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Ring Expansion of Fused Cyclopropylketones. Synthesis of a 12(13→18)-*abeo*-Pregnane.

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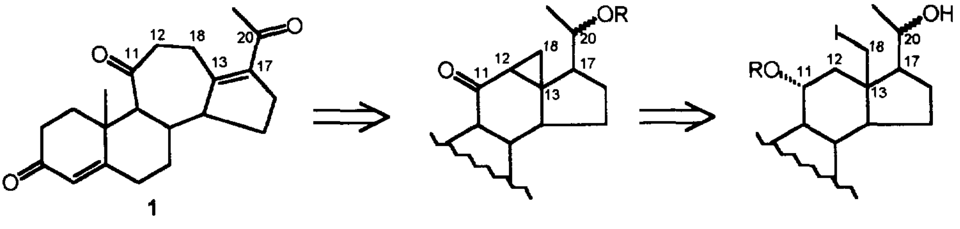
Abstract: A synthetic approach to 12(13→18)-*abeo*-pregnanes by base catalyzed rearrangement of a 12,18-cyclopregnane-11,20-dione is described. The latter steroid was prepared by means of a hypoiodite type reaction.

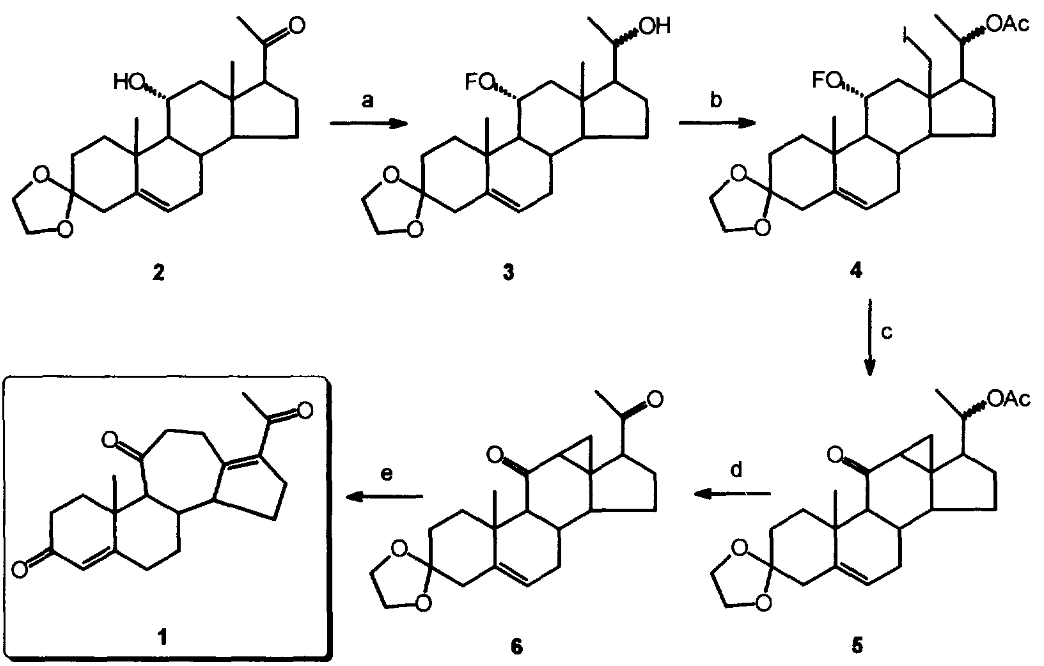
The ring-expansion approach to medium and large rings, has been a powerful strategy in synthetic organic chemistry achieved by both ionic and radical reactions.[1] In this respect, the use of cyclopropyl ketones fused to five or six membered rings for ring enlargement, is an area of considerable interest in organic synthesis.

A large number of homologations introduced in steroid hormones are based in expansions and contractions of the A, B and D rings, however, few examples have been reported for the synthesis of C-homo steroids of which the C-homoestratrienes are known to exhibit a pharmacological activity.[2] In previous papers, we have prepared a variety of steroid hormone analogues, which were used to study their biological activity as well as the conformation and flexibility of the steroid skeleton.[3-5] In particular, we described the synthesis of 17(13→18)-*abeo*-pregnanes by a ring-expansion approach using a radical rearrangement initiated by Bu_3SnH,[3] we now report the first synthesis of a 12(13→18)-*abeo*-pregnene (**1**), using an ionic rearrangement. Fused seven and five membered rings (as in **1**) are present in a variety of natural products of marine and terrestrial origin (*e.g.* guaianolides) many of which exibit interesting biological properties.[6]



Scheme 1

The preparation of compound **1** had two key steps: functionalization of the angular methyl group at C-13 by hydrogen abstraction promoted by an alkoxy radical generated at C-20[7] and rearrangement of the fused 12*β*,18-cyclopropane (Scheme 1).



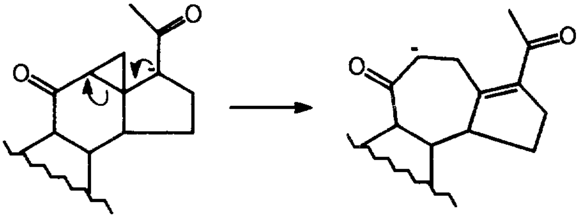
Scheme 2: (a) i) formic-acetic anhydride, Py, 2 h; ii) $BH_3 \cdot Me_2S$, THF, 4 h, 45.5 % overall. (b) i) DIB, I_2, CCl_4, $h\nu$ (300 W tungsten-filament lamp), 2 h, rt; ii) Ac_2O, Py, rt, overnight, 50 % overall. (c) i) K_2CO_3, MeOH, 40 min; ii) PCC-alumina, benzene, 2.5 h; iii) 10 % aqueous NaOH, methanol, 47.6 % overall. (d) i) $LiAlH_4$, THF, 1 h; ii) PCC, $BaCO_3$, 3Å molecular sieves, CH_2Cl_2, 4 h, rt, 80 % overall. (e) i) 10 % aqueous NaOH, methanol, 3 h, (86 %); ii) 5 % aqueous HCl, THF, 36 h, 70 % overall.

The starting point of our synthesis was 20-ketopregnene **2**, which was prepared from 11α-hydroxyprogesterone by a known two-step procedure[8] (Scheme 2). Protection of the 11α-hydroxy group as the formate ester using mixed formic-acetic anhydride[9] followed by reduction of the 20-ketone with borane-methyl sulfide complex in anhydrous THF[10] yielded a mixture of 20(R) and 20(S) alcohols (**3**). Functionalization of the angular methyl group was carried out by irradiation of a solution of **3** in carbon tetrachloride with visible light in the presence of bis(acetoxy)iodobenzene (DIB) and iodine.[7b] Acetylation of the resulting 18-iodo-20-alcohol with acetic anhydride-pyridine yielded iodopregnene **4**. Cyclopropyl steroid **5** was obtained from **4** by selective hydrolysis of the 11α-formate with potassium carbonate, oxidation to the 11-ketone with PCC-alumina[11] in benzene, enolization with sodium hydroxide in methanol and concomitant intramolecular displacement of iodine.[3] Reduction of **5** with lithium aluminum hydride followed by oxidation of the crude diol with PCC in dichloromethane, yielded diketone **6**.[12, 13]

With **6** in hand, we focused our attention on its conversion to the 12(13→18)-*abeo*-pregnene **1**. Homologation of ring C was carried out via a mechanism of eliminative ring fission[14] (Scheme 3), with sodium hydroxide in methanol.[15] The reaction is initiated by enolization of the C-20 carbonyl thus placing a negative charge at C-17 next to the cyclopropane ring. This triggers a coil spring effect with regioselective cleavage of the cyclopropane C-12—C-13 bond and incorporation of C-18 into ring C. Barton *et al.* had reported a related rearrangement to a 19-nor-B-homo-steroid, in the chemistry of the natural tetracyclic triterpenoid cucurbitacin

A.[16] Deprotection of the C-3 carbonyl with 5 % hydrochloric acid in THF afforded the desired C-homo steroid **1**.[17] The structure of **1** was confirmed by 1D and 2D nmr and mass spectrometry.

Attempts to carry out a radical rearrangement of **5** with Bu_3SnH in toluene, analogous to that described by us for the preparation of 17(13→18)-*abeo*-pregnanes[3] failed, recovering unreacted steroid **5** after 3 days. Several attempts to improve this radical rearrangements will be the subject of a forthcoming publication.



Scheme 3

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REFERENCES AND NOTES

1. For recent reviews on ring expansions, see (a) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091-2115. (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749-10784.
2. (a) Haffer, G.; Eder, U.; Neef, G.; Sauer, G.; Weichert, R. *Liebigs Ann. Chem.* **1981**, *3*, 425-438. (b) Neef, G.; Eder, U.; Haffer, G.; Sauer, G.; Weichert, R. *Chem. Ber.* **1977**, *110*, 3377-3387.
3. Ferrara, A.; Benedetti, M. O. V.; Ghini, A. A.; Burton, G. *J. Chem. Research (S)* **1993**, 276-277.
4. (a) Nicoletti, D.; Ghini, A. A.; Brachet-Cota, A. L.; Burton, G. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1089-1093. (b) Brachet-Cota, A. L.; Burton, G. *Z. Naturforsch., Teil. B* **1990**, *45*, 711-715.
5. Burton, G.; Galigniana, M.; De Lavallaz, S.; Brachet-Cota, A. L.; Sproviero, E. M.; Ghini, A. A.; Lantos, C. P. and Damasco, M. C. *Molecular Pharmacology* **1995**, *47*, 535-543.
6. See for example: Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355-394; Fraga, B. M. *Nat. Prod. Rep.* **1994**, *11*, 533-554.
7. (a) De Armas, P.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez. E. *J. Chem. Soc. Perkin Trans. I.* **1989**, 405-411. (b) Benedetti, M. O. V.; Burton G. *Org. Prep. Proced. Int.* **1992**, *24*, 701-704.
8. Miyano, M. *J. Org. Chem.* **1981**, *46*, 1846-1853.
9. Zemlicka, J.; Beranek, J.; Smrt, J. *Coll. Czech. Chem. Comm.* **1962**, *27*, 2784-2795.
10. Mincione, E. *J. Org. Chem.* **1978**, *43*, 1829-1830.
11. Cheng, Y-S.; Liu, W-L.; Chen, S. *Synthesis* **1980**, 223-224.
12. Herscovici, J.; Egron, M-J.; Antonakis, K. *J. Chem. Soc. Perkin Trans. 1.* **1982**, 1967-1973.
13. Data for 3,3-ethylenedioxy-12β,18-cyclo-5-pregnene-11,20-dione (**6**): mp 176-179 °C (from EtOAc) (Found: C, 74.7; H, 7.9. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2 %); ν_{max}(KBr)/cm^{-1} 1707 (C=O, ketone), 1678 (C=O, conjugated ketone), 1364, 1098 (O-C-O) and 1022; δ_H (200.1 MHz, $CDCl_3$) 0.78 (1H, dd, J = 9.2 and 6.1 Hz, 18a-H), 1.07 (3H, s, 10-H_3C), 1.45 (1H, dd, J = 6.1 and 4.1 Hz, 18b-H), 2.07 (3H, s, 20-H_3C), 2.24 (1H, dd, J = 9.2 and 4.1 Hz, 12-H), 3.30 (1H, t, J = 8.5 Hz, 17-H), 3.93 (4H, br s, 3-

OCH_2CH_2O), and 5.41 (1H, br d, *J* = 6.1 Hz, 6-H); δ_C (50.3 MHz, $CDCl_3$) 11.3 (C-18), 18.7 (C-19), 26.1 (C-16), 26.8 (C-15), 30.8 (C-2), 31.2 (C-21), 31.5 (C-7), 31.8 (C-8), 33.5 (C-12), 36.6 (C-1), 36.8 (C-13), 39.4 (C-10), 41.9 (C-4), 45.5 (C-14), 53.4 (C-17), 59.2 (C-9), 64.2 and 64.4 (ketal), 109.0 (C-3), 121.3 (C-6), 141.0 (C-5), 208.2 (C-20) and 209.8 (C-11); eims *m/z* (%) 370 (M^+, 6), 271 (1), 147 (1), 99 (100) and 55 (28).

14. Stirling, C. J. M. *Chem. Rev.* **1978**, *78*, 517-567.
15. To a solution of diketocyclopregnene **6** (0.020 g, 0.057 mM) in methanol (3.72 mL) was added 10 % aqueous sodium hydroxide (0.38 mL, 0.152 mM) and the reaction mixture stirred 3 hs at room temperature under nitrogen. The resulting solution was diluted with ethyl acetate and neutralized with 10 % aqueous hydrochloric acid. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with water, dried and then evaporated to dryness, yielding 3,3-ethylenedioxy-12(13→18)-*abeo*-5-pregnene-11,20-dione (0.018 g, 86 %); δ_H (200.1 MHz, $CDCl_3$) 1.13 (3H, s, 10-H_3C), 2.22 (3H, s, 20-H_3C), 2.78 (1H, ddd, *J* = 13.3, 10.8 and 3.1 Hz, 18a-H), 3.79 (1H, ddd, *J* = 16.5, 4.0 and 3.1 Hz, 12a-H), 3.93 (4H, br s, 3-OCH_2CH_2O) and 5.41 (1H, m, 6-H); δ_C (50.3 MHz, $CDCl_3$) 19.8 (C-19), 27.8 (C-16), 28.3 (C-15), 30.4 (C-21), 30.5 (C-2), 31.4 (C-7), 32.0 (C-18), 35.0 (C-8), 36.0 (C-1), 38.0 (C-10), 40.4 (C-12), 41.1 (C-4), 55.1 (C-14), 64.2 and 64.4 (ketal), 67.2 (C-9), 109.0 (C-3), 121.5 (C-6), 136.6 (C-17), 139.3 (C-5), 155.7 (C-13), 199.4 (C-20) and 215.0 (C-11). The crude product (0.017 g, 0.046 mM) in THF (0.2 mL) was treated with 5 % aqueous hydrochloric acid (0.1 mL, 0.14 mM) and the mixture was stirred 36 hs at room temperature, poured into water, washed with sodium hydrogen carbonate, extracted with dichloromethane, dried and evaporated to dryness. Chromatography on silica gel with hexane-ethyl acetate as eluent yielded 12(13→18)-*abeo*-4,13(17)-pregnadiene-3,11,20-trione (**1**) (0.012 g, 80 %); mp 141-144 °C (from MeOH) (Found: C, 77.7; H, 8.4. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0 %); $[\alpha]_D$ +56,1° (c 0.52, Cl_3CH); λ_{max} (MeOH) 246 nm (ε 22000); ν_{max}(KBr)/cm^{-1} 1705 (C=O, ketone), 1674 (C=O, conjugated ketone) 1616 and 1360; δ_H (200.1 MHz, $CDCl_3$) 1.37 (3H, s, 10-H_3C), 2.21 (3H, s, 20-H_3C), 2.75 (1H, dt, *J* = 3.4 and 13.3 Hz, 18a-H) 3.69 (1H, dt, *J* = 15.4 and 3.4 Hz, 12a-H) and 5.74 (1H, s, 4-H); δ_C (50.3 MHz, $CDCl_3$) 19.5 (C-19), 27.1 (C-16), 28.7 (C-15), 30.4 (C-21), 31.8 (C-7), 32.2 (C-1), 32.3 (C-18), 33.6 (C-2), 35.8 (C-6), 38.9 (C-8), 39.2 (C-10), 40.9 (C-12), 55.7 (C-14), 66.3 (C-9), 124.2 (C-4), 136.9 (C-17), 154.6 (C-13), 167.3 (C-5), 198.7 (C-3 and C-20) and 213.2 (C-11); eims *m/z* (%) 326 (M^+, 44), 283 (M^+-43, 93), 122 (44), 91 (31), 83 (69) and 43 (100); hreims found *m/z* 326.1882 (M^+), $C_{21}H_{26}O_3$ requires 326.1882.
16. Barton, D. H. R.; Garbers, C. F.; Giacopello, D.; Harvey, R. G.; Lessard, J.; Taylor. D. R. *J. Chem. Soc.(C)* **1969**, 1050-1056.
17. Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773-5780.

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