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Ionic hydrogenation of C-20, 22-ketene dithioacetal: stereoselective synthesis of steroidal C (20*R*) aldehydes†

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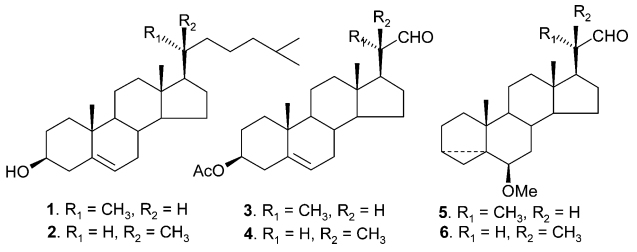
Homologation of 16-dehydropregnenolone acetate 7 leads to excellent stereocontrolled synthesis of unnatural C (20*R*) aldehydes 4 and 6 through compound 13.

The introduction of the properly functionalized side chains onto tetracyclic steroidal starting materials has been the subject matter of several investigations.[1,2] An important problem that arises in this approach is the stereoselective control of the C-20 stereochemistry. These efforts have been spurred by the biological significance of new natural products containing modified side chains and synthetic endeavors towards a variety of ecdysones,[3] vitamin D metabolites,[4] brassinosteroids,[5] squalamine,[6] and various marine steroids,[7] with the epimeric methyl configuration at C-20.

Most of the sterols isolated from plant, marine and animal sources have the C (20*R*) stereochemistry as in cholesterol **1** (Fig. 1). Compounds with unnatural configuration at C-20 have attracted attention because of the interesting biological activities of these epimers[8] and hence methods for their stereoselective synthesis are highly desirable. Tsuda *et al.*[9] have isolated sargasterol from *Sargassum ringgoldianum* and proposed its structure as (20*S*)-fucosterol on the basis of degradation reaction. The presence of 20-isocholesta-5, 22-dien-3β-ol in the scallop *Placopecten magellanicus* has been suggested[10] by Idler *et al*. Koreeda has pointed[11] that 20-isocholesterol **2** with C (20*S*) stereochemistry showed significant in vitro inhibitory activity for the conversion of cholesterol to pregnenolone. Djerassi and co-workers have isolated[12] four sterols having C (20*S*) stereochemistry, from a sea pen, *Ptilosarcus gurneyi* and also devised methods for their synthesis. Stereocontrolled synthesis of C-20 isocholesterol has also been reported.[11*a*,13]

There are several reports[14] of the unsuccessful stereoselective hydrogenation of steroidal C-20, 22-ene to get a single isomer at C-20. These findings on a variety of steroids prompted us to develop a new method for setting the C (20*R*) unnatural stereochemistry in compounds **4** and **6**. Synthesis of the steroidal C-22 aldehydes **3** and **5** with C (20*S*) natural configuration has been reported.[15,16*a*] On the other hand not much attention has been given to the stereocontrolled synthesis of the C-22 aldehydes **4** and **6** with the unnatural configuration at C-20. These aldehydes **4** and **6** are ideal intermediates for the construction of several naturally occurring steroids[8–12] with unnatural stereo-centres at C-20.



1. $R_1 = CH_3$, $R_2 = H$ **2**. $R_1 = H$, $R_2 = CH_3$ **3**. $R_1 = CH_3$, $R_2 = H$ **4**. $R_1 = H$, $R_2 = CH_3$ **5**. $R_1 = CH_3$, $R_2 = H$ **6**. $R_1 = H$, $R_2 = CH_3$

Fig. 1 Cholesterol, isocholesterol and steroidal C-22 aldehydes.

† Electronic supplementary information (ESI) available: experimental details and spectral data. See http://www.rsc.org/suppdata/cc/b4/b407952c/

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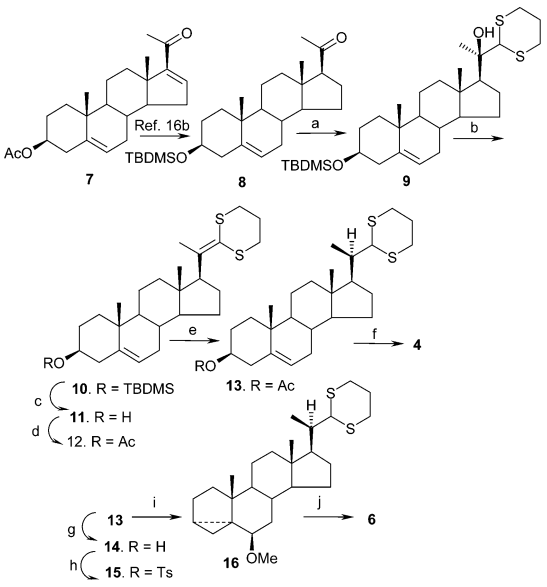
Epimerisation of the C-20 stereo-centre of the C-22 aldehydes led to the unnatural C-22 aldehyde in poor yield.[12] Synthesis of the C (20*R*) aldehyde as an epimeric mixture from 17-keto steroids has been reported.[17]

Herein, we report a highly stereoselective synthesis of the aldehydes **4** and **6** starting from 16-dehydropregnenolone acetate **7**. The salient feature of this synthesis is ionic hydrogenation of C-20, 22-ketene dithioacetal to set the desired chirality at C-20 with one hundred percent stereoselectivity. Homologation of 16-dehydropregnenolone acetate **7** to C-22 aldehydes **4** and **6** with C (20*R*) unnatural configuration is reported for the first time.

16-Dehydropregnenolone acetate[18] **7** was converted[16*b*] to its 3β-*tert*-butyldimethylsilyl ether **8** (Scheme 1). Exposure of compound **8** to 2-lithio-1,3-dithiane furnished the C-20 *tert*-alcohol **9**. Addition of 2-lithio-1,3-dithiane to 20-keto pregnane derivatives is known[19] to generate stereoselectively the C (20*R*) configuration at this centre. The stereochemistry at C-20 has been confirmed by single crystal X-ray studies.

Dehydration of the *tert*-alcohol **9** was very facile and took place with $SOCl_2$–pyridine in CH_2Cl_2 to furnish ketene dithioacetal **10**. Attempted reduction of compound **10** by catalytic hydrogenation with Pd–C, with Mg in methanol and with Zn in acetic acid[20] resulted in recovery of the starting materials.

Ionic hydrogenation of the ketene dithioacetal with



Scheme 1 *Reagents and conditions*: (a) 1,3-dithiane, n-BuLi, THF, −35 °C, 2 h and 0 °C for 12 h, 82%; (b) $SOCl_2$, pyridine, CH_2Cl_2, −5 °C, 5 min., 84%; (c) n-Bu_4NF, THF, 25 °C, 12 h, 93%; (d) Ac_2O, pyridine, DMAP, 30 °C, 3 h, 98%; (e) Et_3SiH, CF_3COOH, CH_2Cl_2, 25 °C, 18 h, 89%; (f) HgO, $HgCl_2$, CH_3CN, H_2O, reflux, 3 h, 96%; (g) KOH, MeOH, THF, 30 °C, 12 h, 92%; (h) *p*-toluenesulfonyl chloride, pyridine, 30 °C, 12 h, 94%; (i) MeOH, CH_3COONa, reflux, 4 h, 83%; (j) Dess–Martin periodinane, CH_3CN, CH_2Cl_2–H_2O, 30 °C, 5 h, 55%.

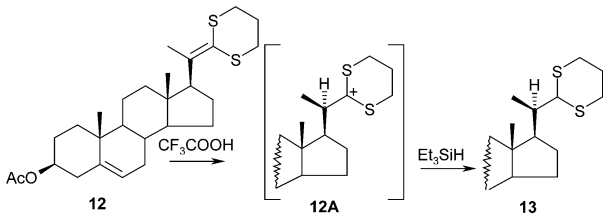


Fig. 2 Mechanism of ionic hydrogenation of ketene dithioacetal.

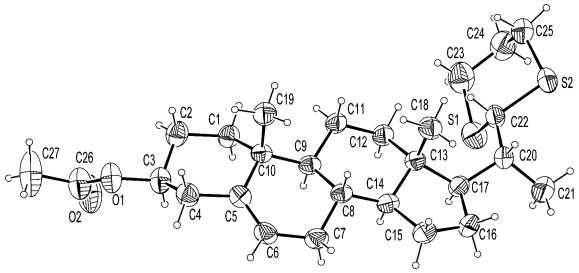


Fig. 3 ORTEP[23] view of 3β-acetoxy-pregna-5-en-20-dithiane **13**.

3β-acetate[21]**12** using triethylsilane and trifluoroacetic acid in dichloromethane afforded the compound **13**. We attribute the exclusive formation of **12A** by protonation of **12** from the less hindered α face (Fig. 2). This generates a sulfur-stabilised intermediate[22] that then captures hydride from the Et_3SiH to give product **13**. Ionic hydrogenation of compound **12** is chemoselective as the 5, 6-double bond is unaffected.

The exclusive formation of C (20*R*)-methyl compound **13** by ionic hydrogenation is confirmed by a single C-21 methyl at δ 1.05 ppm (d, J = 6 Hz) in ^{1}H NMR and by a single methyl signal at δ 15.84 ppm in ^{13}C NMR. This was further confirmed unambiguously by single crystal X-ray analysis (Fig. 3).‡

Removal of the dithiane moiety of compound **13** by oxidative hydrolysis afforded the known aldehyde[15] **4** (Scheme 1). Hydrolysis of the 3β-acetate of compound **13** followed by tosylation of the resulting alcohol **14** furnished compound **15**. Tosylate **15** was converted into the i-methyl ether **16**. The cleavage of the dithiane moiety of **16** was carried out with Dess–Martin periodinane[24] to afford the known[12] aldehyde **6**. Dess–Martin periodinane is the reagent of choice for the acid sensitive i-methyl ether **16**.

In summary, we have achieved a highly efficient chemoselective and stereoselective method for reduction of ketene dithioacetal **12** by ionic hydrogenation to get the compound **13** with unnatural C (20*R*) configuration.

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Notes and references

‡ Crystal data for **13**: C_{27} H_{42} O_2 S_2·0.25(C_6 H_{12}), M = 473.13, crystal dimensions 0.42 × 0.22 × 0.20 mm, crystal system: triclinic, space group $P\bar{1}$, a = 8.1143(12), b = 9.7663(15), c = 19.215(3) Å, α = 99.467(2), β = 99.538(2), γ = 90.654(2) °, V = 1480.0(4) Å^3, Z = 2, D_c = 1.062 g cm^{-3}, μ(Mo–Kα) = 0.1995 mm^{-1}, T = 293(2) K, 14181 reflections collected, 10151 unique [$I > 2\sigma(I)$], R value 0.0554, $wR2$ = 0.1385 (all data R = 0.0639, $wR2$ = 0.1455). The crystal lattice contains two disordered cyclohexane molecules with the occupancy of 0.125 each. CCDC 240193 (compound **13**) and 240194 (compound **9**). See http://www.rsc.org/suppdata/cc/b4/b407952c/ for crystallographic data in .cif format.

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