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A FACILE SYNTHESIS OF THE 20-HYDROXYECDYSONE SIDE CHAIN VIA A DIHYDROFURAN DERIVATIVE

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Abstract: Key steps of a new synthesis of the 20-hydroxyecdysone side chain are (i) addition of **2** to 20-keto-pregnanes and (ii) the stereoselective reduction of the 22-keto group after OH group protection.

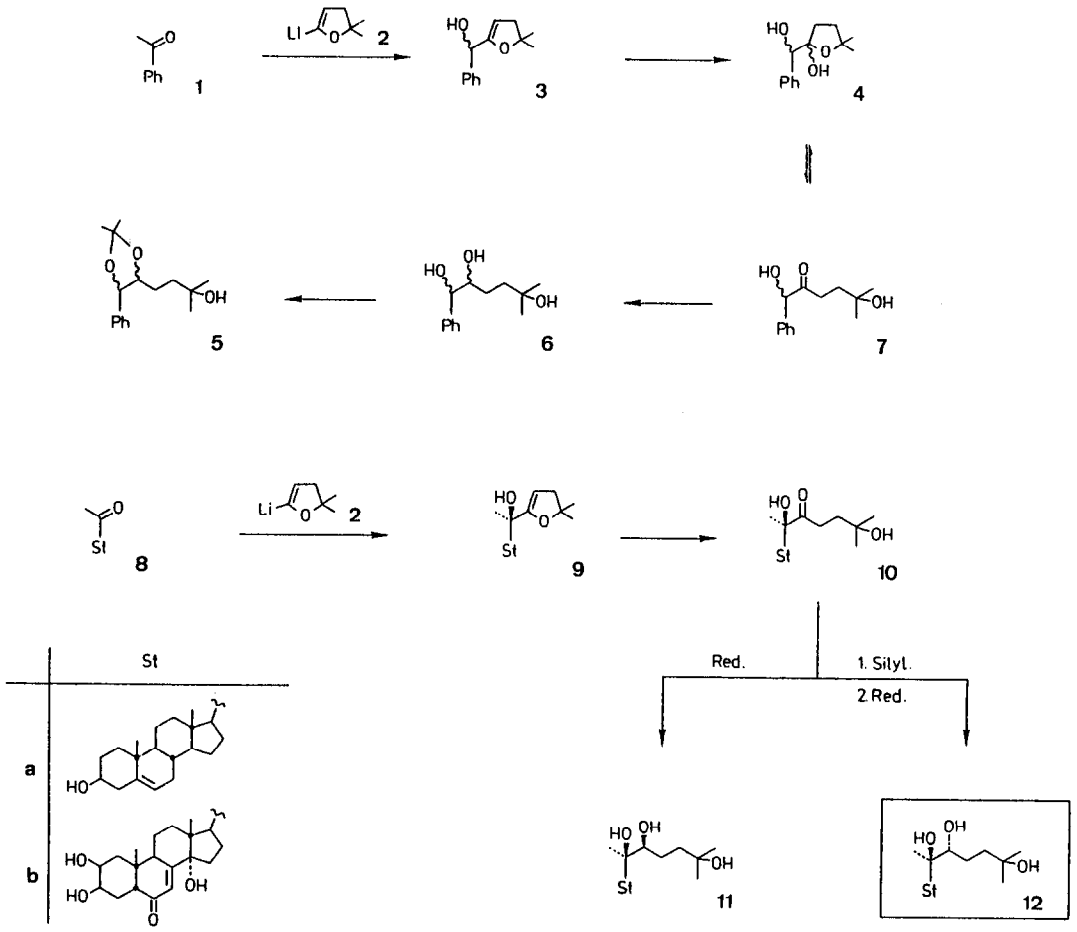
20-Hydroxyecdysone (**12b**) plays a major regulatory role during the postembryonic development of insects and in the crustacean molting cycle.[1] One of the most challenging aspects of the synthesis of this important hormone[2] is the stereocontrolled construction of the side chain[3] with its two centers of chirality. We detail in this communication a highly convergent and stereospecific solution to this problem. Our strategy is centered around the use of **2** as C_{22}-C_{27} fragment. Coupling of **2** with a 20-oxopregnane such as **8a** or **8b** provides in in a single operation the complete carbon framework of **12**.

Lithiation of 2,2-dimethyl-2,3-dihydrofuran[4] to give **2** was performed in THF solution with t-butyllithium (a n-pentane solution of t-butyllithium was added at -78°C, the mixture warmed to 20°C for 2 h and then recooled to -78°C). Reaction of **2** (1.03 equiv) with **1** in THF solution (first at -78°C, then 1 h at 20°C), followed by aqueous work-up and chromatographic separation furnished **3** in 88% yield. Oxymercuration of **3** with $Hg(OAc)_2$ (1 equiv) in THF/water (10 min at 20°C) followed by demercuration with $NaBH_4$ in alkaline solution (10 min at 20°C) led to a mixture of **4** and **7** in 86% yield. This mixture was reduced with $NaBH_4$ and the resulting stereoisomeric diols were separated and characterized after acetonide formation (acetone, BF_3-etherate catalysis, 30 min at 20°C).

Pregnenolone (**8a**) was successfully condensed with **2** (3.7 equiv) under the same experimental conditions to give a mixture of **9a** and **10a** in 85% yield. **9a** was transformed into **10a** by brief treatment with 0.1N HCl in THF/water (30 min at 20°C). A single stereoisomer was obtained to which the 20R-configuration was assigned on the basis of the CH_3-21 chemical shift (δ = 1.46).[5] Similarly, reaction of **2** (12 equiv) with poststerone (**8b**)[6] (3 h at -78°C, H_2O-quench at -30°C) gave a mixture of **9b** and **10b** which on treatment with 0.1N HCl yielded cleanly **10b** in 79% overall yield ($\delta_{(CH_3\text{-}21)}$ = 1.68).

As expected,[7] reduction of the 22-keto group in **10a** and **10b** with lithium tri-t-butoxyaluminium hydride gave mainly the 22S-alcohols **11a** and **11b**, respectively (in both cases, ratio **11**:**12** about 16:1). The configuration at C-22 was determined from the CD of *in situ* complexes with $Mo_2(OAc)_4$.[8,9] The product ratio was, however, completely reversed when the reduction was performed after protection of the OH groups in **10a** and **10b** as trimethylsilyl ethers. Thus, reaction of **10b** with excess bis(trimethylsilyl)acetamide in CH_2Cl_2 (14 h at 40°C), removal of the solvent in vacuo, reduction with lithium tri-t-butoxyaluminium hydride in THF (5.5 h at -78°C), and cleavage of the silyl ether groups with 0.1N HCl (20 h at 20°C) gave 58% 20-hydroxyecdysone (**12b**, identical with an authentic sample) along with 7% **11b**. Similar results were obtained for **10a**.

Of all the published procedures this seems to be the most simple method for introducing the 20-hydroxyecdysone side chain.



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9. These results will be reported elsewhere.

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