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Mendeleev Commun., 1992, **2**(3), 117–118

Mendeleev
Communications

Synthesis of Ecdysone Side Chains *via* Isoxazoline Derivatives

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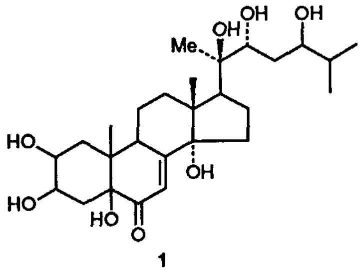
The first synthesis of the side chain of phytoecdysones (ponasterone C and pterosterone) has been achieved *via* 20-hydroxy-20-isoxazolinyl steroids.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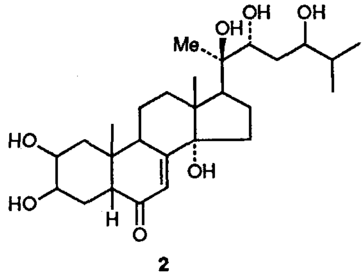
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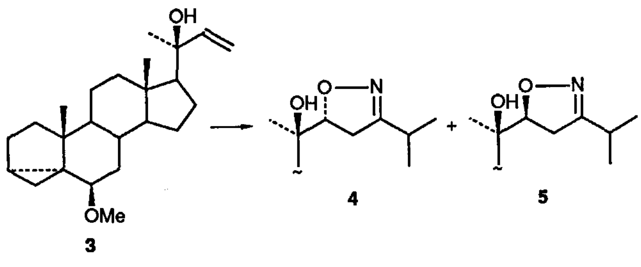
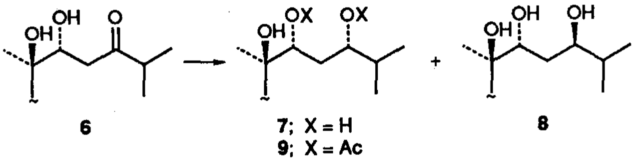
Ecdysteroids bearing a side chain containing a 20,22,24-trihydroxy functionality (ponasterone C **1** and pterosterone **2**) were isolated in 1968[1] and their structure was finally established in 1979.[2] No synthetic work has hitherto been described on the synthesis of these phytoecdysones. This problem is probably associated with the complexity of introducing three asymmetric centres, *i.e.* hydroxy groups, at C-20, C-22 and C-24 with the required stereochemistry. There is much interest in the synthesis of these ecdysone chains, particularly because of the high hormonal activity of ponasterone C and the extremely low content of such ecdysteroids in natural sources.

A new route for C—C bond formation in steroidal side chain syntheses has been proposed previously by our laboratory.[3,4] Based on the reaction of nitrile oxides with terminally unsaturated steroids, it allowed us to introduce new carbon atoms simultaneously with a functionality in a latent form. Here we report an application of the cited approach to a facile synthesis of the unknown (20*R*,22*R*)-dihydroxy-24-ketone **6**, which led us to the synthesis of steroids with an ecdysone side chain bearing the (20*R*,22*R*,24*S*)-triol functionality. The key intermediate **4** was obtained as the major cycloadduct by the reaction of isobutyronitrile oxide with allyl alcohol **3**.[3] The reaction proceeds regio- and stereo-selectively to give a mixture of (22*R*)-**4** and (22*S*)-**5**.†



3 **4** **5**



6 **7**; X = H **9**; X = Ac **8**

When the heterocyclic ring of **4** was subjected to reductive cleavage on Raney nickel with boric acid,[5] the (20*R*,22*R*)-dihydroxy-24-keto derivative **6** was obtained.‡ This compound is a 24-keto analogue of some known ecdysones (murysterone, ponasterone A and B, caladasterone *etc.*) and opens up a completely new route to ecdysteroid synthesis.

Further hydride reduction of **6** with NaBH$_4$ produced the 20,22,24-trihydroxy derivatives **7** and **8**. Their separation by silica gel column chromatography revealed the ratio of the

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† *Spectroscopic data* for **4**: m.p. 108–116 °C (hexane); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (s, 3H, 18-Me), 1.03 (s, 3H, 19-Me), 1.15 (s, 3H, 21-Me), 1.17 (d, 6H, *J* 7 Hz, 26 and 27-Me), 2.69 (sept, 1H, *J* 7 Hz, C$_{25}$-H), 2.78 (m, 1H, C$_6$-H), 2.78 (dd, 1H, J_1 16.8 Hz, J_2 9.6 Hz, C$_{23}$-H), 2.81 (dd, 1H, J_1 16.8 Hz, J_2 10.8 Hz, C$_{23}$-H), 3.33 (s, 3H, OMe), 4.50 (dd, 1H, J_1 10.8 Hz, J_2 9.6 Hz, C$_{22}$-H); IR (KBr) ν/cm^{-1}: 3500, 1630, 1590, 1100; MS *m/z* 443 (M$^+$), 428 (M$^+$ – Me), 414, 400 (M$^+$ – Pr$^{\rm i}$], 313.

For **5**: m.p. 266–268 °C (hexane-EtOAc); ^{1}H NMR (CDCl$_3$) δ 0.87 (s, 3H, 18-Me), 1.03 (s, 3H, 19-Me) 1.17 (d, 6H, *J* 7 Hz, 26 and 27-Me), 1.29 (s, 3H, 21-Me), 2.69 (sept, 1H, *J* 7 Hz, C$_{25}$-H), 2.78 (m, 1H, C$_6$-H), 2.80 (dd, 1H, J_1 16.8 Hz, J_2 10.8 Hz, C$_{23}$-H), 3.03 (dd, 1H, J_1 16.8 Hz, J_2 8.4 Hz, C$_{23}$-H), 3.33 (s, 3H, OMe), 4.46 (dd, 1H, J_1 10.8 Hz, J_2 8.4 Hz, C$_{22}$-H); IR (KBr) ν/cm^{-1} 3500, 1630, 1100; MS *m/z* 444 (M$^+$ + 1), 428 (M$^+$ – Me), 313, 229. The isomers were obtained in a 6:1 ratio (**4**:**5**).

‡ *Spectroscopic data* for **6**: ^{1}H NMR (CDCl$_3$) 0.91 (s, 3H, 18-Me), 1.03 (s, 3H, 19-Me), 1.12 (d, 6H, *J* 7 Hz, 26 and 27-Me), 1.20 (s, 3H, 21-Me), 2.49 (dd, 1H, J_1 16.8 Hz, J_2 9.6 Hz, C$_{23}$-H), 2.60 (dd, 1H, J_1 16.8 Hz, J_2 2 Hz, C$_{23}$-H), 2.64 (sept, 1H, *J* 7 Hz, C$_{25}$-H), 2.78 (m, 1H, C$_6$-H), 3.33 (s, 3H, OMe), 3.95 (dd, 1H, J_1 9.6 Hz, J_2 2 Hz, C$_{22}$-H); IR (KBr) ν/cm^{-1} 3490, 1710, 1100; MS *m/z* 428 (M$^+$ – H$_2$O), 410 (M$^+$ – 2H$_2$O), 331, 299, 281.

epimeric mixture as 2:3. The spectroscopic properties of (24*S*)-**7**§ and its 22,24-diacetate **9**§ were compared with those of ponasterone C and pterosterone[6] and showed that their side chains were identical. It should be noted that the allyl alcohols like **3** of ecdysteroids, with fully functionalized cyclic moieties, are known.[7] If this is so then the synthesis of ponasterone C or pterosterone should be possible *via* similar routes to those considered above.

The approach we have described here has great synthetic potential for the construction of various types of ecdysteroidal side chains. It appears to be useful for the introduction of the side chain and for stereoselective formation of the hydroxy-containing chiral centres at C-20 and C-22 which are characteristic of many natural ecdysones. Almost all the previously known methods for their construction have low selectivity[8] and/or involve many steps.[9]

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§ *Spectroscopic data* for **7**: m.p. 83–85 °C (hexane). ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H, 18-Me), 0.91 (d, 3H, *J* 7 Hz, 26 or 27-Me), 0.92 (d, 3H, *J* 7 Hz, 26 or 27-Me), 1.02 (s, 3H, 19-Me), 1.24 (s, 3H, 21-Me), 2.78 (m, 1H, C_6-H), 3.33 (s, 3H, OMe), 3.58 (dt, 1H, J_1 10 Hz, J_2 5 Hz, C_{24}-H), 3.67 (dd, 1H, J_1 11 Hz, J_2 2 Hz, C_{22}-H); IR (KBr) ν/cm^{-1} 3510, 1100; MS *m/z* 448 (M^+), 398 ($M^+ - MeOH - H_2O$), 331, 299, 255.

For **9**: ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H, 18-Me), 0.88 (d, 6H, *J* 7 Hz, 26 and 27-Me), 1.00 (s, 3H, 19-Me), 1.23 (s, 3H, 21-Me), 2.05 (s, 3H, C_{24}—OAc), 2.09 (s, 3H, C_{22}—OAc), 2.78 (m, 1H, C_6-H), 3.33 (s, 3H, OMe), 4.73 (dt, 1H, J_1 10 Hz, J_2 5 Hz, C_{24}-H), 4.90 (dd, 1H, J_1 10 Hz, J_2 2.5 Hz, C_{22}-H); IR (KBr) ν/cm^{-1} 3520, 1740, 1250, 1100, 1030; MS *m/z* 532 (M^+), 517 ($M^+ - Me$), 477, 331, 299, 281.

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Received: *Moscow, 10th February 1992*
Cambridge, 16th March 1992; *Com. 2/00988I*