Tetrahedron Letters, Vol.32, No.38, pp 5171-5174, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Synthesis of an Ecdysteroid Inhibitor of Ecdysone Biosynthesis

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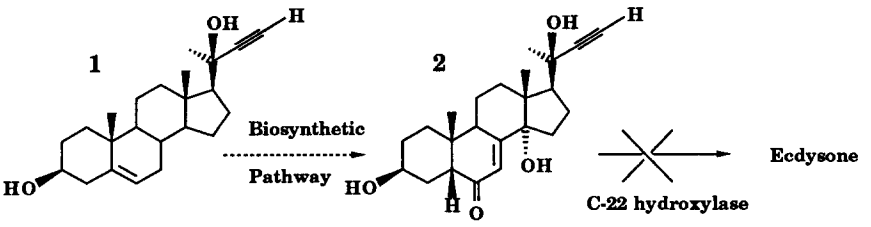
Key words : Ecdysone; Ecdysteroids; Ecdysteroid inhibitor; Hydroboration; Acetylenic derivative.

***Abstract** : The hydroboration-oxidation of a $\Delta^{5,7}$ pregnadiene leads to a Δ^{7} 6α-hydroxyderivative. This is converted to an acetylenic analogue of ecdysteroids, which is an inhibitor of their biosynthesis in vitro.*

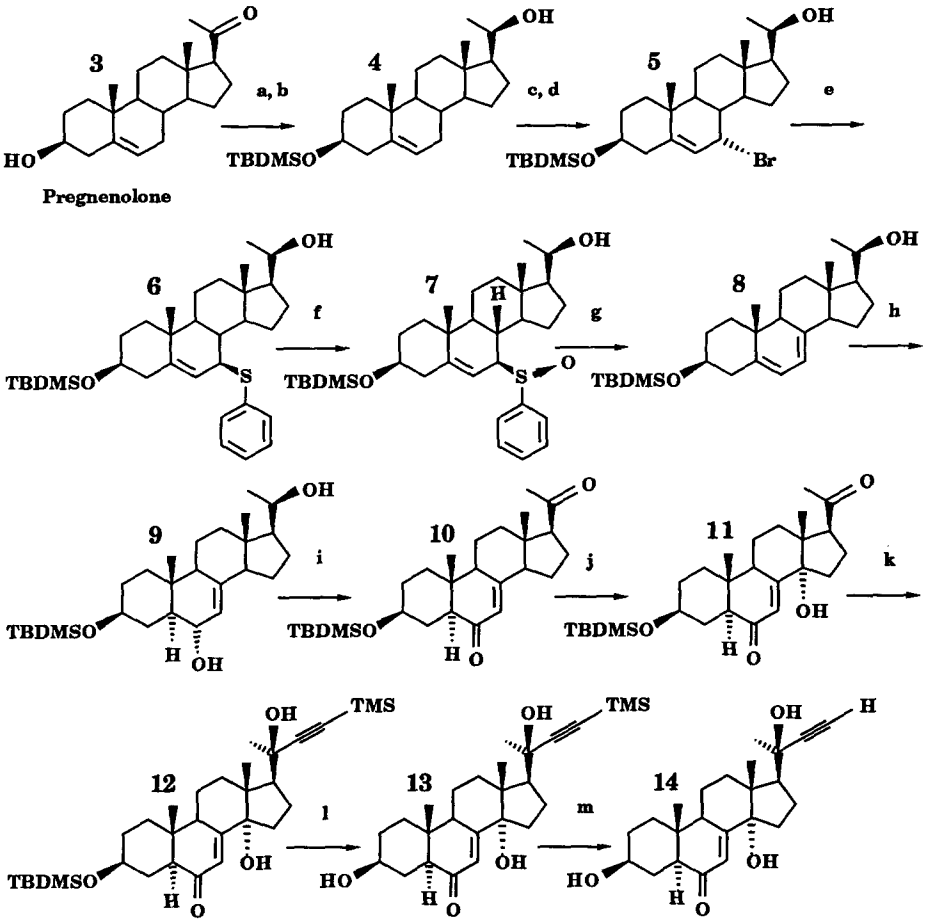
Several acetylenic cholesteryl derivatives have been reported by our group to irreversibly inhibit ecdysone biosynthesis[1, 2]. It was reasonable to assume that the cholesteryl nucleus was transformed into an ecdysteroid precursor by the biosynthetic enzymes before reaching its target, the C-22 hydroxylase, which was inactivated by the acetylenic function (Scheme 1).



Scheme 1

In an attempt to check this hypothesis, we needed to establish a short and efficient synthesis, enabling us to obtain sufficient amounts of products for biological tests. The usual method for synthesizing these molecules consists in either a strong oxidation of a $\Delta^{5,7}$ diene[3, 4], or a bromination in the α position to a C-6 ketone[5, 6];

however, both methods gave moderate yields of the desired product. Therefore, we have investigated the hydroboration of a $\Delta^{5,7}$ diene as an alternate reaction[7], starting from pregnenolone. For this purpose, we have introduced this diene by an allylic bromination followed by the elimination of the corresponding sulfoxide (Scheme 2).



-a- TBDMSCl (1.2 eq.), iPr2EtN, CH_2Cl_2/DMF, rt, 25h, quant.; -b- $NaBH_4$ (5.0 eq.), MeOH, 0°C, 15 mn, 85%; -c- Dibromodimethylhydantoin (1.0 eq.), hexane, reflux, 20 mn; -d- LiBr (2.0 eq.), toluene/acetone, 0°C, 2h; -e- Thiophenol (1.3 eq.), Et_3N, rt, 30 mn; -f- mCPBA (1.1 eq.), AcOEt, 0°C, 45 mn; -g- Et_3N, toluene, 70°C, 30h, 56% starting from 4; -h- BH_3:THF (5.0 eq.), THF, 0°C, 15 mn, NaOH/H_2O_2, 86%; -i- PCC (4.0 eq.), CH_2Cl_2, rt, 20 mn, 81%; -j- SeO_2 (10 eq.), dioxane, 80°C, 5 mn, 82%; -k- Mg, EtBr, TMSacetylene (50 eq.), THF, 0°C, 30 mn, 83%; -l- HF_x:Py, Py/THF, rt, 1h, quant.; -m- nBu_4NF (1.5 eq.), THF, rt, 15 mn, quant.

Scheme 2

We have achieved the synthesis of the intermediate 8[8], possessing a $\Delta^{5,7}$ diene, by reducing TBDMS protected pregnenolone with $NaBH_4$, to give the corresponding 20(R) alcohol 4 as the major diastereomer. Further conversion to the $\Delta^{5,7}$ diene was realized according to a selective procedure described by Confalone *et*

al.[9]. After the classical bromination at C-7 with 2,3-dibromo-5,5-dimethylhydantoin and equilibration with LiBr (or nBu_4NBr), the mixture of bromides, where the 7α epimer **5** predominates, was treated with thiophenol to form the 7β-allylic sulfide as the major product. Oxidation with mCPBA then gave the corresponding sulfoxide **7**. The overall conversion (56% yield) was conducted without chromatography from compound **4** up to the required diene **8**, which was free of the $\Delta^{4,6}$ isomer. Hydroboration of **8** with BH_3:THF followed by oxidation with alkaline hydrogen peroxide yielded the desired allylic alcohol **9**[10]. All attempts to oxidize the crude organoborane in a one pot procedure with PCC[11, 12] were unsuccessful, however, oxidation of alcohol **9** with PCC gave the corresponding diketone **10**[13]. Subsequent treatment with SeO_2[14] furnished the 14α-hydroxy derivative **11** (30% from pregnenolone), already described by Kametani *et al.*[6] (10% yield with the same starting material), in the course of a 2-deoxyecdysone synthesis. Interestingly, condensation of the acetylenic side chain required 50 equivalents of the acetylenic Grignard to reach completion, allowing us to isolate compound **12** in 83% yield[15]. We failed to achieve the deprotection of both TBDMS and TMS in one step with nBu_4NF, but treatment with the HF_x:Py complex gave the TBDMS deprotected molecule **13** as the sole product[16]. TMS was then removed with nBu_4NF, giving the target molecule **14**[17] quantitatively.

Thus in conclusion, we have carried out a versatile method for synthesizing a series of potential inhibitors; we are presently involved in the synthesis of a 2-deoxyecdysteroid acetylenic derivative (5β-H, possessing a A/B cis junction).

ACKNOWLEDGEMENTS

Financial support of this work by a grant from Ciba Geigy is gratefully acknowledged.We express our gratitude to Professor Guy Ourisson for critical reading of this manuscript.

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8. **8** : ^1H NMR 200 MHz ($CDCl_3$), δ : 0.09 (s, 6H, $SiMe_2$), 0.71 (s, 3H, H-18), 0.90 (s, 9H, H-$SiCMe_3$), 0.95 (s, 3H, H-19), 1.17 (d, 3H, J=6.1, H-21), 3.58 (m, 1H, $w_{1/2}$=23, H-3), 3.75 (qd, 1H, J_1=6.1, J_2=3.4, H-20), 5.39 (m, 1H, $w_{1/2}$=24, H-7), 5.56 (m, 1H, $w_{1/2}$=14, H-6). MS 70 eV, m/e (%) : 430 (M^+, 24), 357 (7), 298 (28), 297 (23), 283 (84), 257 (100), 253 (16), 339 (10).
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10. **9** : ^1H NMR 200 MHz ($CDCl_3$), δ : 0.07 (s, 6H, H-$SiMe_2$), 0.64 (s, 3H, H-18), 0,89 (s, 9H, H-

$SiCMe_3$), 0.92 (s, 3H, H-19), 1.16 (d, 3H, J=6.1, H-21), 3.72 (qd, 1H, J_1=6.2, J_2=3.4, H-20), 4.0 (m, 1H, $w_{1/2}$=24, H-3), 5.07 (m, 1H, $w_{1/2}$=10, H-6), 6.47 (s, 1H, H-7). MS 70 eV, m/e (%) : 448 (M^+, 20), 430 (58), 415 (10), 391 (70), 389 (10), 385 (8), 375 (23), 373 (40), 357 (5), 355 (3), 329 (10), 315 (100).

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13. **10** : ^1H NMR 200 MHz ($CDCl_3$), δ : 0.07 (s, 6H, H-$SiMe_2$), 0.57 (s, 3H, H-19), 0.89 (s, 9H, H-$SiCMe_3$), 0.97 (s, 3H, H-19), 2.16 (s, 3H, H-21), 2.23 (dd, 1H, J_1=12, J_2=3.5, H-5), 2.69 (t, 1H, J=9.0, H-9), 3.57 (m, $w_{1/2}$=25, H-3), 5.75 (t, 1H, J=2.2, H-7). MS 70 eV, m/e (%) : 44 (M^+, 1), 429 (2), 387 (100), 385 (7).
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15. In a dry three-necked flask fitted with a reflux condenser, Mg (50 eq., 264 mg, 10.9 mmol.) was covered with dry THF (3.0 ml) and EtBr(50 eq., 0.8 ml, 10.9 mmol.) was introduced dropwise under Ar, in order to maintain a moderate reflux. When Mg was consumed, the reaction mixture was cooled to 0°C and TMSacetylene (60 eq., 1.7 ml, 12.0 mmol) was cautiously added. After 30 mn, compound **11** (100 mg, 0.2 mmol.) in THF (5.0 ml) was transferred on the Grignard via a canula, and the mixture was allowed to stir for another 30 mn. Reaction mixture was then treated with 10% aq. NH_4Cl and extracted with Et_2O. Combined extracts were dried (Na_2SO_4) and evaporated to dryness. Medium pressure chromatography over silica gel, with elution with hexane/AcOEt 90/10, yielded **12** (101 mg, 83%).
16. This reaction was conducted in a polyethylene flask. Compound **12** (25 mg, 45 µmol.) in 1 ml of a HF_x:Py solution (prepared from 6.5 ml of the HF_x:Py complex, 15.7 ml of dry pyridine and 50 ml of dry THF) was stirred for 1h at rt. The reaction mixture was then poured into 50 ml of a saturated aq. $NaHCO_3$ solution. Extraction with Et_2O, followed by drying over $MgSO_4$ and evaporation to dryness gave compound **13** (20 mg, quant.).
17. **14** : ^1H NMR 200 MHz (MeOD), δ : 0.85 (s, 3H, H-18), 0.97 (s, 3H, H-19), 1.48 (s, 3H, H-21), 2.74 (ddd, 1H, J_1=7.5, J_2=3.0, J_3=2.6, H-9), 2.83 (s, 1H, H-23), 3.54 (m, 1H $w_{1/2}$=25, H-3), 5.82 (d, 1H, J=2.7, H-7). MS 70eV, m/e (%) : 372 (M^+, 100), 354 (40), 339 (47), 321 (48), 311 (33), 303 (14).

(Received in UK 8 July 1991)