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Cycloaddition-Oxidative Cleavage Pathways to 14β-Formyl-19-norsteroids

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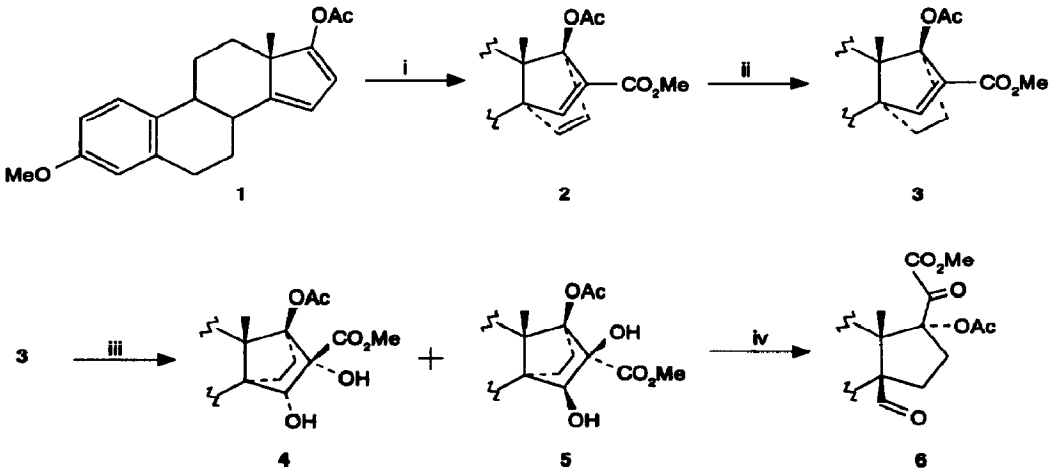
Abstract: Cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate 1 with methyl propiolate, followed by chemoselective modification of the cycloadduct, furnishes intermediates for reduction–oxidative cleavage reaction sequences, leading to the 14β-formyl analogue of estrone and related 14β-formyl-19-norsteroids.

An efficient synthetic route to the 14α-formyl analogue of estrone[1] relies upon cycloaddition of an ethylene equivalent to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **1**, followed by oxidative cleavage of the residual 14α,17α-etheno bridge in the modified cycloadduct. Complementary access to the 14β-formyl analogue of estrone and related 14β-formyl-19-norsteroids was of interest, in order to extend our investigations of structure–activity relationships in ring D modified analogues of steroidal hormones. For this purpose, an alternative cycloaddition mediated pathway was envisaged, in which the 14β,17β-bridge of an appropriate cycloadduct derived from **1** could be chemoselectively cleaved whilst retaining the 14α,17α-bridge. With appropriate choices of functionality on the 14β,17β-bridge it would thus be possible to generate 14β-formyl products variously functionalised at C(17).

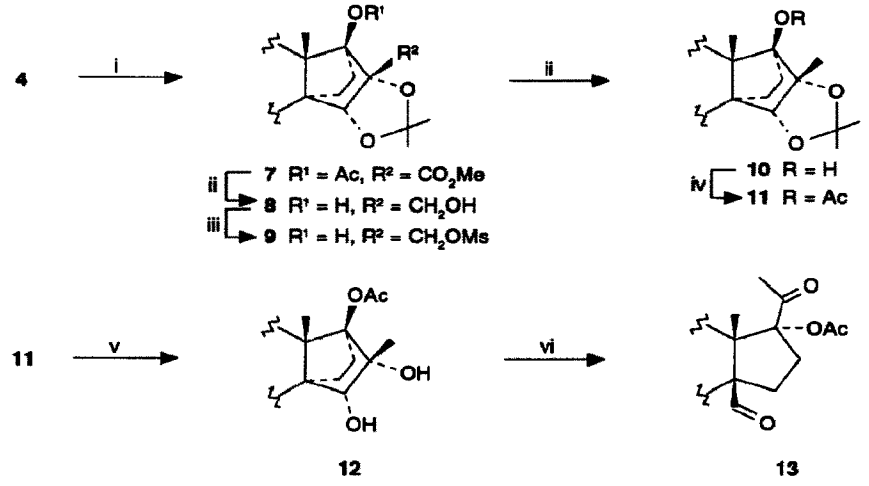


Reagents: (i) $HC{\equiv}CCO_2Me$, C_6H_6, 100 °C (ii) Pd–C, H_2 (iii) OsO_4, C_5H_5N or cat. OsO_4, NMMO, THF (iv) $NaIO_4$, EtOH, H_2O, 20 °C

An approach, in which sequential cycloaddition–oxidative cleavage of a steroidal 17-methyl 14,16-diene provided synthetic access to a 17-methyl cardenolide,[2] was adapted for our purpose. Thus, treatment of the dienyl acetate **1** with methyl propiolate gave the expected[2,3] cycloadduct **2** (85%), catalytic hydrogenation of which proceeded chemoselectively to give the dihydro cycloadduct **3** (83%).[4]

The first objective was to convert the 16-methoxycarbonyl group in **3** into a methyl group, preferably before oxidative cleavage of the C(15)–C(16) bond, in order to avoid the expected problem of conducting such a step chemoselectively thereafter. Oxidative cleavage was then expected to reveal a 14β-formyl 17β-acetyl functional array, isomeric with that generated[5] and further exploited[5,6] in the related series. The second, apparently simpler target was to prepare the 14β-formyl analogue of estrone *via* sequential or concomitant oxidative cleavage of the C(15)–C(16) and C(16)–C(17) bonds in **3**.

Initial attempts to convert **3** into the corresponding 16-methyl intermediate for oxidative cleavage at C(15)–C(16) were frustrated by negligible 1,2-regioselectivity during hydride mediated reduction of the α,β-unsaturated ester moiety. Accordingly, **3** was subjected to *cis*-hydroxylation to give a separable mixture (*ca* 2.5:1) of the diols **4** and **5**, the ready conversion of which into methyl 17-acetoxy-14-formyl-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-trien-21-oate **6** (80%) confirmed the feasibility of generating the 14β-formyl group *via* oxidative cleavage in this series. However, this step was necessarily postponed in pursuit of the first goal, and the 16-methoxycarbonyl 15,16-diols were first converted into the corresponding 16-methyl 15,16-diols in multi-step reaction sequences, exemplified here for the major diol **4**. Thus, **4** was protected as the acetonide **7**, in which the ester moiety was reduced (to **8**), mesylated (to **9**), and reductively deoxygenated (to **10**). Restoration of the 17-acetoxy group (to **11**) followed by 15,16-deprotection furnished the 16β-methyl 15α,16α-diol **12** in an overall yield of 25% from **4**. Oxidative cleavage of **12** with sodium periodate furnished 17-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde **13**.

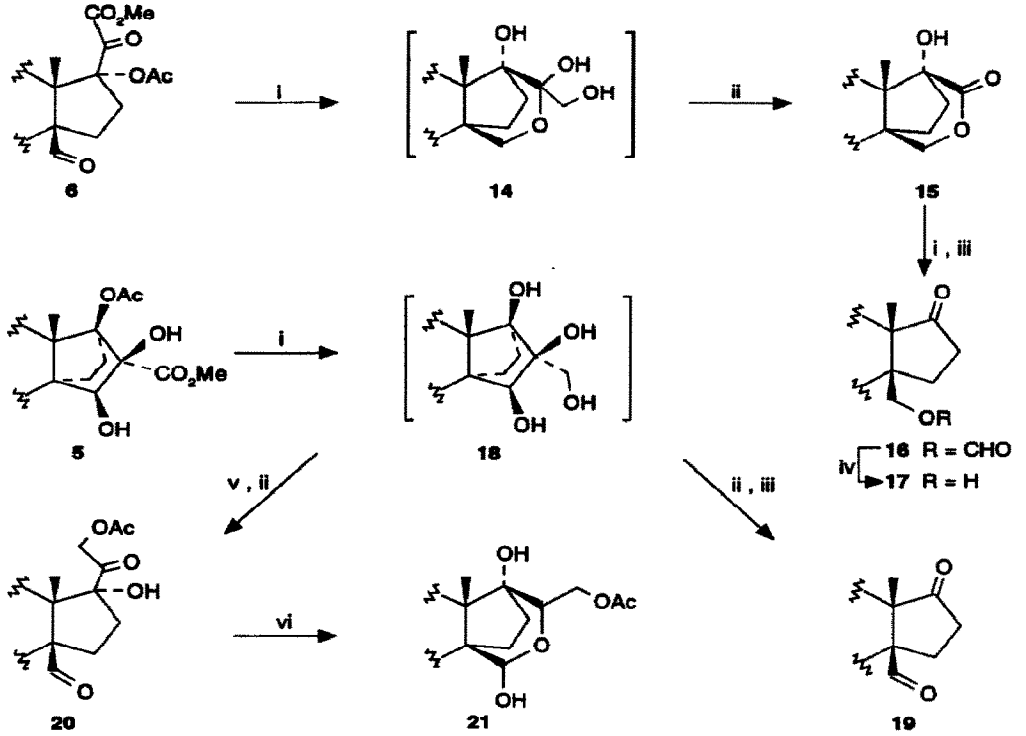


Reagents: (i) Me_2CO, $HClO_4$, 20 °C (ii) LAH, THF, 20 °C (iii) MsCl, C_5H_5N, 0 °C (iv) Ac_2O, C_5H_5N, DMAP, 20 °C (v) I_2, MeOH, Δ (vi) $NaIO_4$, EtOH, H_2O, 20 °C

Consideration of various options for achieving an efficient synthesis of the 17-oxo 14β-carbaldehyde **19** suggested that formal oxidative cleavage of the C(17)–C(20) bond in a suitably primed derivative of **6** offered

scope for a one-pot procedure. However, attempts to achieve the desired chemoselectivity of reduction at C(20) were unsuccessful; treatment of **6** with sodium borohydride or L-Selectride led to mixtures which were not simplified by subsequent reaction with sodium periodate or lead tetraacetate. Exhaustive reduction of **6** with lithium aluminium hydride in refluxing tetrahydrofuran gave a highly polar product, which precluded adequate characterisation, but subsequent treatment with sodium periodate furnished the δ-lactone **15** (55% from **6**). It was concluded that an intermediate arising from initial reduction at C(14[1]) must be intercepted as a 14[1],20-hemiacetal, thus preventing further reduction at C(20) but allowing reduction at C(21), to give a presumed intermediate **14** which undergoes selective periodate cleavage of the C(20)–C(21) bond.

Repetition of the reduction–oxidative cleavage sequence on the δ-lactone **15** yielded the 14β-formyloxymethyl 17-ketone **16**, *via* the evident intermediacy of a δ-lactol, and alkaline hydrolysis of **16** furnished 14-hydroxymethyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one **17**.



Reagents: (i) LAH, THF, Δ (ii) $NaIO_4$, EtOH, H_2O, 20 °C (iii) $Pb(OAc)_4$, THF, 20°C (iv) KOH, MeOH, 20 °C (v) Ac_2O, C_5H_5N, 20 °C (vi) $NaBH_4$, EtOH

Although the overall conversion of **6** into this immediate precursor of the target compound **19** was thus achieved, the number of steps detracted from its utility, and attention was turned to exploring more direct procedures, mediated by formal cleavage of both C(15)–C(16) and C(16)–C(17) in suitably modified derivatives of the bridged diols **4** or **5**. The outcome of these investigations is exemplified here for the 15β,16β-diol **5**, but both isomers behaved similarly. Exhaustive reduction of **5** gave the highly polar tetraol **18**, which could not be directly characterised, but underwent oxidative cleavage with lead tetraacetate to give

the 17-oxo 14β-carbaldehyde **19** (57% from **5**). Interestingly, treatment of **18** with sodium periodate resulted in formation of uncharacterisable, polar material which, upon subsequent treatment with lead tetraacetate, furnished the desired product **19** in greatly improved yield (80% from **5**). It was concluded that preferential oxidative cleavage of **18** must occur at C(16)–C(16^1), accompanied perhaps by competitive C(15)–C(16) cleavage, and that the resultant (mixtures of) α-hydroxy ketone(s) resists further reaction in the presence of periodate. The reason for the diminished efficiency of direct lead tetraacetate oxidation of **18** is obscure, but may arise from less discriminate initial oxidative cleavage, leading to oxidatively less vulnerable intermediates.

In an attempt to clarify the course of events, and perhaps to develop complementary routes to 21-functionalised 14β-carbaldehydes, selective protection of the primary hydroxy group in **18** was attempted as a preamble to oxidative cleavage. Attempts to achieve selective silylation at C(16^1) were inconclusive, but an experiment in which **18** was first treated with acetic anhydride–pyridine at 20 °C, then subjected to periodate oxidation, furnished the 21-acetate **20** (80%), clearly arising from selective 16^1-acetylation followed by C(15)–C(16) cleavage. Reduction of **20** with lithium aluminium hydride gave a complex, polar mixture, which could not be characterised or selectively derivatised. However, reduction of **20** with sodium borohydride proceeded cleanly, to give a product (70%) formulated as the hemiacetal **21**, on the basis of distinctive spectroscopic properties. This result implies an unexpected reversal of the reduction chemoselectivity observed for the α-oxo ester **6**, and invites speculation upon possible protection of the 14β-formyl group as a hydrate under these reaction conditions,thereby promoting reduction at C(20) and subsequent intramolecular hemiacetal formation.

In summary, the original objectives of this investigation were achieved with efficient syntheses of a range of 14β-carbaldehydes **6**, **13**, **19**, and **20**, the further chemistry of which is under investigation. The unexpected course of certain reduction–oxidative cleavage procedures highlights the need for careful control of reaction conditions in order to avoid interfering intramolecular reactions and to optimise product yields.

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References and Notes

1. Bull, J.R.; Thomson, R.I. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 241—251.
2. Atwal, K.S.; Sahoo, S.P.; Tsai, T.Y.R.; Wiesner, K. *Heterocycles*, **1982**, *19*, 641—646.
3. Winterfeldt, E. *Chem. Rev.*, **1993**, *93*, 827—843 and refs cited therein.
4. All new compounds were fully characterised by elemental analyses and spectroscopic data. Selected NMR data ($CDCl_3$, 200 MHz; unqualified assignments refer to methyl singlets): cpd **4**, δ_H 0.82 (13β-Me), 2.14 (17β-OAc), 3.73 (16β-CO_2Me), 4.42 (1H, d, *J* 1.5 Hz, 15β-H); cpd **5**, δ_H 1.23 (13β-Me), 2.07 (17β-OAc) 3.76 (16α-CO_2Me), 4.11 (1H, s, 15α-H); cpd **6**, δ_H 1.31 (13β-Me), 2.11 (17α-OAc), 3.76 (20-CO_2Me), 9.67 (1H, s, 14β-CHO); cpd **13**, δ_H 1.18 (13β-Me), 2.04 (17α-OAc). 2.15 (17β-COMe), 9.67 (1H, s, 14β-CHO); cpd **15**, δ_H 1.0 (13β-Me), 4.15 (1H, dd, *J* 10.7 and 1.9 Hz, 14^1*S**-H), 4.37 (1H, d, *J* 10.7 Hz, 14^1*R**-H); cpd **16**, δ_H 1.04 (13β-Me), 4.05 and 4.38 (each 1H, d, *J* 11.4 Hz, 14^1-H_2), 8.01 (1H, s, 14^1-OCHO); cpd **19**, δ_H 1.12 (13β-Me), 9.62 (1H, s, 14β-CHO); cpd **20**, δ_H 1.17 (13β-Me), 2.14 (21-OAc), 4.86 and 5.41 (each 1H, d, *J* 17.9 Hz, 21-H_2) 9.54 (1H, s, 14β-CHO); cpd **21**, δ_H 1.25 (13β-Me), 2.05 (21-OAc), 4.09 (1H, dd, *J* 11.6, and 7.0 Hz, 21-H), 4.29 (1H, dd, *J* 7.0 and 2.6 Hz, 20-H), 4.5 (1H, dd, *J* 11.6 and 2.6 Hz, 21-H) 5.01 (1H, d, *J* 3.5 Hz → s on D_2O exch., 14^1-H).
5. Bull, J.R.; Bischofberger, K. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2859—2865.
6. An intramolecular aldol condensation of 17β-acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-1,3,5(10)-triene-14-carbaldehyde provides a synthetic route to 14α, 17α-propano-19-norsteroids; Bull, J.R.; Steer, L.M.; Jaworski, K. Unpublished results.

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