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Synthesis of Ecdysteroid Inhibitors of Ecdysone Biosynthesis. Inhibition of the C-25 Hydroxylation.

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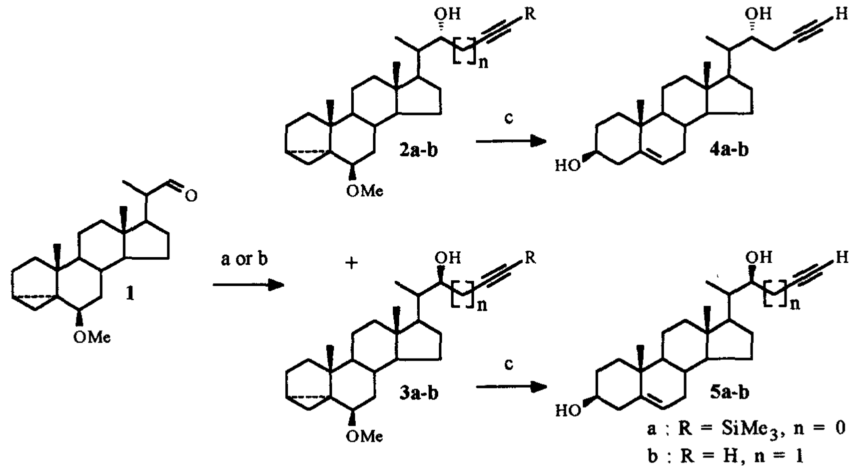
Key words : Ecdysone ; C-25 Hydroxylase ; Acetylenic inhibitor.

Abstract *: Condensation of acetylenic nucleophiles on the i-ether 1 leads to new inhibitors of the ecdysone biosynthesis, possessing a hydroxy group at C-22.*

The synthesis of several acetylenic cholesteryl derivatives have been reported by our group to inhibit C-22 hydroxylase in the ecdysone biosynthesis[1-3]. We assumed it would be possible to inhibit C-25 hydroxylase by simply extending the acetylenic side chain .



a TMS-C≡C-Li, THF, -78°C, 15 mn (85%, n = 1) or **b** HC≡C-CH_2-MgBr, Et_2O, 0°C, 3h (80%, n = 2) **c** pTsOH, dioxane/H_2O 7/3, 80°C, 30 mn (58-73%).

Scheme 1

In this aim, we started our synthesis from i-ether **1**, obtained from ergosterol according to a well known method[4]. We decided to introduce the side chain with an organometallic nucleophile in order to have a second hydroxy group, which favourise solubility during the *in vitro* experiments. Thus, the addition of lithium trimethylsilylacetylide gave compounds **2a** and **3a** (Scheme 1) in good yields. After separation, both of them were treated with pTsOH in a 7/3 mixture of dioxane and water, to give **4a** and **5a** in moderate yields[5]. Products **4b** and **5b**[5] were obtained in a very similar way, using propargyl magnesium bromide. Diastereoselectivity was extremely low, giving a slight diastereomeric excess of the (22*S*) configuration

Possessing these two series of diastereomers, we performed experiments on *Locusta migratoria* Inhibitory effects have been measured *in vitro* on the ecdysone biosynthesis in larval prothoracic glands[1]. Results are clearly indicating that the inhibition is higher either when the acetylenic side chain is longer (**4b** and **5b** : 66% and 37% at 10^{-5}M respectively) or when the configuration at C-22 is *R* (**4a** and **4b** · 36% at 10^{-5}M with **4a**), this one from ecdysone. Compound **5a** does not inhibit at all.

Acknowledgements

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References and Notes

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5. ^{1}H NMR 200 MHz ($CDCl_3$) ;
4a : δ 0.71 (s, 3H, H-18), 1.01 (s, 3H, H-19), 1 05 (d, 3H, J=6.5 Hz, H-21), 2 29 (s, 1H, H-24), 3 52 (m, 1H, $w_{1/2}$=25 Hz, H-3), 4.42 (bs, 1H, H-22), 5.35 (d, 1H, J=5.0 Hz, H-6). Anal. Calcd for $C_{24}H_{36}O_2$ (356.55) : C, 80.85 ; H, 10 18. Found : C, 80.62 , H, 10 28
5a : 0 70 (s, 3H, H-18), 1.01 (s, 3H, H-19), 1.12 (d, 3H, J=6.6 Hz, H-21), 2.27 (s, 1H, H-24), 3.52 (m, 1H, $w_{1/2}$=25 Hz, H-3), 4 46 (bs, 1H, H-22), 5.35 (d, J=4.9 Hz, H-6). Anal Calcd for $C_{24}H_{36}O_2$ (356 55) . C, 80.85 ; H, 10 18 Found : C, 80.45 , H, 10 22
4b 0 70 (s, 3H, H-18), 1.01 (s, 3H, H-19), 1.05 (d, 3H, J=6 5 Hz, H-21), 2 49 (s, 1H, H-25), 3 53 (m, 1H, $w_{1/2}$=25 Hz, H-3), 4.44 (bs, 1H, H-22), 5.35 (d, 1H, J=5.1 Hz, H-6). Anal. Calcd for $C_{25}H_{38}O_2$ (370 58) : C, 81.03 ; H, 10.34. Found · C, 81.00 , H, 10.41
5b : 0.69 (s, 3H, H-18), 1.01 (s, 3H, H-19), 1.11 (d, 3H, J=6.5 Hz, H-21), 2.43 (s, 1H, H-25), 3.52 (m, 1H, $w_{1/2}$=25 Hz, H-3), 4 46 (bs, J=5 5 Hz, H-6). Anal. Calcd for $C_{25}H_{38}O_2$ (370 58) : C, 81.03 ; H, 10 34. Found : C, 81.18 ; H, 10 30