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Mendeleev Commun., 1995, **5(6)**, 215–216
Mendeleev Communications

Stereochemically Unusual Cycloaddition of Nitrile Oxides to Δ^{23}-Steroids

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Previously unknown 22-isoxazolinyl steroids have been obtained by 1,3-dipolar cycloaddition of nitrile oxides to a steroidal 23-ene.

The chemistry of isoxazolinyl steroids has been used by us for the efficient side-chain construction of a number of natural steroids such as ecdysones,[1] brassinosteroids,[2] marine sapogenins[3] and others.

It was of great interest from a synthetic point of view to verify whether the same conditions as employed in the above cases would be suitable for the cycloaddition of ^{23}-steroids with nitrile oxides. We now describe the synthesis of hitherto unknown 22-isoxazolinyl steroids, which are additional examples of precursors of the important functionalised polyhydroxysteroids. The main goal of such a synthesis is the stereoselective introduction of chiral centres at the C(22) and C(23) positions.

The requisite 23-en-22-ol **2** for use in the present study was prepared in high yield from the known (20*S*)-3α,5-cyclo-6,6-ethylenedioxy-5α-pregnan-20-carboxaldehyde **1**.[1] The latter was alkylated with vinylmagnesium bromide and the resulting mixture of 22-epimers was separated by silica gel chromatography or by fractional crystallisation. Cycloaddition of the major epimer **2** [5†] (22*S*-isomer) and acetonitrile oxide generated *in situ* by oxidation of the aldoxime under action of *N*-chlorosuccinimide resulted in only one detectable regiomer (in 85% yield) which consisted of two epimers **3** (23*R*) and **4** (23*S*) in 4:1 ratio. The individual epimers **3**[‡] and **4**[§] were isolated as an oil after column chromatography on silica gel using an ethyl acetate–hexane mixture as eluent (1:8).

Significant differences due to the C(23) configuration of **3** and **4** were observed for the ^{1}H NMR chemical shifts of protons at C(22), C(23) and C(4′). However, all attempts to assign the stereochemistry of the C(23) chiral centre using spectral data failed. The absolute configuration at this centre of the major adduct was determined after conversion of **3** to 22-acetoxy derivative **5**.[¶] Crystals of the latter suitable for X-ray analysis were produced by slow recrystallisation from methanol–hexane. X-ray diffraction of **5** [5] has established the 23*R* stereochemistry. This was surprising, because the *syn*-directing effect of the allylic oxygen substituent[6] had not been observed before. In contrast, the reaction of nitrile oxides with analogous ^{22}-steroids shows *anti*-selective cycloaddition.[7]

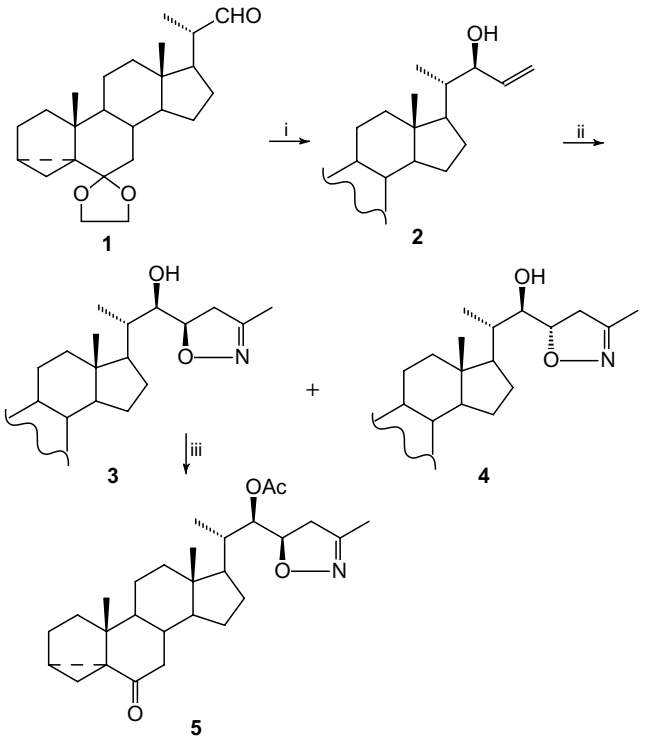
In connection with the well-known transformation of isoxazoline derivatives into β-ketols,[8] the regio- and stereoselective synthesis of an isoxazoline such as **3** is useful for the preparation of the corresponding 22*R*,23*R*-diols. Taking into account that these functional groups are typical of natural

† *Spectroscopic data for* **2**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.38 m and 0.65 m (3H, cycloprop.), 0.77 s (3H, 18-Me), 0.88 d (3H, *J* 7 Hz, 21-Me), 1.02 s (3H, 19-Me), 3.84 m (4H, OCH_2CH_2O), 4.27 m (1H, $C_{22}H$), 5.20 m (2H, C_{24}), 5.83 m (1H, C_{23}); IR (KBr) ν/cm^{-1}: 3480, 905; MS *m*/*z* 400 $[M]^+$, 385 $[M–Me]^+$, 382 $[M–H_2O]^+$.

‡ *Spectroscopic data for* **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.34 m and 0.62 m (3H, cycloprop.), 0.74 s (3H, 18-Me), 0.98 d (3H, *J* 7 Hz, 21-Me), 1.02 s (3H, 19-Me), 2.01 s (3H, 3′-Me), 2.61 dd (1H, J_1 8 Hz, J_2 17 Hz, $C_{4'}H$), 3.00 dd (1H, J_1 10 Hz, J_2 17 Hz, $C_{4'}$), 3.54 d (1H, *J* 8 Hz, $C_{22}H$), 3.84 m (4H, OCH_2CH_2O), 4.56 m (1H, $C_{23}H$); IR (film) ν/cm^{-1}: 3470; MS *m*/*z* 458 $[M+1]^+$, 457 $[M]^+$, 442 $[M–Me]^+$.

§ *Spectroscopic data for* **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.34 m and 0.62 m (3H, cycloprop.), 0.76 s (3H, 18-Me), 0.95 d (3H, *J* 7 Hz, 21-Me), 1.01 s (3H, 19-Me), 2.01 s (3H, 3′-Me), 3.00 dd (2H, J_1 2 Hz, J_2 9 Hz, $C_{4'}H$), 3.50 d (1H, *J* 5 Hz, $C_{22}H$), 3.84 m (4H, OCH_2CH_2O), 4.48 m (1H, $C_{23}H$); IR (film) ν/cm^{-1}: 3470; MS *m*/*z* 458 $[M+1]^+$, 457 $[M]^+$, 442 $[M–Me]^+$.

¶ *Spectroscopic data for* **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.34 m and 0.62 m (3H, cycloprop.), 0.74 s (3H, 18-Me), 1.00 d (3H, *J* 7 Hz, 21-Me), 1.02 s (3H, 19-Me), 2.00 s (3H, 3′-Me), 2.12 s (3H, OAc), 2.60 dd (1H, J_1 8 Hz, J_2 17 Hz, $C_{4'}H$), 2.97 dd (1H, J_1 10 Hz, J_2 17 Hz, $C_{4'}$), 4.65 m (1H, $C_{23}H$), 5.03 d (1H, *J* 8 Hz, $C_{22}H$); IR (KBr) ν/cm^{-1}: 1720, 1630, 1250; MS *m*/*z* 499 $[M]^+$, 484 $[M–Me]^+$, 439 $[M–AcOH]^+$.



Scheme 1 *Reagents and conditions*: i, CH_2=CHMgBr, THF, room temperature, 2 h; ii, MeCNO, THF, room temperature, 4 h; iii, Ac_2O, pyridine, room temperature, 12 h.

phytohormone brassinosteroids,[9] the reported approach is quite promising for brassinolide side-chain synthesis.

The research described in this publication was made possible in part by grant no. MWC000 from the International Science Foundation.

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Received: Moscow, 16th August 1995
Cambridge, 21st September 1995; Com. 5/05555E