

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

Raissa P. Litvinovskaya,* Svetlana V. Drach and Vladimir A. Khripach

Institute of Bioorganic Chemistry, Academy of Sciences of Belarus, 220141 Minsk, Belarus. Fax: +7 0172 648 647

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

The chemistry of isoxazolinyll 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 sapogenins³ 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 Δ^{23} -steroids with nitrile oxides. We now describe the synthesis of hitherto unknown 22-isoxazolinyll 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*)-3 α ,5-cyclo-6,6-ethylenedioxy-5 α -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**[‡] (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 ¹H 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**[‡] has established the 23*R* stereochemistry. This was surprising, because the *syn*-directing effect of the allylic oxygen substituent⁶ had not been observed before. In contrast, the reaction of nitrile oxides with analogous Δ^{22} -steroids shows *anti*-selective cycloaddition.⁷

In connection with the well-known transformation of isoxazoline derivatives into β -ketols,⁸ the regio- and stereo-selective 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

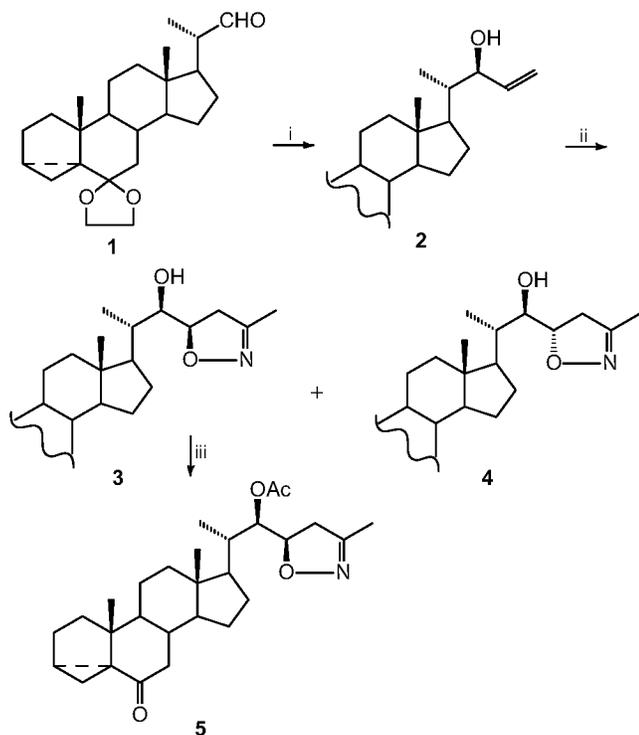
[‡] Spectroscopic data for **2**: ¹H NMR (360 MHz, CDCl₃) δ 0.38 m and 0.65 m (3H, cycloprop.), 0.77 s (3H, 18-Me), 0.88 d (3H, *J* 7 Hz, 21-Me), 1.02 s (3H, 19-Me), 3.84 m (4H, OCH₂CH₂O), 4.27 m (1H, C₂₂H), 5.20 m (2H, C₂₄), 5.83 m (1H, C₂₃); IR (KBr) ν /cm⁻¹: 3480, 905; MS *m/z* 400 [M]⁺, 385 [M–Me]⁺, 382 [M–H₂O]⁺.

[‡] Spectroscopic data for **3**: ¹H NMR (200 MHz, CDCl₃) 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, C₄H), 3.00 dd (1H, *J*₁ 10 Hz, *J*₂ 17 Hz, C₄'), 3.54 d (1H, *J* 8 Hz, C₂₂H), 3.84 m (4H, OCH₂CH₂O), 4.56 m (1H, C₂₃H); IR (film) ν /cm⁻¹: 3470; MS *m/z* 458 [M+1]⁺, 457 [M]⁺, 442 [M–Me]⁺.

[§] Spectroscopic data for **4**: ¹H NMR (200 MHz, CDCl₃) 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, C₄H), 3.50 d (1H, *J* 5 Hz, C₂₂H), 3.84 m (4H, OCH₂CH₂O), 4.48 m (1H, C₂₃H); IR (film) ν /cm⁻¹: 3470; MS *m/z* 458 [M+1]⁺, 457 [M]⁺, 442 [M–Me]⁺.

[¶] Spectroscopic data for **5**: ¹H NMR (200 MHz, CDCl₃) 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, C₄H), 2.97 dd (1H, *J*₁ 10 Hz, *J*₂ 17 Hz, C₄'), 4.65 m (1H, C₂₃H), 5.03 d (1H, *J* 8 Hz, C₂₂H); 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, $\text{CH}_2=\text{CHMgBr}$, 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.

References

- 1 V. A. Khripach, R. P. Litvinovskaya and A. V. Baranovskii, *Mendeleev Commun.*, 1992, 117.
- 2 V. A. Khripach, R. P. Litvinovskaya, A. V. Baranovskii and A. A. Akhrem, *Dokl. Akad. Nauk SSSR*, 1991, **318**, 597 (in Russian).
- 3 R. P. Litvinovskaya, A. V. Baranovskii and V. A. Khripach, *Mendeleev Commun.*, 1994, 89.
- 4 W. Sucrow and M. Van Nooy, *Liebigs Ann. Chem.*, 1982, 1987.
- 5 R. P. Litvinovskaya, V. A. Tereshko, S. V. Drach and V. A. Khripach, *Zh. Obshch. Khim.*, in press.
- 6 A. P. Kozikowski and A. K. Grosh, *J. Org. Chem.*, 1984, **49**, 2762.
- 7 A. V. Baranovskii, R. P. Litvinovskaya and V. A. Khripach, *Usp. Khim.*, 1993, **62**, 704 (*Russ. Chem. Rev.*, 1993, **62**, 661).
- 8 V. A. Khripach, R. P. Litvinovskaya and A. V. Baranovskii, *Bioorg. Khim.*, 1990, **16**, 1700 [*Sov. J. Bioorg. Chem. (Engl. Transl.)*, 1990, **16**, 963].
- 9 V. A. Khripach, F. A. Lakhvich and V. N. Zhabinskii, *Brassinosteroidy (Brassinosteroids)*, Nauka i tekhnika, Minsk, 1993 (in Russian).

Received: Moscow, 16th August 1995

Cambridge, 21st September 1995; Com. 5/05555E