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Synthesis of C(1)–C(11) oxygen-bridged pregnanes

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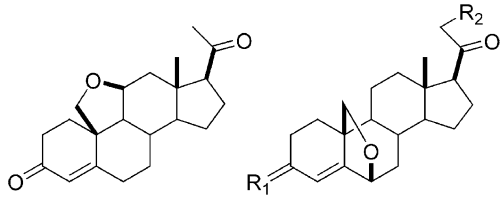
Abstract—A general procedure for the synthesis of 1α,11α- and 1β,11α-epoxysteroids is described, using an intramolecular remote functionalization reaction involving the photolysis of 11α-hydroxysteroids in the presence of diacetoxyiodobenzene and iodine. Three 1,11-epoxypregnanes were prepared, two of them (compounds **10** and **14**) are conformationally constrained analogues of steroidal hormones, compound **13** is a synthetic precursor of neurosteroids.

The introduction of oxygen bridges involving selected carbons of the steroid nucleus produces major changes in the overall shape of steroid molecules. Some of these bridged steroids have been shown to possess selective activities, thus molecules derived from progesterone with a planar overall conformation, as the highly flat 11,19-epoxyprogesterone (**1**), exhibit potent sodium-retaining activity and have gained interest as mineralocorticoid analogues.[1,2] In contrast, a 6,19-epoxy bridge bends Δ^4-steroids at the A/B ring junction giving rise to molecules with unusual activities such as 21-hydroxy-6,19-epoxyprogesterone (**2**), a selective antiglucocorticoid devoid of mineralocorticoid and progestational activities[3] and the pregnanolone analogue **3**, a potent anticonvulsant.[4] 1,11-Oxygen bridges can also result in rigid flat or bent structures at the A/B ring junction of the steroid nucleus, however they have only been obtained in low yields as byproducts[5] precluding analogues with this functionality to be prepared for biological testing. Using an intramolecular remote functionalization reaction with Suarez reagent (diacetoxyiodobenzene/I_2, *hν*),[6] we have synthesized 1,11-epoxypregnanes from readily available 11α-hydroxypregnanes.

The hydroxyl group in 11α-hydroxypregnanes (e.g., **4**) is spatially close to the hydrogens at C-1, so that a hypoiodite type reaction may be attempted. Whether H-1α or H-1β is within range depends on the stereochemistry and functionality at the A/B ring junction (5αH, 5βH or Δ^4). When the remote functionalization reaction using Suarez reagent was attempted on 11α-hydroxyprogesterone (**4**), the Δ^1 derivative **5** was obtained in 87% yield (Table 1, entry 1).[7] Although we observed the



1

2 R_1 = O, R_2 = OH
3 R_1 = β–H,α–OH, R_2 = H

Table 1. Photolysis reaction of 11α-hydroxysteroids **4**, **6**, **7** and **12** in the presence of DIB/iodine[a]

Entry	Steroid	Time (min)	Products (yield)
1	**4**[b]	60	**5** (87%)
2	**6**[b]	30	**8** (88%)
3	**6**[c]	60	**6** (39%), **8** (39%), **9** (7%)
4	**7**[b]	20	**10** (66%), **11** (22%)
5	**12**[b]	20	**13** (89%)

[a] In dichloromethane under irradiation with a 300 W tungsten lamp (5000 lm) at room temperature. Yields correspond to isolated products purified by flash chromatography on Florisil (ethyl acetate/hexane).
[b] Steroid/DIB/iodine (1:1.2:1).
[c] Steroid/DIB/iodine (1:0.4:0.4).

Keywords: Steroid; 1,11-Epoxypregnane; Remote functionalization reaction; DIB; Diacetoxyiodobenzene.
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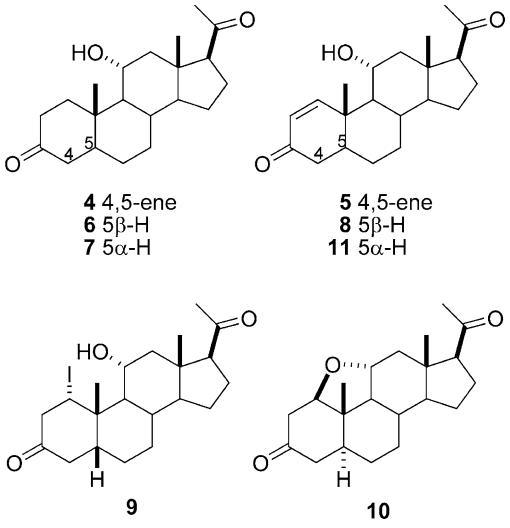
presence of a less polar yellowish intermediate when the reaction was monitored by TLC (probably the 1-iodo derivative of **4**), attempts to isolate this compound by preparative chromatography were unsuccessful as it gave compound **5** upon contact with the stationary phase (silica gel, Florisil or octadecyl-functionalized silica gel).

Although the iodine atom in this intermediate is expected to be in an equatorial orientation, the conformational equilibrium of ring A in 11α-hydroxyprogesterone (**4**) (quasi-*cis* vs quasi-*trans* A/B fusion) allows the iodine at C-1 to occupy an axial orientation and facilitates its elimination. Thus we decided to try the reaction on 11α-hydroxypregnanes with a fixed conformation of ring A. This would lead to more stable 1-iodo intermediates or eventually to 1,11-epoxy bridges. The reduced analogues 11α-hydroxy-5β-pregnanodione (**6**) and 11α-hydroxy-5α-pregnanodione (**7**) were prepared by catalytic hydrogenation of **4**.[8]



Reaction of 11α-hydroxy-5β-pregnanodione (**6**) with DIB/I_2/*hv* gave the Δ^1 derivative **8** in 88% yield (Table 1, entry 2),[9] a yellowish intermediate was also observed when the reaction was monitored by TLC. When the reaction was carried out using a steroid/DIB/iodine ratio of 1:0.4:0.4, the intermediate could be isolated as a minor product and characterized as the 1α-iodo derivative **9** (entry 3).[10] The EIMS showed a molecular ion at *m*/*z* 458 and a peak at *m*/*z* 331 corresponding

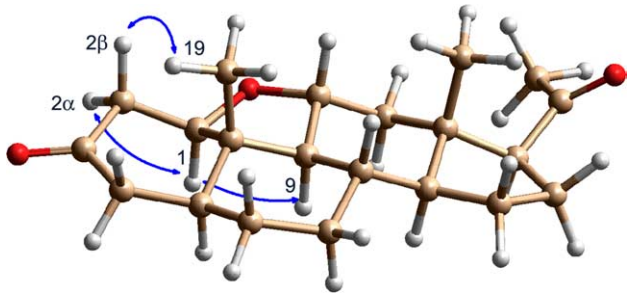
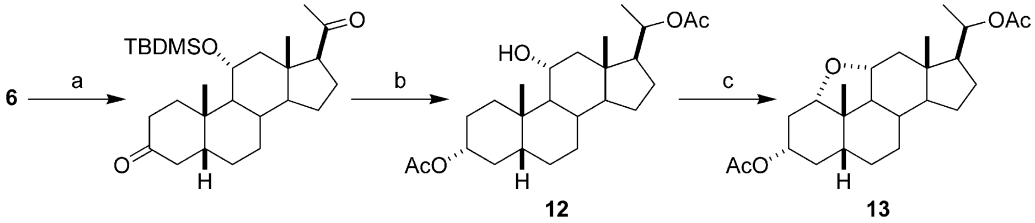


Figure 1. AM1 calculated structure of 1β,11α-epoxy-5α-pregnane-3,20-dione (**10**) showing observed NOEs.

to the loss of iodine in accordance with the proposed structure. The double doublet at δ 5.35 observed in the ^{1}H NMR spectrum of **9** was assigned to H-1, the couplings to hydrogens at C-2 (5.2 and 14.1 Hz) being indicative of the expected α orientation (equatorial) of the iodo substituent at C-1.

The 1,11-epoxy analogue **10** was the main product when the reaction was carried out with 11α-hydroxy-5α-pregnane-3,20-dione (**7**),[11] the Δ^1 derivative **11** being isolated as a minor product (Table 1, entry 4).[9] The ^{1}H–^{1}H correlations observed in the COSY 45 spectrum of **10** allowed the assignment of the double doublet at δ 3.82 to H-1 (6.4 and 11.4 Hz) and the double double doublet at δ 3.84 to H-11. The presence in the ^{13}C NMR of two methynes at δ 83.2 and 75.4, which correlated to the protons at δ 3.82 and 3.84, respectively, confirmed the assignments. The NOESY spectrum showed correlations between H-1 (δ 3.82) and hydrogens at positions 2α (δ 2.70), and 9α (δ 1.18) and between H-19 (δ 0.91) and H-2β (δ 2.76), indicating a 1β-orientation for the oxygen bridge (Fig. 1).

As elimination of the 1-iodo substituents would still be favoured by the formation of an α,β-unsaturated ketone (compounds **5**, **8** and **11**), we next attempted the remote functionalization reaction on a 3-reduced substrate. Compound **12** was obtained from **6** (Scheme 1) by protection of the 11α-hydroxy group as the *tert*-butyldimethylsilyl ether, followed by reduction of the 3,20-diketone with $NaBH_4$. Acetylation of the resulting 3,20-diol with acetic anhydride–pyridine and cleavage of the TBDMS ether, with 40% hydrofluoric acid, gave **12** in 55% overall yield. The 1,11-epoxy steroid **13** was obtained in 89% yield by reaction of compound **12** with DIB/I_2,[12] no elimination product being detected in this case (Table 1, entry 5).



Scheme 1. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 50 °C; (b) i. $NaBH_4$, MeOH, CH_2Cl_2, 0 °C; ii. Ac_2O, py, 25 °C; iii. HF 40%, THF, acetonitrile, 25 °C; (c) DIB, I_2, CH_2Cl_2, *hv*, 25 °C.

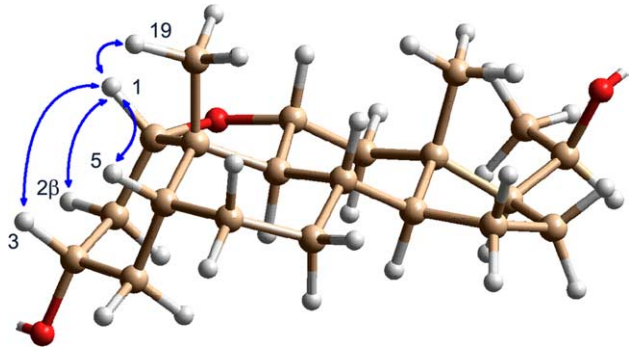
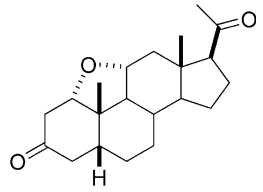


Figure 2. AM1 calculated structure of 3,20-diacetoxy-1α,11α-epoxy-5β-pregnane (**13**) showing observed NOEs (acetates are not shown for clarity).

The ^{1}H NMR spectrum of **13** showed a double doublet at 3.95 ppm assigned to H-1, with couplings (7.9 and 9.6 Hz) to H-2α and H-2β consistent with a 1α-orientation for the oxygen bridge. The ^{13}C NMR spectrum had signals at δ 84.5 and 75.8 assigned to C-1 and C-11, respectively. The stereochemistry at C-1 was confirmed by the 500 MHz NOESY spectrum. Thus the correlations observed between H-1 (δ 3.95) and hydrogens at positions 19 (δ 1.08), 2β (δ 2.27), 3 (δ 4.65) and 5 (δ 1.89) were in agreement with the distances predicted in the most stable conformer of **13** (AM1) (Fig. 2).

Compound **13** may be easily converted into analogues of steroidal hormones and neurosteroids. In particular we synthesized the analogue **14** by removal of the acetate groups ($LiAlH_4$, THF, 0 °C) followed by oxidation with PCC (4 Å MS, $BaCO_3$, CH_2Cl_2).[13]



14

Although iodoalcohols are generally accepted as intermediates in the formation of cyclic ethers in remote functionalization reactions with DIB/I_2, this may not be the case here as their formation apparently led to elimination products. This is further supported by the fact that iodoalcohol **9** did not cyclize to give the 1,11-epoxysteroid. No iodinated intermediates were observed in the reaction of **12** with DIB/I_2. Compounds **10** and **14** are conformationally constrained analogues of progesterone[14] and their biological activity will be reported elsewhere. Compound **13** is also a synthetic precursor of analogues of the neurosteroid pregnanolone.

Acknowledgements

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10. Data for 11α-hydroxy-1α-iodo-5β-pregnane-3,20-dione (**9**): Amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (dd, J = 14.1 and 5.2 Hz, 1H, H-1), 4.00 (m, 1H, H-11), 3.41 (dd, J = 13.2 and 5.2 Hz, 1H, H-2β), 2.84 (dd, J = 15.0 and 13.5 Hz, 1H, H-4α), 2.56 (t, J = 9.34 Hz, 1H, H-17), 2.40 (dd, J = 15.0 and 4.3 Hz, 1H, H-4β), 2.34 (dd, J = 11.8 and 5.2 Hz, 1H, H-12β), 2.14 (s, 3H, H-21), 1.95 (dd, J = 14.1 and 13.2 Hz, 1H, H-2α), 1.55 (m, 1H, H-12α), 1.13 (s, 3H, H-19), 0.65 (s, 3H, H-18); ^{13}CNMR (50 MHz, $CDCl_3$) δ 208.7 (C-20), 203.7 (C-3), 67.9 (C-11), 63.2 (C-17), 55.4 (C-14), 54.2 (C-2), 50.3 (C-12), 47.0 (C-9), 46.2 (C-5), 44.1 (C-13), 41.0 (C-4), 40.0 (C-10), 35.6 (C-1), 34.4 (C-8), 31.4 (C-21), 26.6 (C-7), 25.7 (C-6), 24.3 (C-16), 23.1 (C-15), 22.4 (C-19), 14.3 (C-18). EIMS *m/z* 458 (M^+, 5), 440 (7), 331 (13), 313 (45), 299 (4), 271 (11), 254 (59), 55 (100).
11. Data for 1β,11α-epoxy-5α-pregnane-3,20-dione(**10**): White solid, mp 205 °C (from ethanol), IR ν_{max} (KBr) (cm^{-1}) 2928, 1707, 1630, 1350, 965; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (dt, J = 11.4, 11.0 and 5.0 Hz, 1H, H-11), 3.82 (dd, J = 11.4 and 6.4 Hz, 1H, H-1), 2.76 (dd, J = 14.0 and 6.4 Hz, 1H, H-2β), 2.70 (dd, J = 14.0 and 11.4 Hz, 1H, H-2α), 2.65 (t, J = 9.0 Hz, 1H, H-17), 2.44 (dd, J = 11.0 and 5.0 Hz, 1H, H-12β), 2.26 (m, 1H, H-16β), 2.25 (m, 1H, H-5), 2.14 (s, 3H, H-21), 2.05 (m, 2H, H-4), 2.01 (m, 1H, H-6a), 1.83 (m, 1H, H-16α), 1.75 (m, 1H, H-15α), 1.70 (m, 1H, H-8), 1.65 (m, 2H, H-7), 1.39 (t, J = 11.0 Hz, 1H,

H-12α), 1.34 (m, 1H, H-14), 1.30 (m, 1H, H-15β), 1.18 (m, 1H, H-9), 1.05 (m, 1H, H-6b), 0.91 (s, 3H, H-19), 0.68 (s, 3H, H-18); ^{13}CNMR (125 MHz, $CDCl_3$) δ 211.2 (C-3), 209.0 (C-20), 83.2 (C-1), 75.4 (C-11), 63.9 (C-9), 61.5 (C-17), 58.7 (C-14), 48.4 (C-13), 45.7 (C-2), 42.9 (C-12), 42.8 (C-4), 40.1 (C-5), 38.9 (C-10), 31.8 (C-6), 31.2 (C-8 and C-21), 26.2 (C-7), 24.5 (C-16), 22.7 (C-15), 15.8 (C-19), 14.5 (C-18); EIMS *m/z* 330 (M^+, 61), 314 (20), 301 (14), 287 (13), 269 (15), 79 (100). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found C, 76.63; H, 9.09.

12. *Representative experimental procedure* (Table 1, entry 5): Compound **12** (108.0 mg, 0.26 mmol) was dissolved in recently distilled dichloromethane (23 ml) and DIB (99.8 mg, 0.31 mmol) and iodine (65.9 mg, 0.26 mmol) were added. The reaction mixture was vigorously stirred at 25 °C in a water jacketed flask, while irradiating with a 300 W tungsten lamp (5000 lm) for 20 min. The solution was washed with aqueous sodium thiosulfate, dried with sodium sulfate and the solvent was evaporated. The resulting solid was purified by flash chromatography (Florisil, hexane/ethyl acetate 60:40) to give 3α,20β-diacetoxy-1α,11α-epoxy-5β-pregnane (**13**) (95.8 mg, 89% yield) as a white solid, mp 180 °C (from methanol/water); IR ν_{max} (KBr) (cm^{-1}) 2949, 2928, 2874, 1736, 1445, 1377, 1246, 1026, 953; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.82 (m, 1H, H-20), 4.65 (m, 1H, H-3), 3.95 (dd, *J* = 9.6 and 7.9 Hz, 1H, H-1), 3.88 (dt, *J* = 11.0, 11.0 and 4.3 Hz, 1H, H-11), 2.32 (dd,, *J* = 11.0 and 4.3 Hz, 1H, H-12β), 2.27 (m, 1H, H-2α), 2.02 (s, 3H, CH_3COO), 2.12 (m, 1H, H-16α), 1.89 (m, 1H, H-5), 1.82 (m, 2H, H-6), 1.70 (m, 1H, H-17), 1.65 (m, 1H, H-15α), 1.67 (m, 2H, H-4), 1.64 (m, 1H, H-7a), 1.63 (m, 1H, H-16β), 1.48 (m, 1H, H-2β), 1.41 (m, 1H, H-8), 1.35 (m, 1H, H-9), 1.19 (m, 1H, H-14), 1.18 (t, *J* = 11.0 Hz, 1H, H-12α), 1.15 (m, 1H, H-15β), 1.14 (d, *J* = 7.0 Hz, 3H, H-21), 1.08 (s, 3H, H-19), 0.98 (m, 1H, H-7b), 0.67 (s, 3H, H-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4-170.3 (CH_3COO), 84.5 (C-1), 75.8 (C-11), 72.4 (C-20), 70.3 (C-3), 57.5 (C-14), 53.5 (C-17), 51.2 (C-9), 46.3 (C-13), 45.4 (C-12), 38.5 (C-5 and C-10), 38.0 (C-2), 31.6 (C-8), 31.5 (C-4), 26.8 (C-7), 26.6 (C-6), 26.2 (C-15), 22.3 (C-16), 21.5–21.3 (CH_3COO), 21.3 (C-19), 19.8 (C-21), 14.1 (C-18); EIMS *m/z* 418 (M^+, 3), 403 (2), 390 (2), 358 (100), 343 (23), 316 (9), 298 (68), 283 (45). HRMS (EI) calcd for $C_{25}H_{38}O_5(M)^+$ 418.2719. Found 418.2713.
13. Data for 1α,11α-epoxy-5β-pregnane-3,20-dione (**14**): White solid, mp 212 °C (from ethanol). IR ν_{max} (KBr) (cm^{-1}) 3462, 2930, 1705, 1356, 1001; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (dd, *J* = 7.5, and 5.0 Hz, 1H, H-1), 3.87 (dt, *J* = 11.0, 11.0 and 4.6 Hz, 1H, H-11), 2.69 (ddd, *J* = 14.4, 7.5 and 1.4 Hz, 1H, H-2α), 2.64 (t, *J* = 9.0 Hz, 1H, H-17), 2.53 (m, 1H, H-4α), 2.49 (ddd, *J* = 14.4, 5.0 and 1.0 Hz, 1H, H-2β), 2.47 (dd, *J* = 11.0 and 4.8Hz, 1H, H-12β), 2.25 (m, 2H, H-5 and H-16α), 2.19 (m, 1H, H-4β), 2.13 (s, 3H, H-21), 1.89 (m, 1H, H-6a), 1.80 (m, 1H, H-16β), 1.73 (m, 1H, H-15α), 1.71 (m, 1H, H-7a), 1.55 (m, 1H, H-8), 1.43 (m, 1H, H-6b), 1.39 (t, *J* = 11.0Hz, 1H, H-12α), 1.34 (m, 1H, H-14), 1.27 (m, 1H, H-9), 1.25 (m, 1H, H-15β), 1.17 (s, 3H, H-19), 1.04 (m, 1H, H-7b), 0.68 (s, 3H, H-18); ^{13}CNMR (125 MHz, $CDCl_3$) δ 210.2 (C-3), 208.8 (C-20), 86.8 (C-1), 75.1 (C-11), 61.8 (C-17), 58.3 (C-14), 52.9 (C-9), 47.5 (C-13), 47.1 (C-2), 44.3 (C-12), 40.3 (C-4), 39.0 (C-10), 38.4 (C-5), 31.7 (C-21), 31.3 (C-8), 26.8 (C-7), 26.8 (C-6), 24.3 (C-16), 22.5 (C-15), 21.0 (C-19), 14.9 (C-18); EIMS *m/z* 330 (M^+, 44), 315 (2), 312 (19), 294 (4), 287 (2), 269 (12), 109 (75), 43 (100). HRMS (EI) calcd for $C_{21}H_{30}O_3(M)^+$ 330.2195. Found 330.2201.
14. Stability of the 1,11-epoxy bridges was tested for **10** and **14** in both acid (acetic acid/dichloromethane and HCl/methanol) and basic (KOH/methanol) media. Compound **10** was recovered unaltered after 24 h in both media, while **14** although stable in base, slowly decomposed to give **8** over a 24 h period in acid media.