Tetrahedron Letters, Vol. 34, No. 27, pp. 4337-4340, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

21,24-Dinorchol-5-en-22-yne-3β,17,20-triol : Stereoselective Synthesis of the Four Diastereomers as Inhibitors of Ecdysone Biosynthesis

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Key words : Ecdysone; Inhibitors; Trimethylsilylacetylene magnesium bromide; diastereoselectivity.

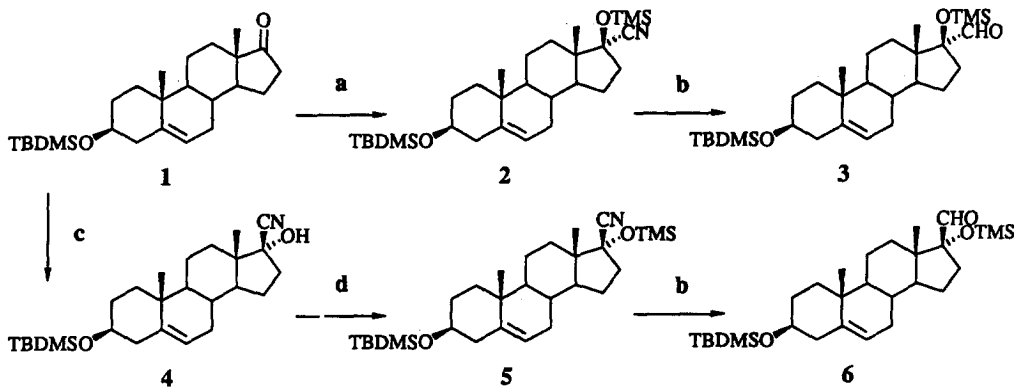
Abstract : Starting from the two silylated cyanohydrins (**2** and **5**) we synthesized the four diastereomers of the title compound. This was achieved by adding either lithium trimethylsilylacetylide or the trimethylsilylacetylide magnesium bromide on the corresponding aldhehydes **3** and **6**, at -78°C. These compounds are to be tested as inhibitors of the ecdysone biosynthesis.

In the course of a preceding research, we have synthesized several acetylenic steroids to irreversibly inhibit the C-22 hydroxylase[1-3]. Our results indicated that the presence of a hydroxyl group, either at C-17 or C-20, resulted in a stronger inhibition (up to 10^{-8}M). To go into this study thoroughly, we decided to synthesize inhibitors where both of those positions are hydroxylated, and therefore developed a stereoselective approach.

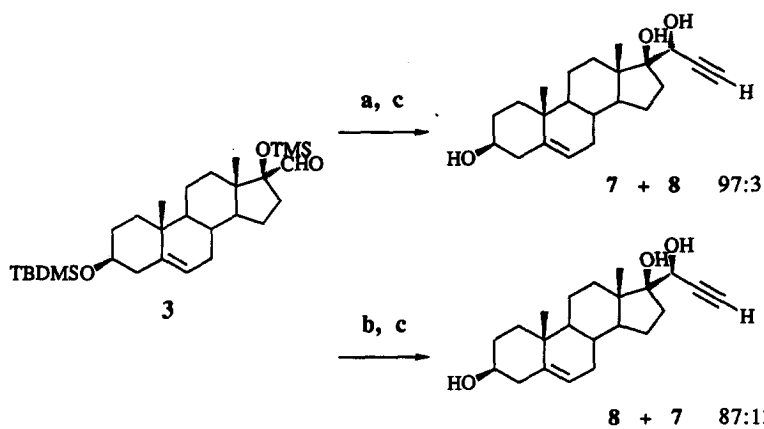
Our strategy was based upon the silylated hydroxy-aldehydes **3** and **6**, which were prepared from the corresponding cyanohydrins, according to a procedure described by Reid *et al.*[4]. Reaction of TBDMS protected dehydroepiandrosterone with TMS cyanide[5] gave the silylated cyanohydrin **3** in very good yield, while reaction with potassium cyanide catalysed by acetic acid in methanol gave pure **4** upon cristallisation[6]. Silylation with TMSCl and imidazole then furnished the isomer **6** in 95% yield. Reduction of both protected cyanohydrins with DIBAL in MTBE/THF 95/5 followed by acidic work up (30% AcOH), gave the desired aldehydes **3** and **6** in almost quantitative yields.

Condensation of lithium trimethylsilylacetylide with the aldehyde **3**, followed by deprotection with TBAF, led to the 3β,17β,(20*R*) triol **7**; a small amount of the (20*S*) diastereomer was also isolated (**7**/**8** : 97/3). Surprisingly, we found the corresponding Grignard did reverse this ratio (**7**/**8** : 13/87), following the predictions of the chelation control (Cram's cyclic model)[7]. This reversal of stereoselectivity only occured when the reaction was performed at -78°C and allowed to warm up to room temperature[8]. When conducted at 0°C, we

obtained the same stereoselectivity as with lithium trimethylsilylacetylide, which corresponds to the Felkin model.



a TMSCN, ZnI_2, CH_2Cl_2, r.t., 15 mn (Quant.) b DIBAL, MTBE/THF 95/5, -20°C, 10 mn; AcOH 50% (95%)
c KCN, AcOH, MeOH, r.t., 24h (95%) d TMSCl, Imidazole, CH_2Cl_2, r.t., 5 mn (95%).

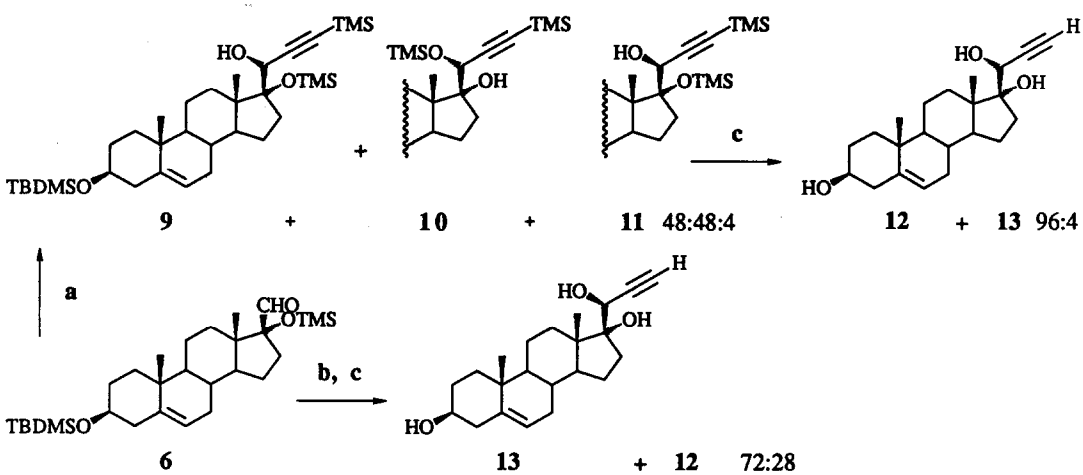


a TMS-C≡CLi, THF, -78°C, 15 mn (86%) b TMS-C≡CMgBr, THF, -78°C to r.t., 1h (89%) c nBu_4NF, THF, r.t., 24h (Quant.).

Similarly, we repeated both experiments with the aldehyde **6**. With lithium trimethylsilylacetylide, we obtained a mixture of three products, where **9** and **10**, in equimolar amounts, corresponded to the same diastereomer, (since in **10** the TMS group was shifted from the C-17 to the C-20 position, as shown by NMR data). Therefore, the diastereomeric ratio was 96:4 and we obtained the 3β,17α,(20R) triol quantitatively after deprotection. When the condensation was repeated with addition of trimethylsilylacetylide magnesium bromide at -78°C and the reaction mixture allowed to reach room temperature, we also observed a reversed diastereoselectivity, though in a lower extent. Furthermore the results in this case were difficult to reproduce.

However, we were able to synthesize the fourth diastereomer **13**. Our NMR data are also consistent with the work of Chaudhuri *et al.*[9], upon the synthesis of 17α,20α-dihydroxycholesterol.

We have also looked for salt effects in the course of the condensation with lithium trimethylsilylacetylide, but we did not observe significant changes with either LiBr or $MgCl_2$.



9 + **10** + **11** 48:48:4 → **12** + **13** 96:4

6 → **13** + **12** 72:28

a TMS-C≡CLi, THF, -78°C, 15 mn (84%) b TMS-C≡CMgBr, THF, -78°C to r.t., 1h (90%) c nBu_4NF, THF, r.t., 24h (quant.).

In conclusion, we have been able to synthesize the four desired diastereomers stereoselectively thanks to the different reactivity of the two nucleophiles at -78°C. Thus, we established a simple and efficient route to 22-yne-17, 20-diols, starting from easily accessible silylated hydroxy-aldehydes. We have now started biological studies with those new compounds and will further report our results.

The inhibitory effect of the compounds **7**, **8**, **12** and **13** has been measured *in vitro* on the ecdysone biosynthesis in larval prothoracic gland of *Locusta migratoria*[1]. All of them were active at a concentration of 10^{-5}M and presented a depressory effect of 50 to 60%.

Acknowledgements. Financial support of this work by a grant from Ciba-Geigy is gratefully acknowledged.

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8. In a dry three-necked flask fitted with a reflux condenser, Mg (5 eq., 48 mg, 2.0 mmol.) was covered with dry THF (1 ml) and freshly distilled ethyl bromide (5 eq., 150 µl, 2.0 mmol.) was added dropwise without stirring under argon : once the reaction started, the solution was stirred and the addition maintained in order to obtain a moderate reflux. After 15 mn, the magnesium was consumed and the solution was cooled to 0°C. THF (5 ml) was added, followed by trimethylsilylacetylene (5.5 eq., 320 µl, 2.2 mmol.) dropwise. Ice bath was then removed until ethane bubling ceased. The Grignard was then cooled down to -78°C and the silylated hydroxyaldehyde **3** or **6** (200 mg, 0.4 mmol.) in THF (4 ml) was transfered with the help of a canula. The reaction mixture was allowed to reach r. t. progressively and 10% aqueous NH_4Cl was introduced. After extraction with Et_2O, the combined organic phases were dried over Na_2SO_4 and evaporated to dryness. Medium pressure chromatography over silica eluted with 5°/°° AcOEt in hexane furnished the desired protected diastereomers.
9. Chaudhuri N.K., Williams J.G., Nickolson R. and Gut M., *J. Org. Chem.*, **1969**, *34*, 3759. In the case of 17α,(20*R*)-dihydroxycholesterol, the chemical shifts at C-18 and C-19 are 0.90 and 1.01 ppm, respectively (0.84 and 1.02 ppm for **12** in our case). Similarly for 17α,(20*S*)-dihydroxycholesterol., Chaudhuri *et al.* report 0.85 and 1.01 ppm (0.81 and 1.02 ppm for **13**).

(Received in France 16 April 1993; accepted 14 May 1993)