Stereocontrol in Intramolecular Michael–Aldol Reaction Sequences of 3-Acetoacetoxycholest-4-en-6-ones

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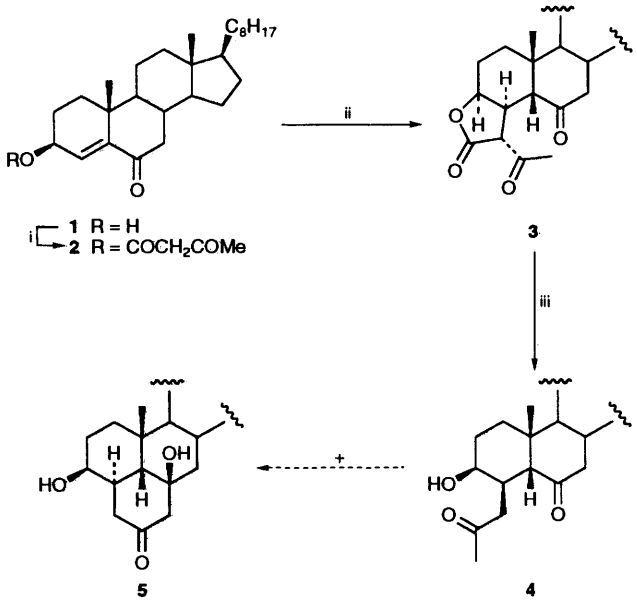
An intramolecular Michael–aldol reaction sequence upon 3-acetoacetoxycholest-4-en-6-ones leads stereoselectively to the corresponding 3,6-dihydroxytetrahydrobenzo[4,5,6]cholestan-5′(6′*H*)-ones.

Conjugate addition of masked acetonyl equivalents to cholest-4-en-6-one provides ready access to 4β-acetonyl 6-ketones, the 5β-isomer of which undergoes intramolecular aldol condensation and isomerisation to 4α,5α-dihydrobenzo[4,5,6]-cholestan-5′(6′*H*)-one, from which 4α,5α,6α- and 4α,5α,6β-hexahydrobenzo[4,5,6]cholestane derivatives have been prepared.[1,2] These isomers are representative of a family of eight stereoparents based upon the natural 10β-steroid family, in which rings A, B and E constitute conformationally constrained models for the perhydrophenalene ring system. It is thus possible to use such systems to study the veracity of molecular mechanics predictions about relative steric energies,[2,3] and to examine the properties of non-chair conformers which occur in the series.

The limitation of the conjugate alkylation approach is the stereoselective 4β-attachment of the acetonyl (or related) equivalent(s), and alternative approaches to stereocontrolled introduction of 4α-acetonyl equivalents for the elaboration of routes to 4β,5α,6α- and 4β,5α,6β-hexahydrobenzo[4,5,6]-cholestanes have hitherto been unsuccessful.[2]

An interesting possibility for stereocontrolled introduction of an acetonyl equivalent at C-4 in cholest-4-en-6-ones is suggested by an approach to the synthesis of forskolin,[4,5] in which ring formation with attendant fixation of the stereogenic centres at C-1 and C-10 in the target molecule is determined by intramolecular addition of an allylic acetoacetate upon the terminus of a cyclohexenoid Michael acceptor. Subsequent intramolecular aldol condensation completes the assembly of the forskolin ring system. This approach invites application in steroidal 3-acetoacetoxy Δ^4-6-ketones, since the configuration at C-3 should thus control the stereoselectivity of attachment of a potential acetonyl group at C-4, with the attendant prospect of generating versatile intermediates for synthesis of an array of hexahydrobenzo[4,5,6]cholestanes.

Treatment of 3β-hydroxycholest-4-en-6-one **1** with acetyl Meldrum's acid[6] in refluxing benzene for 1 h gave the corresponding 3β-acetoacetate **2**, which readily underwent intramolecular Michael reaction under mildly basic conditions, to give a single product (95%) formulated as the lactone **3** (Scheme 1). IR absorption at ν_{max}/cm^{-1} 1774 (1-CO), 1715 (3-CO) and 1698 (6′-CO) supported the functional group assignment, and the ^1H NMR signals at δ 1.82 (1 H, d, J 12.1, 5′β-H), 3.06 (1 H, dd, J 12.1 and 5, 4′α-H), 3.57 (1 H, s, 2-H) and 4.63 (1 H, br m, $W_{\frac{1}{2}}$ 11, 3′α-H) (verified by a COSY spectrum) confirmed the configurational assignments at C-2, C-3′, C-4′ and C-5′. In particular, the magnitudes of $J_{4'\alpha,5'\beta}$ (12.1) and $J_{2,4'\alpha}$ ($\sim$0) are uniquely accommodated by structure **3**, and a 5β-configuration was further demonstrated by diagnostic ^{13}C chemical shifts of C-9′ (d, 40.8) and C-19′ (q, 23.15).[7] This striking control in the generation of three stereogenic centres is mediated by obligatory *syn* C(2)–C(4′) bond formation, in which the distal orientation of the carbonyl groups in the acetoacetate moiety during bond-forming approach also



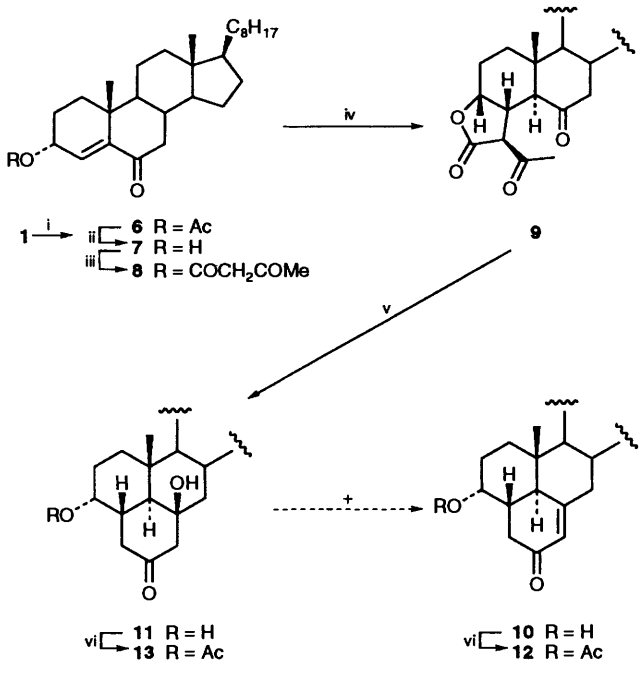
Scheme 1 *Reagents and conditions:* i, acetyl Meldrum's acid, C_6H_6, reflux; ii, K_2CO_3, EtOH–H_2O, 60 °C; iii, KOH, dioxane–H_2O, reflux

generates a 2*R*-configuration, whereafter 5′β-protonation of the derived enolate furnishes the thermodynamically favoured isomer in which the C(2)–C(4′) bond is equatorial.

A consequence of this reaction outcome is that the acetyl group in **3** is unfavourably orientated for direct aldol closure with the 6′-oxo group. Although it was evident that epimerisation at C-2 would overcome this problem, we have hitherto failed to generate ring E whilst keeping the lactone ring intact. For example, **3** was inert to conditions (*p*-TsOH–C_6H_6, heat) under which an analogous cyclisation was conducted.[5] However, it was equally evident that lactone opening and accompanying decarboxylation would free the thus-revealed 4β-acetonyl group for aldol closure. Attempts to achieve this by treating **3** with potassium hydroxide in refluxing aqueous ethanol were unsuccessful, but the simple expedient of conducting the reaction at higher temperature, in refluxing aqueous dioxane for 5 h, gave a separable mixture of the 4β-acetonyl compound **4** (34%) and the derived aldol condensation product **5** (34%). Prolongation of the reaction at elevated temperature was ineffective in completing the conversion of **4** into **5**, and the attendant absence of a β-elimination product of **5** suggested that these reaction conditions may facilitate **4**$\rightleftarrows$**5** equilibration. However, an experiment, in which the reaction mixture was first refluxed for 5 h, then kept at 0 °C for 14 h, resulted in a 70% conversion into **5**, the functional group array and C-5 configuration of which were evident from spectroscopic data [ν_{max}/cm^{-1} 3611 (OH) and 1708 (CO); δ_H 1.21 (10β-Me), 2.12 (1 H, dt, J 12.7 and 2 × 2.6, 6′α-H),

2.34 (1 H, dd, J 13 and 2.6, 4'α-H), 2.56 (1 H, d, J 13, 4'β-H), 2.65 (1 H, t, J 2 × 12.7, 6'β-H) and 3.76 (1 H, br, $W_{\frac{1}{2}}$ 8, 3α-H); δ_C 27.1 (q, C-19) and 40.55 (d, C-9)].

The foregoing results are complementary to those obtained *via* conjugate alkylation of cholest-4-en-6-one,[1] and demonstrate the feasibility of using this intramolecular approach to assembly of the pentacyclic targets. Attention was then turned to applying this approach to the hitherto more elusive 4α-acetonyl 6-oxo intermediates and their derived aldol closure products. For this purpose, an efficient synthesis of 3α-acetoacetoxycholest-4-en-6-one **8** was developed. Thus, treatment of **1** under Mitsunobu conditions[8] gave 3α-acetoxycholest-4-en-6-one **6** (90%), and the derived 3α-alcohol **7** was readily converted into the corresponding 3α-acetoacetate **8** (94%) upon treatment with acetyl Meldrum's acid in refluxing benzene for 2 h (Scheme 2).



Scheme 2 *Reagents and conditions:* i, HOAc, Ph_3P–DEAD, C_6H_6, reflux; ii, KOH, MeOH, 20 °C; iii, acetyl Meldrum's acid, C_6H_6, reflux; iv, K_2CO_3, EtOH–H_2O, 60 °C; v, KOH, dioxane–H_2O, reflux; vi, Ac_2O, C_5H_5N, 20 °C

The intramolecular Michael reaction of **8** proceeded more slowly (4 h) than that of **2**, and formation of the lactone **9** (60%) was accompanied by the product **7** of competing hydrolysis. Nevertheless, the reaction also proved to be highly stereoselective, giving only **9** [ν_{max}/cm^{-1} 1771 (1-CO), 1718 (3-CO) and 1704 (6'-CO); δ_H 2.17 (1 H, d, J 11.7, 5'α-H), 3.02 (1 H, dd, J 11.7 and 4.6, 4'β-H), 3.22 (1 H, s, 2-H) and 4.72 (1 H, br, $W_{\frac{1}{2}}$ 7, 3'β-H); δ_C 12.6 (q, C-19') and 53.2 (d, C-9')], in a process which parallels the foregoing result (**2**→**3**). The slower reaction course and attendant intervention of hydrolysis may arise from additional steric crowding, and possible dipole repulsion between carbonyl groups during approach to the C(2)–C(4') bond-forming process, owing to the pseudoaxial orientation of the 3α-ester function.

Again, the structure of **9** precluded direct aldol closure without prior epimerisation at C-2 or lactone opening. The latter reaction proceeded smoothly (and more rapidly than that of **3**) in the presence of potassium hydroxide in refluxing aqueous dioxane (1 h) to give an inseparable two-component mixture (*ca.* 1:1) of **10** and **11**, the derived 3α-acetates **12** and **13** of which were separated and characterised [compound **12**: ν_{max}/cm^{-1} 1731 (3α-OAc), 1659 (5'-CO) and 1614 (C:C); δ_H 4.95 (1 H, br, $W_{\frac{1}{2}}$ 7, 3β-H) and 5.82 (1 H, t, J 2 × 2, 4'-H); compound **13**: ν_{max}/cm^{-1} 3591 (6β-OH), 1723 (3α-OAc) and 1712 (5'-CO); δ_H 1.03 (10β-Me), 2.2–2.55 (4 H, br m, 4'- and 6'-H_2) and 4.91 (1 H, br, $W_{\frac{1}{2}}$ 8, 3β-H)].

In contrast to the 3β-series, a 4α-acetonyl intermediate was not detected during the alkaline reaction of **9**. Furthermore, the 6β-hydroxy group in the primary aldol product **11** is axial with respect to ring E, and unsaturation at C(6)–C(4') can be accommodated without attendant ring deformation;[1] accordingly, β-elimination was readily achieved in this case. Indeed, more protracted base treatment of **9** resulted in progressive accumulation of the final product **10**, and it was thus possible to achieve an overall conversion of **9** into **10** in *ca.* 70% yield.

In summary, the stereocontrol manifested in these Michael–aldol reaction sequences provides a versatile synthetic entry into representative perhydrobenzo[4,5,6]steroids, and opens the way for extended investigations into the interrelationships and conformational properties of their stereoisomers.

Experimental

Intramolecular Michael Reactions.—(*a*) Aq. 1 mol dm^{-3} potassium carbonate (14 cm^3) was added to a solution of 3β-acetoacetoxycholest-4-en-6-one **2** * (3.7 g, 7.64 mmol) in ethanol (200 cm^3) at 60 °C, with vigorous stirring. After 2 h at 60 °C, starting material was absent (TLC), and the reaction mixture was filtered, and the filtrate was concentrated to *ca.* 50 cm^3, diluted with water, and extracted with ethyl acetate (× 2). The combined extracts were washed successively with aq. 1 mol dm^{-3} hydrochloric acid, water, saturated aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give (2R)-2-(3β-*hydroxy*-6-*oxo*-5β-*cholestan*-4β-*yl*)-3-*oxobutanoic acid* 1,3'-*lactone*, **3** (3.51 g, 95%), m.p. 130–133 °C (from Me_2CO–MeOH); $[\alpha]_D$ +1 (*c* 1.1) (Found: C, 76.5; H, 9.6%; M$^+$, 484. $C_{31}H_{48}O_4$ requires C, 76.8; H, 10.0%; *M*, 484).

(*b*) Similar treatment of the 3α-acetoacetate **8** (390 mg, 0.81 mmol) at 60 °C for 4 h, and chromatography of the resultant product on silica gel (30 g) with ethyl acetate–hexane (1:3) as eluent gave (2S)-2-(3α-*hydroxy*-6-*oxo*-5α-*cholestan*-4α-*yl*)-3-*oxobutanoic acid* 1,3'-*lactone* **9** (235 mg, 60%), m.p. 155–157 °C (from Me_2CO–MeOH); $[\alpha]_D$ −11 (*c* 1.2) (Found: C, 76.4; H, 9.8%; M$^+$, 484), followed by the 3α-alcohol **7** (112 mg, 35%).

Alkaline Treatment of the Lactones.—(*a*) The lactone **3** (307 mg, 0.63 mmol) and aq. 2 mol dm^{-3} potassium hydroxide (3 cm^3) in dioxane (12 cm^3) and water (1 cm^3) was heated under reflux for 5 h. The cooled solution was neutralised (aq. 1 mol dm^{-3} HCl) and concentrated to a small volume under reduced pressure. Water was added to the residue and the pH of the mixture was adjusted to 5 (aq. 1 mol dm^{-3} HCl); the mixture was then extracted with ethyl acetate (× 3). The combined extracts were washed with saturated aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica gel (16 g) with ethyl acetate–toluene (7:13) as eluent gave 4β-*acetonyl*-3β-*hydroxy*-5β-*cholestan*-6-*one* **4** (96 mg, 34%), m.p. 124–127 °C (from hexane); $[\alpha]_D$ −37 (*c* 0.8) (Found: C, 78.25; H, 10.7%; M, 458. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%; *M*, 458), and further elution with ethyl acetate–toluene (13:7) gave 3β,6-*dihydroxy*-4α,4',5β,6β-*tetrahydrobenzo*[4,5,6]*cholestan*-5'(6'H)-*one* **5** (98 mg, 34%), m.p. 180–183 °C (from MeOH); $[\alpha]_D$ +3 (*c* 1.0) (Found: H, 78.7; H, 10.8%; M, 458).

* All new compounds were fully characterised by elemental analysis and spectroscopic data; IR, ν_{max}($CHCl_3$)/cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$); *J*/Hz; ^{13}C NMR (50 MHz, $CDCl_3$); $[\alpha]_D$ values (in $CHCl_3$) are given in units of 10^{-1} deg cm^2 g^{-1}. Diagnostic spectroscopic data are included in the text.

(*b*) The foregoing reaction was repeated on the lactone **3** (2.6 g, 5.4 mmol), and the reaction mixture, after 5 h reflux, was kept at 0 °C for 14 h. Work-up and chromatography gave compound **5** (1.72 g, 70%).

(*c*) The reaction of lactone **9** (175 mg, 0.36 mmol) for 1 h under the conditions described in (*a*), followed by acetylation (Ac_2O–C_5H_5N, 20 °C, 2 h), and chromatography of the product on silica gel (10 g) with ethyl acetate–toluene (1:9) as eluent gave 3α-*acetoxy*-4β,5α-*dihydrobenzo*[4,5,6]*cholestan*-5′(6′H)-*one* **12** (86 mg, 50%), m.p. 180–182 °C (from MeOH); $[\alpha]_D$ −50 (*c* 0.9) (Found: C, 79.3; H, 10.25%; M, 482. $C_{32}H_{50}O_3$ requires C, 79.6; H, 10.4%; *M*, 482), followed by 3α-*acetoxy*-6-*hydroxy*-4β,4′,5α,6β-*tetrahydrobenzo*[4,5,6]*cholestan*-5′(6′H)-*one* **13** (90 mg, 50%), m.p. 167–170 °C (from MeOH); $[\alpha]_D$ −22 (*c* 1.0) (Found: C, 76.5; H, 10.2%; M, 500. $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.5%; *M*, 500).

Acknowledgements

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