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SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—XII[1]

SYNTHESIS OF SCEPTRUMGENIN AND ISONUATIGENIN

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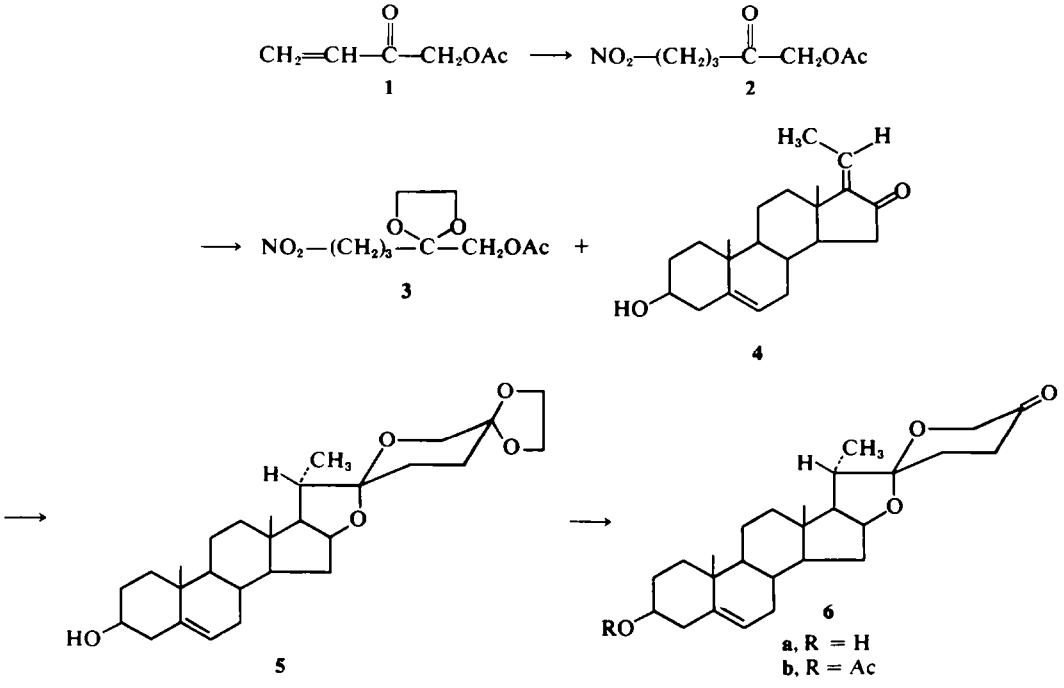
Abstract—The Michael adduct of 5-nitro-2,2-ethylene-dioxypentan-1-ol acetate with E-5,17(20)-pregnadien-3β-ol-16-one gave on reduction with sodium borohydride and deketalisation, spirost-5-en-3β-ol-25-one. This intermediate was converted to sceptrumgenin through reaction with triphenyl phosphonium methylide and to isonuatigenin by treatment with dimethyl oxosulfonium methylide followed by lithium aluminium hydride.

In continuation of our work on steroidal sapogenins, we now report a method for synthesizing C-25 carbonyl spirostanes. These are versatile intermediates enabling introduction, in ring F, of diverse functionalities present in atypical sapogenins as illustrated by synthesis of sceptrumgenin and isonuatigenin.

Michael addition of nitromethane to but-3-en-1-ol-2-one acetate (**1**) in presence of Triton B gave the compound **2** which reacted with ethylene glycol. Reaction of the ketal **3** with E-5,17(20)-pregnadien-3β-ol-16-one (**4**)[2], in *t*-butanol containing potassium *t*-butoxide, followed by treatment with sodium borohydride afforded the intermediate **5**. Obviously, the adduct from the second Michael reaction had, on exposure to sodium borohydride and subsequent work-up, up, undergone (i) reduction of the C-16 CO group, (ii) hydrolysis of C-26 acetate, (iii) virtual Nef† reaction at C-22 and (iv) a double ring closure. Deketalisation of **5** was accomplished by exchange with excess acetone and the product acetylated to secure the ketone **6b** which was



†Conversion of C-22 nitro to a keto group may entail a Nef type reaction or may proceed through reduction, to a C=N-moiety, followed by hydrolysis. Simple γ-nitro ketones do not undergo this reaction. In the present case forced proximity of the two functional groups[3] seems to result in this unexpected course.

identical* with the material prepared by Minato[4] through degradation of a mixture of narthogenin and isonarthogenin.

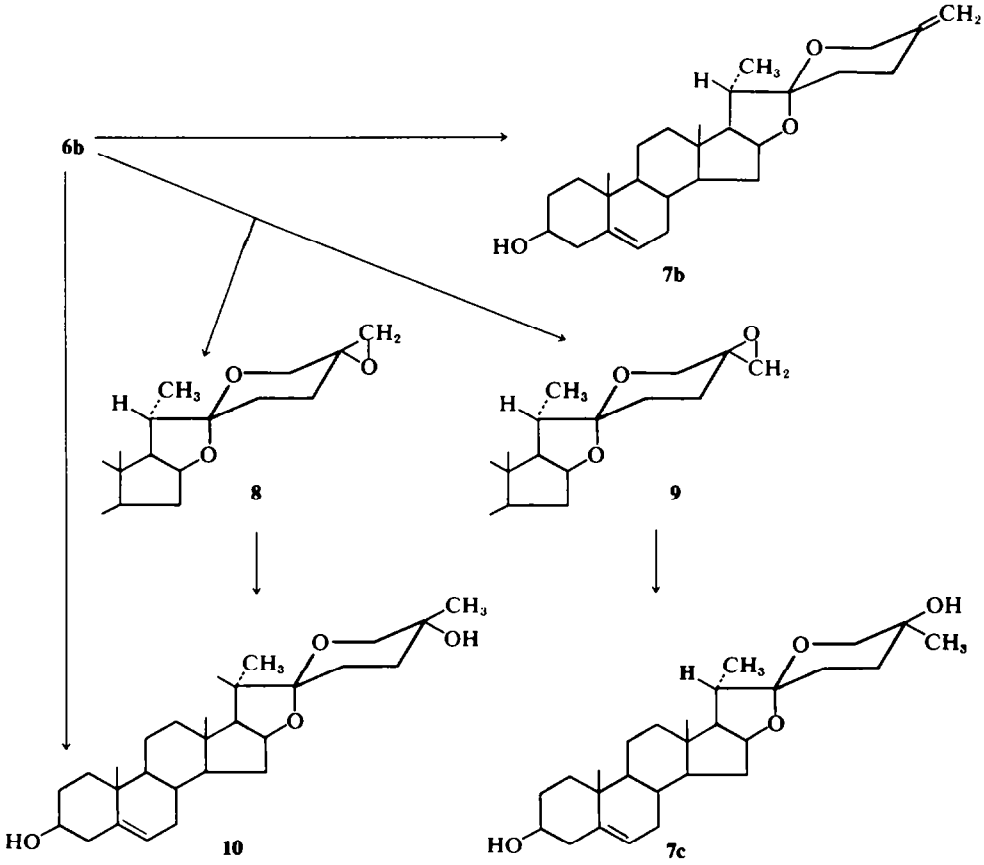
From *Isoplexis sceptrum* Freire *et al*[5] recently reported isolation of a new sapogenin, sceptrumgenin, to which the structure **7b** was assigned. In view of the possibility that this compound may be an intermediate in the yamogenin–diosgenin interconversion in plants,[6] it was considered especially important to confirm the proposed structure by synthesis. The acetate **6b** on Wittig reaction with triphenyl phosphonium methylide afforded a product with a m.p. (179–81°) very close to that reported[5] for sceptrumgenin (182–84°) and with an identical IR spectrum.† The structure of the synthetic material was further confirmed through its mass spectrum which showed, besides the molecular ion at *m/e* 412, characteristic[7] sapogenin peaks (*m/e* 271, 300, 342, 345) postulated to arise from fragmentations entailing loss of the C-25 moiety. The base peak in the mass spectrum of **7b** appeared at *m/e* 137 (**13b**) instead of 139 (**13a**) which is typical of normal sapogenins like diosgenin. This difference can be readily understood in terms of its proposed genesis (**7**→**11**→**12**→**13**).

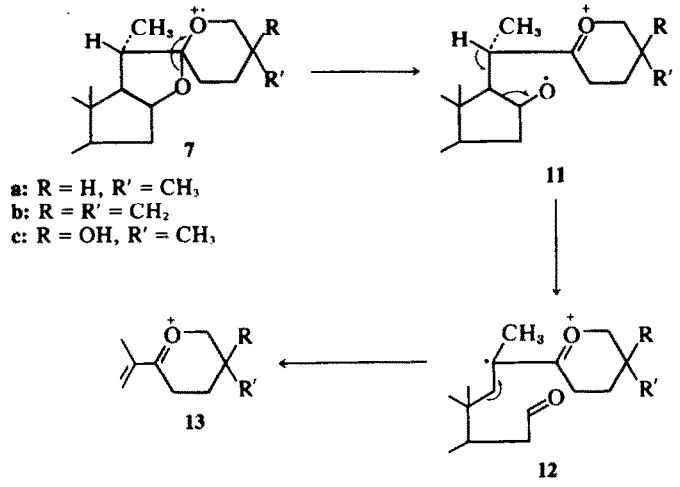
Tschesche and Richert[8] have reported isolation of isonuatigenin (**7c**, m.p. 248–51°) from *Solanum sisymbrifolium*. Conversion of **6b** to this structure was first attempted through a Grignard reaction with methyl magnesium iodide. The IR spectrum of the product **10** (m.p. 215–18°) showed bands at 850, 900 (w), 915 (s), 992 cm^{-1}, expected[9] for a spirostane with an equatorial OH group. The isomeric alcohol **7c** could not be isolated from the crude mixture even after careful chromatography, although TLC did show a faint second spot. Almost exclusive axial attack by the Grignard reagent on 6-membered ring ketone **6b** is somewhat surprising.[10a]‡ One reason could be the absence of an axial hydrogen making approach from this side less hindered than usual. A more likely possibility is prior complexing of the Grignard reagent with the C-26 oxygen ensuring delivery of the Me group from the axial side. Accordingly, it was thought that

*We are grateful to Prof. Minato for comparison of our ketone **6a** and its acetate with their materials and for sending a sample of **7b** acetate.

†We are grateful to Prof. Gonzàlez for supplying the IR spectrum of natural sceptrumgenin. Unfortunately no sample was available for direct comparison by mixed m.p. etc.

‡Normally, Grignard reaction on cyclohexanones results in predominant entry from the equatorial side.[10b]





a: R = H, R′ = CH_3
b: R = R′ = CH_2
c: R = OH, R′ = CH_3

if the Grignard reaction was carried out in the presence of a strong external complexing agent, like triethylamine, the axial:equatorial ratio may get favourably altered. Reaction under these conditions, however, proceeded slowly and did not give any of the desired diols. The following alternate approach was then adopted.

The acetate **6b** was treated with dimethyl oxosulfonium methylide[11] and the mixture of the oxiranes formed was, without separation, reduced with LAH. Chromatography on neutral alumina gave **7c** (10%) along with the earlier obtained diol **10** (62%). As the natural sample was not available for direct comparison, structure **7c** was confirmed through mass spectrometry. In addition to the characteristic spirostane peaks discussed above, the base peak was now observed at *m/e* 155 due to the presence of the additional oxygen at C-25 (**13a**).

Since all the starting materials are available by synthetic methods,[12] the present work constitutes a formal total synthesis of sceptrumgenin and isonuatigenin.

EXPERIMENTAL

5-Nitro-pentan-1-ol-2-one acetate (**2**). Compound **1** (19·3 g) was added, dropwise in 3 hr, to a refluxing mixture of nitromethane (91·5 g), dry ether (20 ml) and Triton B (1 ml). After additional refluxing for 25 hr, the mixture was cooled, acidified with HCl (10%), washed with brine and dried. Ether and unreacted nitromethane were distilled off and the residue carefully fractionated to obtain **2** as a pale yellow oil (9 g), b.p. 115–17°/0·5 mm, ν_{max} 1740, 1550, 1250 cm^{-1}. (Found: C, 44·85; H, 5·85; N, 7·75. $C_7H_{11}O_5N$ requires: C, 44·44; H, 5·86; N, 7·41%).

5-Nitro-2,2-ethylenedioxypentan-1-ol acetate (**3**). A soln of **2** (9 g) ethylene glycol (4 ml) and *p*-toluenesulfonic acid (100 mg) in benzene (50 ml) was refluxed for 20 hr with continuous water removal. Anhyd K_2CO_3 (100 mg) was added and the mixture kept for 12 hr with occasional shaking. The organic layer was decanted and the solvent distilled off. The residue upon fractionation afforded **3** as an oil (14·5 g), b.p. 165–67°/0·9 mm, ν_{max} 1740, 1550, 1240, 1060 cm^{-1}. (Found: C, 46·10; H, 6·00; N, 6·21. $C_9H_{15}O_6N$ requires: C, 46·35; H, 6·48; N, 6·01%).

25,25-Ethylenedioxyspirost-5-en-3β-ol (**5**). A soln of K salt of **3** [from **3**, (1·74 g) K metal, (117 mg)] in *t*-BuOH (9 ml) was added to the E-ketone **4** (942 mg) dissolved in *t*-BuOH (6 ml) and the mixture allowed to stand at room temp. Periodically a small portion of the heterogeneous mixture was withdrawn, neutralised with dil AcOH, diluted with water and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$ aq and water, dried and the solvent evaporated. The amount of unreacted **4** in the residue was estimated by TLC. When the starting material had completely disappeared (20 days), EtOH (20 ml) and $NaBH_4$ (1·8 g) were added and the mixture allowed to stand for 24 hr at room temp. It was then made just acidic with HCl (10%) and diluted with water (250 ml). The ppt was collected by filtration and crystallised from MeOH to get a colourless solid (340 mg), m.p. 235–37°, $(\alpha)_D$ −75·11°. (Found: C, 73·56; H, 9·30; $C_{29}H_{42}O_5$ requires: C, 73·32; H, 9·23%).

Spirost-5-en-3β-ol-25-one (**6a**). A soln of **5** (300 mg) in acetone (100 ml) and HCl (10%; 15 ml) was refluxed for 20 hr, water (200 ml) was then added and the ppt collected, washed with water and dried. It was crystallised from acetone to obtain **6a** (210 mg), m.p. 212–15° (mixed m.p. with Minato's[4] synthetic sample 212–15°), $(\alpha)_D$ −137·3°, ν_{max} 1725 cm^{-1}, (Found: C, 75·43; H, 9·36. $C_{26}H_{38}O_4$ requires: C, 75·32; H, 9·24%).

The ketone **6a** was acetylated with pyridine -Ac_2O in the usual manner. Crystallisation from MeOH afforded pure **6b**, m.p. 183–85° (mixed m.p. with Minato's[4] sample 183–85°), ν_{max} 1725, 1250 cm^{-1} (Found: C, 73·36; H, 9·17. $C_{28}H_{40}O_5$ requires: C, 73·65; H, 8·83%).

Sceptrumgenin (**7b**). BuLi in *n*-hexane (1 N, 2·5 ml) was added dropwise to a soln of methyl triphenylphosphonium bromide (1 g) in dry ether with stirring under N_2 while the temp was maintained between 0–5°. After 1·5 hr a soln of the acetate **6b** (200 mg) in dry THF (30 ml) was added slowly (40 min). The mixture was further stirred for 3 hr at room temp and then evaporated to dryness. Dry THF (30 ml) was added and the whole refluxed for 2 hr, diluted with water (75 ml) and extracted with ether. The organic layer was washed with HCl (2%), 5% $KHCO_3$ aq, water and dried. The gummy residue obtained was crystallised from MeOH to get pure **7b** (125 mg), m.p. 180–82°, $(\alpha)_D$ −

117°, ν_{max} 980, 960, 920, 895, 880 cm^{-1} (KBr); [Mass 412 (M^+), 345 (21), 342 (16), 300 (97), 285 (28), 283 (27), 282 (99), 271 (37), 159 (22), 145 (25), 137 (100) *m/e*]. Its acetate was prepared in the usual manner, m.p. 190–92°, mixed m.p. with the sample obtained from Minato and Shimaoka[14] 190–92°.

Reaction of spirost-5-en-3β-ol-25-one acetate (**6b**) *with methyl magnesium iodide.* A soln of **6b** (100 mg) in dry THF (2 ml) was added dropwise with stirring to Grignard reagent prepared from Mg (62 mg), MeI (250 mg) and dry ether (15 ml). The mixture was refluxed for 1·5 hr, cooled and decomposed with ammonium chloride soln. The organic layer was separated and the aqueous layer extracted with chloroform. The combined organic layer was washed with water and dried. Evaporation of the solvent left a gummy material which was chromatographed over neutral alimina. Elution with ether–benzene (1:1) afforded a solid (70 mg) which was crystallised from MeOH, m.p. 215–18°, ν_{max} 850, 900 (w), 915 (s), 992 cm^{-1} (Found: C, 75·5; H, 9·35. $C_{27}H_{42}O_4$ requires: C, 75·35; H, 9·77%). TLC on silica gel (ether–light petroleum–EtOAc 5:5:2·5) of the crude material showed a very faint spot (R_f 0·38) besides the main product (R_f 0·35).

Reaction of dimethyl oxosulfonium methylide with acetate **6b** *and lithium aluminium hydride reduction of the product.* A mixture of NaH [9·5 mg (50%), washed with dry hexane by decantation], trimethyl oxosulfonium iodide (99 mg) and dry DMSO (11 ml) was stirred for 3 hr at room temp under N_2. The acetate **6b** (100 mg) dissolved in DMSO (4 ml) was introduced, the mixture stirred for 16 hr at room temp and then for 2 hr at 50°. The soln was poured onto cold water (20 ml), extracted with EtOAc, washed with water and dried. Removal of the solvents afforded a solid material (90 mg) which gave two spots (R_f 0·5 and 0·45) on TLC on silica (ether–light petroleum–EtOAc 5:5:2). This material (80 mg) was dissolved in dry THF (8 ml) and stirred with LAH (200 mg) for 3 hr at room temp. The excess hydride was decomposed with EtOAc and the mixture poured onto dil HCl (20 ml; 10%). The organic material was taken up in ether, washed with water, $NaHCO_3$ aq, water and dried. Evaporation of the solvent left a gummy residue (70 mg) which was chromatographed over neutral alumina (5 g). Elution with ether–benzene (1:13) afforded a solid (10 mg) which when crystallised from MeOH, m.p. 245–48°, gave a single spot on TLC in a number of solvent systems. [Mass 430 (M^+) 399 (36), 342 (80), 300 (17), 282 (27), 271 (56), 253 (18), 155 (100) *m/e*]. Elution with ether–benzene (1:1) furnished another solid (59 mg) which was crystallised from MeOH, m.p. 215–18°. It was identical (IR, TLC, mixed m.p.) with the diol **10** obtained from the Grignard reaction.

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