above afforded cleanly the diastereomeric mixture of steroidal aldols **11** in comparable yields.

Our earlier suggestion[8] that the final ring-enlarged compound **9** can be derived from **3** via ionic species **i**, **ii** and **iii**, successively, has been validated by carrying out the cascade transformations in CD_3CO_2D. The structure of deuterium labeled A-ring modified, B-ring expanded **14** corresponding to acylation of postulated charged intermediates **i** and **iii** (Scheme 5) provided support for this hypothesis. The results of isotope labeling experiments afforded experimental evidence in accord with this scheme and demonstrated some intramolecular delivery of acyl ion in the formation of the ring expanded products. In Scheme 5, it is proposed that the organolead intermediate **i** is first acylated, before the ring expansion step, either intramolecularly by the acyl anions originating from the reagent or intermolecularly, by the acyl anions originating from the solvent. A second acylation follows the ring expansion step, as illustrated, leading to the ring expanded compound **9** via the resonance stabilized α-oxo carbocation species **iii**. The competitive pathways involving participation of the reagent's acetate group versus the solvent's one can be explained by the presence of ca. 7% of not fully deuterated **14**, as determined by spectroscopic



Scheme 5. The origin of acetate delivery in a carboxyl rich environment is mainly intermolecular (from the solvent, most abundant), consistent with deuterium incorporation in the C-2 and C-4 positions: very little CH_3COO incorporation

methods. Thus, careful observation of proton and carbon NMR spectra revealed the presence of acetate's methyl group. Better still, chemical ionization mass spectra of **14**, using ammonia, revealed a molecular ion $[M_A+NH_4]^+$ at m/z 502, along with a second one $[M_B+NH_4]^+$ at m/z 499 (containing only one CD_3). The latter fragment could only be obtained by a mixed transfer of acetate ions, from the deuterated solvent (intermolecularly) and from the reagent $Pb(OAc)_4$ (most likely intramolecularly). In retrospect, the fragment at m/z 499 confirms that the proposed transformation should occur as shown in Scheme 5. The detailed mechanism of the key ring-expansion step has been investigated further, and the influence of the solvent, the metal and the substitution at C-4, C-6, C-10, together with additional labeling experiments will be discussed in a later paper.

3. Conclusion

Extension of the one-pot multistage transformation methodology to involve steroidal unsaturated 1,2-diols was successful, permitting as many as seven consecutive bond-breaking/making in one synthetic operation (one-pot transformation of **3** to **9**). The studies presented above have resulted in the development of a new cascade-type methodology for the rapid construction of homo-steroids. The effect of solvent was briefly investigated in the reaction of **3** with $Pb(OAc)_4$. Replacing acetonitrile with other solvents, such as acetic acid and *O*-acetyl lactic acid led to an increase of reaction rate and improvement in yield. The most important feature of the molecules investigated (**4**–**13**) is linked to the numerous ways in which they can be converted to other building blocks, thus offering potential for molecular diversity and for the synthesis of a great number of analogues for biological evaluation. The clinical utility of the compounds synthesized in this report, as well as those which could result from them using standard methodology, remains to be assessed.

4. Experimental

4.1. General

Experimental protocols such as the drying and purification of reaction solvents, instrumentation and other such details are identical with those previously described.[17] NMR spectra were run in $CDCl_3$ and optical rotations were measured in chloroform. 'Usual workup' 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).

4.2. Preparation of the key intermediate, the unsaturated steroidal 1,2-diol **3**

Commercially available testosterone was protected as its C-17 *tert*-butyl ether on a 9.0 g (31.26 mmol) scale according to published procedures,[18] and was purified chromatographically (EtOAc:heptane, 1:1) to give 86% of **1b**: mp 146–148°C (pentane); $[\alpha]_D$ +103 (*c* 1.04); IR ($CHCl_3$): 2971, 2938, 2858, 1679, 1616, 1451, 1435, 1362, 1329, 1268, 1225, 1189, 1133, 1115, 1080, 902, 827, 735 cm^{-1}; ^1H NMR (400 MHz): 0.76 (3H, s, Me), 0.85–1.10 (4H, m), 1.13 (9H, s, *t*Bu), 1.19 (3H, s, Me), 1.29 (1H, m), 1.35–1.61 (5H, m), 1.62–1.92 (4H, m), 2.05 (1H, m), 2.30 (1H, m), 2.35–2.50 (3H, m), 3.37 (1H, t, *J*=7.9, H-17), 5.72 (1H, br. s, H-4); ^{13}C NMR (75 MHz): 11.5 (Me-13), 17.4 (Me-10), 20.6 (CH_2), 23.7 (CH_2), 28.7 (*t*Bu), 31.1 (CH_2), 31.6 (CH_2), 32.8 (CH_2), 33.9 (CH_2), 35.6 (CH), 35.7 (CH_2), 36.9 (CH_2), 38.6 (Cq), 42.3 (Cq), 50.5 (CH), 54.1 (CH), 72.1 (Cq-*t*Bu), 80.6 (C-17), 123.7 (C-4), 171.1 (C-5), 199.1 (C-3). EIMS: 344 ($M^{+\cdot}$, 14), 288 (M–[$Me_2C{=}CH_2$], 68), 57 (100). HREIMS calcd for $C_{23}H_{36}O_2$: m/z 344.2715; found: 344.2722.

Steroidal acetoxy enones **2a** and **2b** were synthesized using the procedure described in our previous work.[11] Thus, **1b** was treated with 4 molar equiv. of $Pb(OAc)_4$ in refluxing benzene under argon, for 4 days, to give the epimeric mixture of acetoxy enones **2a**, **2b** in 80% isolated yield and ca 1:1 ratio, along with the recovered starting material. Chromatography (methylene chloride:EtOAc, 30:1) afforded **2a** (faster eluting isomer): mp 147–148°C (heptane–Et_2O); $[\alpha]_D$ −58 (*c* 1.43); IR (film): 2972, 2936, 2871, 2850, 1749, 1687, 1617, 1458, 1363, 1237, 1198, 1130, 1111, 1073, 1035, 881, 736 cm^{-1}; ^1H NMR (300 MHz): 0.75 (3H, s, Me-18), 0.91–1.15 (4H, m), 1.13 (9H, s), 1.20 (3H, s, Me-19), 1.30 (1H, dd, *J*=5.7, 11.9), 1.35–1.62 (3H, m), 1.66–1.73 (2H, m), 1.80 (1H, dt, *J*=2.9, 12.4), 1.86 (1H, t, *J*=13.3), 1.88–2.01 (2H, m), 2.15 (3H, s), 2.24 (1H, ddd, *J*=2.7, 4.2, 12.4), 2.29 (1H, dd, *J*=5.0, 13.5), 2.50 (1H, ddt, *J*=1.2, 5.0, 12.4), 3.37 (1H, dd, *J*=7.7, 8.5, H-17), 5.32 (1H, dd, *J*=5.0, 12.7, H-2), 5.77 (1H, s, H-4); ^{13}C NMR (75 MHz): 11.6, 20.9, 22.1, 22.2, 23.6, 28.6 (*t*Bu), 31.0, 32.8, 34.1, 35.6, 36.7, 37.4, 41.1, 42.7, 50.2, 50.8, 70.3, 72.2, 80.3, 120.3, 170.1, 173.3, 193.5. CIMS: 403 ($[M+H]^+$, 49), 343 (100), 287 (9), 146 (26). Analysis calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; found: C, 74.36; H, 9.54; and **2b** (slower eluting isomer): mp 192–193°C (heptane–Et_2O); $[\alpha]_D$ +77 (*c* 1.16); IR (film): 3056, 2966, 2946, 2871, 2852, 1748, 1690, 1663, 1617, 1452, 1435, 1377, 1362, 1266, 1224, 1198, 1130, 1114, 1075, 1025, 888, 739, 704 cm^{-1}. ^1H NMR (300 MHz): 0.70 (3H, s, Me-18), 0.80–0.97 (4H, m), 1.07 (9H, s), 1.19–1.59 (6H, m), 1.27 (3H, s, Me-19), 1.68–1.88 (4H, m), 2.10 (3H, s), 2.17 (1H, dd, *J*=5.3, 12.5), 2.26–2.33 (2H, m), 3.30 (1H, dd, *J*=7.7, 8.5, H-17), 5.38 (1H, dd, *J*=5.3, 14.0, H-2), 5.68 (1H, s, H-4). Diagnostic NOEs: {Me-19}: H-2β; {H-2β}: Me-19; ^{13}C NMR (75 MHz): 11.4, 17.9, 20.3, 20.7, 23.4, 28.5 (*t*Bu), 30.9, 31.3, 32.2, 34.8, 36.5, 40.5, 41.3, 42.1, 50.1, 54.4, 71.0, 72.0, 80.3, 121.5, 169.9, 170.8, 193.3. CIMS: 403 ($[M+H]^+$, 29), 343 (100), 287 (9), 269 (5). Analysis calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; found: C, 74.79; H, 9.46.

Key intermediate **3** was then obtained straightforwardly by reducing the C-2 epimeric mixture **2a**, **2b**, via standard literature procedures. Lithium aluminium hydride (380 mg, 10 mmol) was suspended in dry ether (120 mL) and the mixture cooled to 0°C. The diastereomeric mixture of **2a**,**b** (2.0 g, 5 mmol, epimeric mixture, 58:42 ratio) 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, H_2O (0.4 mL) and aqueous NaOH (10%, 0.4 mL) and again H_2O (1.14 mL) were added and the mixture stirred at room temperature for 30 min. The white solid was filtered off and the filtrate concentrated under reduced pressure to give quantitatively (1.82 g) the title compound **3** as an epimeric mixture, taken as such for the next step.

4.3. The interrupted cascade: preparation of A-nor-steroids **4**–**8**

4.3.1. Synthesis of A-nor-steroid **4**

In a flame dried flask, **3** (362 mg, 1.0 mmol) and $Pb(OAc)_4$ (487 mg, 1.1 mmol) were placed under vacuum and flashed with argon, cooled to −20°C and 5 mL of acetonitrile was added. TLC control upon 30 min room temperature stirring, indicated total consumption of the starting diol and appearance of a higher spot corresponding to the product of the half-cascade **4**. The A-nor steroid thus obtained was purified by chromatography (EtOAc:heptane, 1:4) to afford 98% of **4**: $[\alpha]_D$ +23 (*c* 1.00); IR (film): 3070, 2931, 1631, 1451, 1390, 1378, 1198, 1146, 1076, 1034, 991, 959, 933, 874, 825, 795, 724 cm^{-1}; ^1H NMR (400 MHz): 0.72 (3H, s, Me-18), 1.05 (3H, s, Me-19), 1.12 (9H, s), 0.90–1.89 (13H, m), 1.76 (1H, dt, *J*=3.4, 15.7), 1.90 (1H, d, *J*=13.9, H-1βeq), 1.98 (1H, dt, *J*=2.8, 13.5), 2.19 (1H, dd, *J*=5.9, 13.9, H-1αax), 3.35 (1H, dd, *J*=7.9, 8.7, H-17), 4.79 (1H, d, *J*=6.1, H-4), 5.58 (1H, d, *J*=5.6, H-2), 6.18 (1H, d, *J*=6.1, H-3). Diagnostic NOEs: {Me-19}: H-4, H1βeq; {H-4}: Me-19, H-3; {H-2}: H1αax; ^{13}C NMR (75 MHz): 11.7 (Me-18), 13.9 (Me-19), 21.4 (CH_2), 23.7 (CH_2), 25.6 (CH_2), 28.7 (*t*Bu), 28.9 (CH_2), 31.2 (C-16), 35.1 (C-8), 37.3 (CH_2), 42.7 (Cq-13), 47.6 (CH), 47.7 (C-1), 50.5 (CH), 52.8 (Cq-10), 72.1 (Cq-*t*Bu), 80.7 (C-17), 83.0 (Cq-5), 99.4 (C-2), 110.9 (C-4), 139.0 (C-3). EIMS: 360 ($M^{+\cdot}$, 54), 316 (16), 304 (50), 260 (70), 241 (29), 107 (47), 95 (98), 57 (100). HREIMS calcd for $C_{23}H_{36}O_3$: 360.2664; found: 360.2672.

4.3.2. Ozonolysis and Cannizzaro type, mild base-catalyzed oxidoreduction of **5**; preparation of the A-nor-steroids **6a**, **6b**, **7a**, **7b** and **8**

Olefin **4** (360 mg, 1.0 mmol) was dissolved in dry methylene chloride (12 mL) and 1 mL of pyridine at −78°C. Ozone was bubbled through the solution until a blue color persisted and stirred for 5 additional minutes at this temperature. The flask was then flushed with argon, to discharge excess of ozone, Me_2S (310 mg, 0.4 mL, 5 mmol) was added dropwise and the solution was stirred for 1 h. Water was added portionwise and the mixture was extracted with methylene chloride. Usual workup, followed by chromatography (heptane:EtOAc, 1:1) furnished 302 mg (77%) of **5**: mp 112–114°C (ether–heptane); $[\alpha]_D$ +34 (*c* 1.70); IR ($CHCl_3$): 2971, 2938, 2871, 1727, 1461, 1387, 1362, 1126, 1080, 968 cm^{-1}; ^1H NMR (400 MHz): 0.73 (3H, s), 0.85–1.85 (16H, m), 1.01 (3H, s), 1.13 (9H, s), 2.59 (1H, dd, *J*=6.0, 13.9), 3.37 (1H, t, *J*=7.7), 6.55 (1H, t, *J*=6.0), 8.13 (1H, s), 9.91 (1H, s); ^{13}C NMR (75 MHz): 11.6, 14.2, 21.2, 23.6, 24.5, 24.7, 28.7 (*t*Bu), 31.2, 34.7, 37.1, 42.5, 44.0, 47.0, 47.3, 50.6, 72.1, 80.5, 92.9, 97.8, 160.2, 203.8. EIMS: 392 ($M^{+\cdot}$, 0.5), 363 (65), 335 (100), 317 (76), 261 (53), 243 (26).

Steroidal formylacetal-aldehyde **5** (270 mg, 0.70 mmol) was dissolved in a mixture of methanol (5 mL) and water (0.5 mL), and 200 mg (1.45 mmol, 1.17 equiv.) of potassium carbonate were added. The mixture was stirred at room temperature overnight, diluted with water, and extracted with ether (in large scale preparations methanol should be removed first under reduced pressure). Following usual workup, the residue was purified by chromatography to afford 200 mg (0.55 mmol, 80%) of **6a**: mp 172–174°C (ether–heptane); $[\alpha]_D$ +29 (*c* 1.60); IR (film): 3347, 3055, 2976, 2936, 2874, 2360, 2342, 1769, 1751, 1452, 1422, 1389, 1363, 1266, 1212, 1195, 1126, 1095, 1079, 1055, 1028, 937, 897, 740, 705 cm^{-1}; ^1H NMR (300 MHz): 0.73 (3H, s), 0.85–1.60 (13H, m), 1.10 (3H, s), 1.12 (9H, s), 1.75–1.99 (3H, m), 2.37 (1H, d, *J*=17.1), 2.84 (1H, d, *J*=17.1), 3.36 (1H, t, *J*=8.2), 3.60 (1H, d, *J*=12.3), 3.78 (1H, d, *J*=12.3); ^{13}C NMR (75 MHz): 11.6, 13.9, 21.9, 23.6, 25.3, 26.9, 28.7 (*t*Bu), 31.1, 35.0, 37.0, 42.4, 43.6 (2C), 48.3, 50.5, 67.9, 72.2, 80.5, 89.3, 177.8. CIMS: 382 ($[M+NH_4]^+$, 29), 365 ($[M+H]^+$, 100), 347 (9), 309 (15), 233 (16), 146 (13), 73 (40). Analysis calcd for $C_{22}H_{36}O_4$ C, 72.49; H, 9.95; found: C, 72.59; H, 9.89.

The A-nor-steroidal lactone **6a** (32 mg, 0.088 mmol) thus obtained was first acetylated at C-4 under standard conditions (0.15 mL of Ac_2O, 1.5 mL of Py, catalytic DMAP, 0°C) to give after chromatography (heptane:EtOAc, 2:1) 33 mg (93%) of **6b**: $[\alpha]_D$ +28 (*c* 1.66); IR (film): 2974, 1778, 1748, 1451, 1388,

1364, 1238, 1128, 1075, 939, 900, 738, 703 cm^{-1}; ^1H NMR (300 MHz): 0.73 (3H, s), 0.87–1.64 (12H, m), 1.06 (3H, s), 1.12 (9H, s), 1.79 (1H, dt, *J*=3.4, 12.5), 1.90 (1H, m), 2.03 (1H, dt, *J*=3.1, 14.8), 2.09 (3H, s), 2.43 (1H, d, *J*=17.2), 2.66 (1H, d, *J*=17.2), 3.36 (1H, dd, *J*=7.8, 7.9), 4.09 (1H, d, *J*=12.2), 4.17 (1H, d, 12.2); ^{13}C NMR (75 MHz): 11.6, 14.1, 20.9, 22.0, 23.5, 25.0, 27.3, 28.7 (*t*Bu), 31.1, 34.9, 37.0, 42.4, 43.2, 43.6, 48.1, 50.5, 68.1, 72.2, 80.4, 86.8, 170.2, 176.3. CIMS: 407 ($[M+H]^+$, 100), 347 (13), 233 (4), 146 (3), 113 (3), 89 (3), 73 (13).

The boron trifluoride mediated C-17 O*t*Bu-deprotection of **6b** was then achieved proceeding as described in the literature.[14] The C17-*t*Bu protected steroidal lactone **6b** (29.8 mg, 0.071 mmol) dissolved in dry toluene (5 mL) under argon was treated with borontrifluoride etherate (0.03 mL, 0.24 mmol) at 0°C for 1 h, then at room temperature for 4 h (TLC monitoring). Following disappearance of the starting material, the reaction mixture was diluted with CH_2Cl_2 and washed with an aqueous solution of sodium hydrogen carbonate. Usual work up and chromatography (heptane:EtOAc, 1:1 to 1:2) afforded 24.5 mg (98%) of **8**: $[\alpha]_D$ +23 (*c* 1.22); IR (film): 3489, 2938, 2875, 1775, 1747, 1422, 1388, 1266, 1240, 1036, 738, 704 cm^{-1}; ^1H NMR (300 MHz): 0.75 (3H, s), 0.88–1.67 (13H, m), 1.06 (3H, s), 1.85 (1H, dt, *J*=3.3, 12.6), 1.99–2.12 (2H, m), 2.07 (3H, s), 2.42 (1H, d, *J*=17.2), 2.65 (1H, d, *J*=17.2), 3.63 (1H, dd, *J*=8.4, 8.6), 4.08 (1H, d, *J*=12.2), 4.15 (1H, d, *J*=12.2); ^{13}C NMR (75 MHz): 11.1, 14.0, 20.8, 22.0, 23.1, 24.9, 27.3, 30.4, 35.0, 36.5, 42.8, 43.1, 43.6, 47.9, 50.5, 68.1, 81.3, 86.7, 170.1, 176.2. CIMS: 351 ($[M+H]^+$, 100), 333 (4), 293 (16), 291 (14), 233 (14), 73 (14).

Ozonolysis of **4** in MeOH and preparation of A-nor-steroidal furanosides **7a** and **7b** was carried out as follows. An amount of 254 mg (0.70 mmol) of **4** in 10 mL of MeOH, in the presence of 1 mL of methylene chloride as co-solvent at −78°C were ozonolyzed proceeding as above. Chromatography (heptane:EtOAc, 5:1) afforded 256 mg (93%) of the corresponding dialdehyde. The latter was dissolved in methanol and stirred overnight at room temperature. After evaporation to dryness the crude was chromatographed (heptane:EtOAc, 15:1), to yield 43 mg (17%) of **7a** (faster eluting, minor isomer) and 184 mg (75%) of **7b** (slower eluting, major isomer). **7a**: $[\alpha]_D$ +39 (*c* 1.55); IR (film): 2975, 2360, 1724, 1457, 1389, 1362, 1266, 1199, 1080, 1022, 973, 705 cm^{-1}; ^1H NMR (300 MHz): 0.71 (3H, s), 0.86–1.95 (16H, m), 0.95 (3H, s), 1.12 (9H, s), 2.44 (1H, dd, *J*=5.8, 13.9), 3.36 (1H, t, *J*=8.2), 3.47 (3H, s), 5.21 (1H, t, *J*=5.8), 9.95 (1H, s); ^{13}C NMR (75 MHz): 11.6, 14.4, 21.2, 23.6, 24.5, 25.0, 28.7 (3C), 31.2, 34.8, 37.2, 42.4, 45.0, 46.8, 47.4, 50.7, 56.1, 72.1, 80.6, 91.5, 105.2, 205.8. CIMS: 379 ($[M+H]^+$, 2), 347 (100), 335 (17), 319 (40), 305 (10), 291 (10), 273 (7), 263 (6), 245 (7), 89 (3), 73 (9). **7b**: $[\alpha]_D$ +142 (*c* 1.44); IR (film): 2974, 1729, 1450, 1389, 1362, 1266, 1198, 1080, 1028, 971, 740 cm^{-1}; ^1H NMR (300 MHz): 0.73 (3H, s, Me-18), 0.92–1.96 (15H, m), 0.98 (3H, s, Me-19), 1.13 (9H, s), 1.80 (1H, dd, *J*=6.7, 13.7, H-1β), 2.05 (1H, d, *J*=13.7, H-1α), 3.36 (1H, dd, *J*=7.6, 8.8, H-17), 3.42 (3H, s, CH_3O), 5.31 (1H, d, *J*=6.3, H-2), 9.62 (1H, s, H-4); ^{13}C NMR (75 MHz): 11.6 (Me-18), 15.0 (Me-19), 20.9, 23.6, 24.9, 25.0, 28.7 (*t*Bu), 31.2, 35.2 (CH), 37.1, 42.4, 43.5, 44.0 (C-1), 45.4 (CH), 50.5 (CH), 55.6 (OMe), 72.1 (Cq-*t*Bu), 80.6 (C-17), 92.1 (C-5), 104.4 (C-2), 204.5 (C-4).

*4.4. One-pot preparation of steroidal bis-acetoxy acetal **9** from **3**: the full-cascade transformations*

Using acetonitrile as solvent: to a stirred solution of 1.00 g (2.8 mmol) of **3** in acetonitrile (50 mL) was added 2.48 g (5.6 mmol) of $Pb(OAc)_4$ at room temperature. The mixture was stirred at room temperature for 50 h, diluted with ether and filtered through Celite. The residue was purified on silica gel (heptane:EtOAc, 2:1) to yield 25% of **4** along with 803 mg (60%) of **9**: $[\alpha]_D$ −2 (*c* 1.50); IR (film): 2964, 1755, 1590, 1364, 1230, 1197, 1070, 917 cm^{-1}; ^1H NMR (400 MHz): 0.75 (3H, s, Me-18), 0.90–2.10 (14H, m), 1.12 (9H, s, *t*Bu), 1.33 (3H, s, Me-19), 1.62 (1H, dd, *J*=5.8, 14.5, H-1β), 1.90 (1H, dd, *J*=3.1, 14.5, H-1α), 2.07 (3H, s, C*H*$_3$CO), 2.10 (3H, s, C*H*$_3$CO), 2.43 (1H, t, *J*=5.1), 3.15 (1H, d, *J*=3.6, H-5), 3.36 (1H, t, *J*=8.1, H-17), 6.25 (1H, t, *J*=4.1, H-2), 6.39 (1H, d, *J*=3.6, H-4). Diagnostic NOEs: {Me-19}:

H-5, H-4, H-1β; {H-5}: H-4, Me-19; {H-17}: H-16, H-14; {H-2}: H-1α, H-1β; {H-4}: H-5, Me-19; ^{13}C NMR (75 MHz): 11.5 (Me-18), 21.1 (2CO*C*H$_3$), 22.1 (Me-19), 22.6 (CH$_2$), 24.7 (CH$_2$), 24.8 (CH$_2$), 28.7 (*t*Bu), 30.7 (C-16), 36.8 (C-14), 36.9 (CH$_2$), 37.8 (Cq), 38.2 (C-1), 41.2 (C-6′), 42.4 (Cq), 49.0 (CH), 49.3 (CH), 56.0 (C-5), 72.2 (Cq-*t*Bu), 80.6 (C-17), 89.4 (C-4), 91.1 (C-2), 168.9 (CH$_3$*C*O), 169.1 (CH$_3$*C*O), 208.9 (C-6). EIMS: 478 ($M^{+\cdot}$, 0.5), 418 (22), 362 (29), 335 (35), 57 (100). HREIMS calcd for $C_{25}H_{38}O_5$: (M–AcOH) m/z 418.2719; found: 418.2722. Analysis calcd for $C_{27}H_{42}O_7$: C, 67.74; H, 8.85; found: C, 67.96; H 8.70.

Using acetic acid as solvent: 601 mg (1.66 mmol) of diol **3** and 2.2 g (4.98 mmol, 3 equiv.) of Pb(OAc)$_4$ (vacuumed and flashed with argon) were stirred in 10 mL of dry and degassed acetic acid, under argon atmosphere, at room temperature for 20 h. After usual workup, the crude (900 mg) was chromatographed (heptane:EtOAc, 10:1 to 1:1) to afford 56 mg (9%) of lactone **10** followed by 570 mg (72%) of the full cascade product **9**. Lactone **10**: $[\alpha]_D$ +45 (*c* 1.15); IR (film): 2974, 2933, 2873, 1751, 1671, 1457, 1378, 1363, 1266, 1227, 1197, 1125, 1082, 1034, 999, 962, 934 cm^{-1}; ^{1}H NMR (300 MHz): 0.73–2.29 (15H, m), 0.72 (3H, s), 1.06 (3H, s), 1.12 (9H, s), 1.79 (1H, dt, *J*=3.3, 12.4), 2.38 (1H, dd, *J*=5.8, 14.7), 2.47 (1H, d, *J*=18.7), 2.78 (1H, d, *J*=18.7), 3.35 (1H, dd, *J*=7.6, 8.7), 5.77 (1H, d, *J*=5.3); ^{13}C NMR (75 MHz): 11.6, 15.9, 21.6, 23.6, 25.9, 28.7 (*t*Bu), 31.2, 31.5, 34.9, 37.2, 41.2, 42.5, 45.0, 48.6, 49.1, 50.7, 72.2, 80.6, 84.8, 101.1, 168.5. CIMS: 377 ([M+H]$^+$, 100), 333 (29), 279 (9), 163 (22), 146 (13), 117 (9), 113 (9), 73 (49).

4.5. One-pot fused to bridged ring system interchange: preparation and derivatization of steroidal aldol ***11***

To a magnetically stirred solution of bis-acetoxy acetal **9** (495 mg, 1.03 mmol) in methanol (24 mL) and water (3 mL) was added potassium carbonate (786 mg, 5.69 mmol). The mixture was stirred at room temperature for 13 h, whereupon the solvent was removed in vacuo and the residue taken up in methylene chloride. After usual workup, the residual oil was purified by chromatography (heptane:EtOAc, 1:1) to give 342 mg (95.3%) of the bicyclic aldols **11** as an inseparable epimeric mixture. The latter was oxidized to the corresponding 1,3-dicarbonyl derivative **12** using TPAP, thus allowing for characterization, as follows: to a stirred solution of **11** (70 mg, 0.201 mmol) in dry CH$_3$CN (2 mL) under argon was added powdered 4Å molecular sieves (100 mg), NMO (35.3 mg, 0.30 mmol) and a catalytic amount of *n*-Pr$_4$NRuO$_4$ (2.8 mg, 0.008 mmol) at room temperature. After 30 min the solvent was evaporated under reduced pressure and the residue purified by chromatography (heptane:EtOAc, 7:1) to afford 60 mg (85%) of 1,3-dicarbonyl compound **12**: mp 198–199°C (ether–heptane); $[\alpha]_D$ +43 (*c* 0.78); IR (film): 2970, 2928, 1732, 1708, 1459, 1445, 1361, 1255, 1230, 1199, 1134, 1122, 1093, 1081 cm^{-1}; ^{1}H NMR (300 MHz): 0.72 (3H, s), 1.10 (3H, s), 1.11 (9H, s), 0.95–1.93 (12H, m), 2.06 (1H, d, *J*=19.3), 2.13 (1H, ddd, *J*=4.4, 9.0, 13.6), 2.28 (1H, d, *J*=19.5), 2.66 (1H, dd, *J*=2.9, 19.5), 2.67 (1H, dd, *J*=3.2, 19,3), 3.26 (1H, d, *J*=9.3), 3.34 (1H, dd, *J*=7.7, 8.7); ^{13}C NMR (75 MHz): 12.0, 23.5, 25.4, 28.3, 28.6 (*t*Bu), 31.0, 33.3, 34.2, 37.0, 37.2, 42.7, 47.7, 50.7, 52.6, 54.7, 64.9, 72.2, 80.3, 207.8, 208.5. CIMS: 347 ([M+H]$^+$, 100), 319 (12), 291 (12), 125 (8), 113 (8), 73 (56). Analysis calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; found: C, 76.24; H, 9.91.

Deprotection of the C-17 O*t*Bu protective group was then achieved, proceeding as above. To a stirred solution of 1,3-diketone **12** (70 mg, 0.2 mmol) in dry toluene (5 mL) was added $BF_3 \cdot OEt_2$ (0.09 mL, 0.7 mmol) under argon at 0°C and the mixture was allowed to reach room temperature (TLC monitoring, ca 2 h). Chromatography (heptane:EtOAc, 1:1 to 1:2) afforded 96% of **13**: mp 175–176°C (ether–heptane); $[\alpha]_D$ +39 (*c* 2.22); IR (film): 3412, 2957, 2928, 1727, 1700, 1446, 1317, 1250, 1201, 1137, 1058, 734 cm^{-1}; ^{1}H NMR (300 MHz): 0.76 (3H, s), 1.11 (3H, s), 1.04–1.63 (10H, m), 1.78 (1H, dq, *J*=3.5, 13.1), 1.85 (1H, dt, *J*=3.3, 12.5), 2.00–2.17 (2H, m), 2.07 (1H, d, *J*=19.2), 2.28 (1H, d, *J*=19.5), 2.67 (1H, dd,

J=2.9, 13.5), 2.67 (1H, dd, *J*=3.2, 25.7), 3.27 (1H, d, *J*=9.3), 3.63 (1H, td, *J*=5.0, 8.5); ^{13}C NMR (75 MHz): 11.4, 23.1, 25.3, 28.2, 30.3, 33.1, 34.1, 36.7, 37.1, 43.2, 47.7, 50.6, 52.4, 54.6, 64.7, 81.2, 207.8, 208.3. CIMS: 291 ([M+H]$^+$, 100], 263 (21), 125 (19), 73 (14). Analysis calcd for $C_{18}H_{26}O_3$ 0.4 H_2O: C, 72.65; H, 9.08; found: C, 72.81; H, 8.98.

4.6. Deuterium labeling experiment: one-pot multistage transformations in acetic acid$_{D4}$

To a flask charged with **3** (83.7 mg, 0.23 mmol) and $Pb(OAc)_4$ (255.6 mg, 0.58 mmol), placed under vacuum and flushed with argon, was added 2 mL of CD_3CO_2D and the mixture was stirred under argon for 15 h at room temperature. Purification by chromatography (heptane:EtOAc, 3:1) afforded, by order of elution, 4 mg (3%) of **4**, along with 7 mg (6%) of A-nor-steroidal lactone-acetal **10** and 74 mg (66%) of the deuterium labeled A-nor-B-homosteroid **14**: mp 154–156°C (ether–heptane); $[\alpha]_D$ −38 (*c* 1.68); IR (film): 2975, 2875, 1756, 1694, 1588, 1475, 1443, 1394, 1362, 1237, 1194, 1125, 1075, 1037, 950 cm^{-1}; ^{1}H NMR (300 MHz): 0.74 (3H, s, Me-13), 0.95–2.09 (14H, m), 1.11 (9H, s, *t*-Bu), 1.32 (3H, s, Me-19), 1.62 (1H, dd, *J*=4.9, 14.8), 2.40–2.44 (2H, m), 3.15 (1H, d, *J*=3.6), 3.35 (1H, t, *J*=8.3), 6.25 (1H, t, *J*=3.9), 6.38 (1H, d, *J*=3.5); ^{13}C NMR (75 MHz): 11.5, 22.1, 22.6, 24.7 (2C), 28.7 (*t*Bu), 30.7, 36.6, 36.9, 37.8, 38.1, 41.2, 42.4, 49.1, 49.3, 55.8, 72.3, 80.6, 89.4, 91.1, 169.0, 169.2, 209.0. CIMS: 502 ([M+NH_4]$^+$, 54), 439 (28), 423 (28), 422 (100), 378 (14), 377 (14), 361 (11), 88 (16). Analysis calcd for $C_{27}H_{36}D_6O_7$: C, 66.91; H, 7.49; found: C, 66.76; H, 7.37.

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