Pergamon

Tetrahedron Letters 40 (1999) 7679–7682

TETRAHEDRON LETTERS

# $Pb(OAc)_4$ mediated oxidative cleavage of steroidal unsaturated 1,2-diols: influence of the angular substitution

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Received 10 July 1999; accepted 17 August 1999

**Abstract**

To evaluate the effect of angular substitution at C-10, the required precursor **2b** was prepared by the methods described earlier and subjected to oxidative cleavage with lead tetraacetate. 

During the course of our investigations on the lead tetraacetate-mediated oxidative cleavage of 1,2-unsaturated steroidal diols such as **2a**,[1] we became interested in whether angular substitution at C-10 (steroid numbering) was crucial and if so, how this factor would affect the one-pot multistage transformation process.[2] Accordingly, we turned our attention towards **2b** in the hope that it would provide an insight into the rearrangement consequences of the two different substitution patterns at C-10.

On the basis of the studies carried out on unsaturated bicyclic[3] and steroidal 1,2-diols,[1] for which electrophilic attack of $Pb^{4+}$ on the electron-rich C3–C4 olefin **3** (the 1,3-dioxene part of the isolable intermediate, en route from **2a** to **4**)[4] occurred from the least hindered direction, it would be predicted that in the absence of the angular methyl substituent on type **5** substrates, β-face attack would be preferred. The results presented in this communication confirm this prediction; Scheme 1 portrays the rapid increase in molecular complexity, obtained upon treatment of steroidal unsaturated diols with $Pb(OAc)_4$.[5]

The preparation of the requisite target lacking the angular methyl substituent is readily achieved in a series of steps involving conversion of an enone to the α-acetoxy derivative (Scheme 2).[6] The known 17β-(*tert*-butyldimethylsilyloxy)estr-4-ene-3-one **7**[7] which is readily available from commercial 19-nortestosterone **1b**, was reacted with lead tetraacetate in refluxing benzene to give a mixture of two C-2 epimeric acetoxyenones, in about 80% yield and nearly 1:1 ratio. Subsequent reduction of the crude reaction mixture with lithium aluminum hydride in ether, afforded the desired fragmentation precursor **2b**, thus setting the stage for the oxidative cleavage. Exposure of the latter (10 mmol scale) to 1.1 equiv. of the reagent at 0°C, in acetonitrile, effected a smooth conversion into **8** [40%, $[\alpha]_D$ +57 (*c* 1.15)] along

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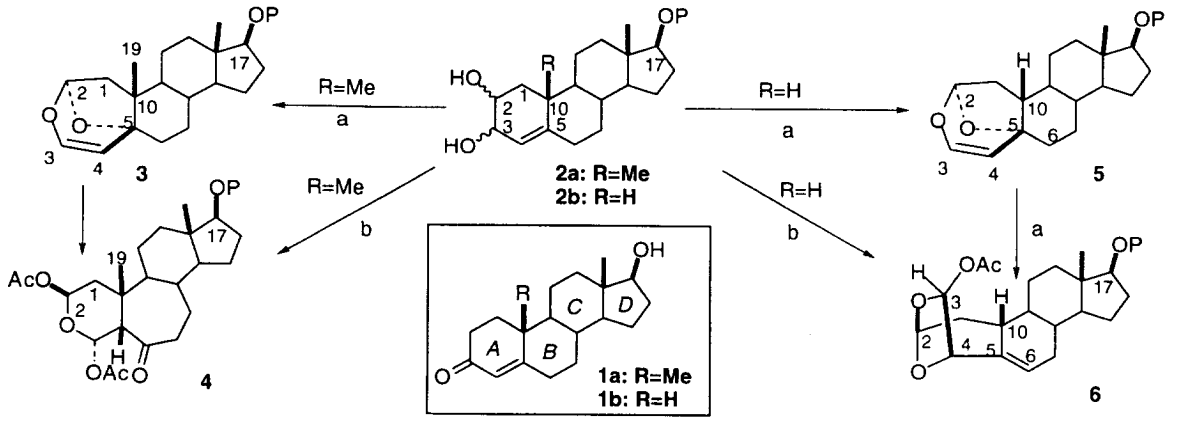
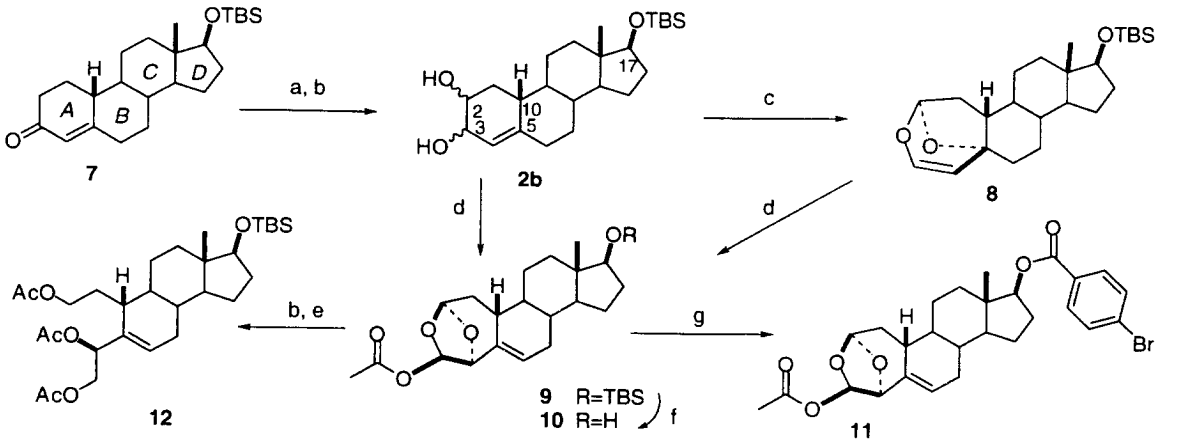
*PII:* S0040-4039(99)01565-8




Scheme 1. (a) 1.1 equiv. $Pb(OAc)_4$, $CH_3CN$; (b) 2.2 equiv $Pb(OAc)_4$, $CH_3CN$ or AcOH (P stands for *t*Bu or TBS protection)

with the corresponding C2–C3 dialdehyde (30%). Using a slight excess (2.2 equiv.) of $Pb(OAc)_4$, under the same conditions, **2b** afforded **8** (17%), along with **9** [35%, mp: 119–121°C, ($CH_2Cl_2$–EtOH), $[\alpha]_D$ –42 (*c* 1.99)] 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). Diol **2b** as well as enolether **8** failed to give any trace of B-homosteroid when treated with excess lead tetraacetate (3 to 5 equiv.), in acetonitrile or acetic acid or *O*-acetyllactic acid. Prolonged room temperature stirring or heating did not produce a trace of the alternative ring expanded type **4** product, but instead afforded **9** in 50% isolated yield from **8**.




Scheme 2. (a) $Pb(OAc)_4$, PhH, reflux, 4 days; (b) $LiAlH_4$, THF; (c) 1.1 equiv. $Pb(OAc)_4$, $CH_3CN$, –20°C to rt; (d) 2.2 equiv $Pb(OAc)_4$, AcOH, rt; (e) $Ac_2O$, Py, DMAP, 0°C to rt; (f) HF–$CH_3CN$, 0°C; (g) *p*-BrBzCl, Py–DMAP, 0°C

Structural assignments were based on 800 MHz NMR spectra and corroborated by a single-crystal X-ray analysis on **11**. The synthesis of the latter was accomplished utilizing known protocols as follows: deprotection of **9** with 40% aq. HF in $CH_3CN$ for 1 h at 0°C afforded an 85% isolated yield of C-17 free hydroxy derivative **10**.[8] This, upon treatment with *p*-bromobenzoyl chloride in dry pyridine in the presence of DMAP (0°C to room temperature, 12 h), provided the desired *p*-bromobenzoate **11** which crystallized and thus allowed a single crystal X-ray diffraction analysis the result of which is shown in Fig. 1.

Hydride reduction of **9** with $LiAlH_4$ in dry THF (0°C to rt, 5 h) gave the corresponding triol.

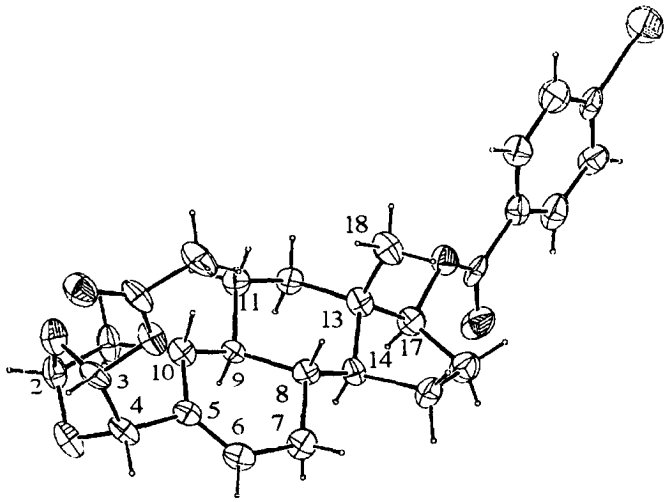



Figure 1. Perspective drawing of the X-ray structure of **11**

Subsequent reaction of the crude triol thus obtained with $Ac_2O$ in pyridine, in the presence of 4-DMAP, followed by silica gel chromatography afforded the A-*seco* derivative **12** (75%, two steps) which was characterized by usual analytical techniques.[9] The experiments have been carried out on both diols **2b** and cyclic acetal **8** to ascertain whether **8** might be an intermediate in the formation of the new product **9**.

Thus **2a** (10-Me), and **2b** (10-H), give rise to different products via different bond migration. The difference in reactivity between **2a** and **2b** can be understood through an examination of molecular models. From this analysis and with regard to the proposed mechanism,[10] it can be seen that the approach from the β-face in the absence of the angular methyl group Me-19 would be preferred. The organolead intermediate which derives from electrophilic attack of the metal to the C4–C3 double bond of **8**, can not attain a conformation with the C–Pb bond antiperiplanar to C10–C5 bond and undergoes C5–O bond migration (the carbon–oxygen bond is perfectly aligned for a backside colinear displacement) instead.

In conclusion, the lack of angular methyl substitution at C-10 led to a different cascade transformation in complete agreement with the influence of the bond alignment between the migrating and leaving groups.[11] The steric and electronic factors involved in the cascade transformations along with the solvent effect and the nature of the oxidant are currently being investigated and products may serve as useful mechanistic probes.[12]

## Acknowledgements

The authors thank Ministerio de Educacion y Cultura (Spain) for fellowship to Dr. J. I. Martin Hernando and the European Commission for a Research Training Grant to Dr. J. I. Candela Lena.

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8. Compound **10**: mp 129–131°C (ether–heptane–EtOAc). $[\alpha]_D$ –53 (*c* 0.88). IR (film): 3259, 2925, 1765, 1434, 1365, 1217, 1129, 991, 880, 853, 812, 758 $cm^{-1}$. $^1H$ NMR (800 MHz): 0.69 (3H, s, Me-18), 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, OAc), 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-18), 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 (*OCO*Me). CIMS: 289 ($[MH]^+$–AcOH, 100), 271 (17), 245 (13), 146 (8), 100 (16). Analysis calcd for $C_{20}H_{28}O_5x0.55H_2O$: C, 67.04; H, 8.19 found: C, 67.06; H, 7.97.
9. Compound **12**: $[\alpha]_D$ +45 (*c* 1.80). IR (film): 2956, 2857, 1743, 1658, 1471, 1368, 1243, 1142, 1098, 1044, 943, 904, 873, 837, 776 $cm^{-1}$. $^1H$ 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, –4.6, 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 ($[M+NH_4]^+$, 100), 510 (36), 452 (9), 241 (7), 192 (23), 184 (9), 152 (11), 132 (5), 118 (16), 88 (10). Analysis calcd for $C_{30}H_{50}O_7Si$: C, 65.42; H, 9.15; found: C, 65.72; H, 9.11.
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12. Complete IR, Mass, $^1H$ and $^{13}C$ NMR (in $CDCl_3$) data were obtained for each compound synthesized. Optical rotations were measured in $CHCl_3$.