Steroids 76 (2011) 1458–1464

Contents lists available at SciVerse ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Microwave assisted preparation of C(1)–C(11) oxygen-bridged pregnanes

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ARTICLE INFO

Article history:
Received 3 June 2011
Received in revised form 24 July 2011
Accepted 30 July 2011
Available online 9 August 2011

Keywords:
1,11-Epoxypregnane
Remote functionalization
Microwave irradiation
Diacetoxyiodobenzene

ABSTRACT

1,11-Epoxysteroids may be obtained by an intramolecular remote functionalization using Suarez reagent (diacetoxyiodobenzene/I_2) and irradiation with visible light. We have found that photolysis with visible light may be advantageously replaced by microwave irradiation to prepare 1,11-oxygen bridges resulting in higher yields and shorter reaction times especially in the case of sensitive substrates. Both methodologies were compared on a set of representative 11-α-hydroxypregnanes (**3**, **8**, **10** and **11**).

1. Introduction

The incorporation of bridges involving selected carbons of the steroid nucleus, provides conformationally restricted analogues that can mimic or change in a controlled way the molecular shape of steroids. Using this approach we have prepared rigid flat or bent structures at the A/B ring junction of the steroid nucleus, and some of these bridged steroids have been shown to be analogues of steroidal hormones or neurosteroids with interesting properties [1–3]. Recently Komatsu et al. synthesized several 6β,19-bridged androstenedione analogues that exhibited moderate inhibition of aromatase [4]. In previous publications, we described a procedure for the synthesis of 1,11-epoxysteroids using an intramolecular remote functionalization reaction with Suarez reagent (diacetoxyiodobenzene/I_2) under photochemical conditions [5] and prepared rigid analogues of the neuroactive steroids pregnanolone and allopregnanolone [6].

When the remote functionalization reaction was attempted on 3-ketosteroids (**1**–**3**), the elimination of the 1-iodo substituent competed with the formation of the 1,11-epoxysteroids giving the corresponding α,β-unsaturated ketones **4**–**6** (see Fig. 1 for structures). Only in the case of compound **3**, the 1β,11α-epoxysteroid **7** was the major product (66% yield), with the Δ^1 derivative (**6**) being detected as a minor product (20% yield). On the other hand, reaction of the 3-reduced steroid **8** with DIB/I_2/*hv* gave the corresponding 1α,11α-epoxysteroid **9** and no elimination byproducts [5]. Costa et al. reported that ultrasonic irradiation may be used to improve the formation of tetrahydrofurans in hypoiodite reactions using the DIB/I_2 system [7]. On the other hand, microwave irradiation has proved to be a convenient alternative to many thermally initiated reactions, especially when sensitive substrates or products are involved, but has not been used as an energy source in hypoiodite type reactions. We have now found that the remote functionalization using DIB/I_2 and subsequent cyclization, may be achieved with less side reactions using microwave irradiation instead of visible light, allowing its use on sensitive substrates.

2. Experimental

2.1. General

Mps were taken on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded in thin films using KBr disks on a Nicolet Magna 550 FT-IR spectrophotometer, values are given in cm^{-1}. NMR spectra were recorded on Bruker AC-200 (^1H at 200.13 MHz, ^{13}C at 50.32 MHz) or Avance II 500 (^1H at 500.13 MHz, ^{13}C at 125.77 MHz) spectrometers. Chemical shifts are given in ppm downfield from TMS as internal standard, *J* values are given in Hz. Multiplicity determinations and 2D spectra (COSY, NOESY, HSQC and HMBC) were obtained using standard Bruker software. The electron impact mass spectra (MS) were collected on a Shimadzu QP-5000 mass spectrometer at 70 eV by direct inlet. Exact mass spectra were obtained using a VG 7070 spectrometer or a Bruker micrOTOF-Q II mass spectrometer, equipped with an ESI source operating in positive mode. Microwave assisted reactions were carried out on a CEM Discover reactor, mode Discover (closed

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doi:10.1016/j.steroids.2011.07.016

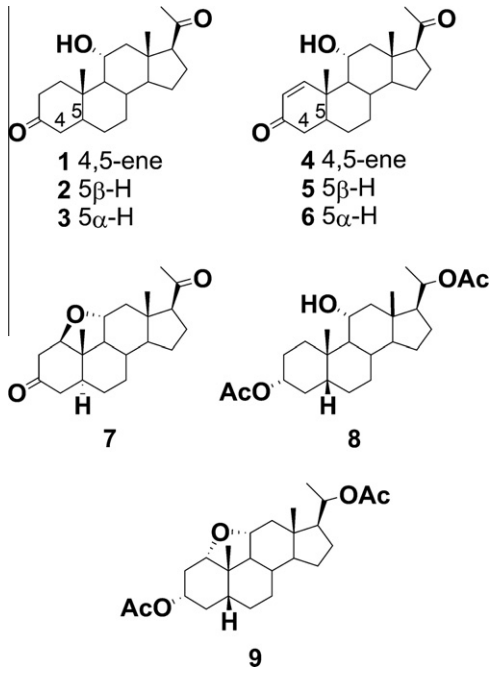


Fig. 1. Structures of compounds **1**–**9**.

vessel) Power max: on, with air cooling of the reaction vessel during irradiation. Flash column chromatography was carried out on Kieselgel S 0.040–0.063 mm. Thin layer chromatography (TLC) analysis was performed on silica gel 60 F254 (0.2 mm thick). The homogeneity of all compounds was confirmed by TLC. Solvents were evaporated at reduced pressure and ca. 40–50 °C. Compounds **3**, **7** and **9** were obtained from 11α-hydroxyprogesterone (Steraloids Inc.) following the procedures described previously by us [5]. Compound **12** was obtained from 11α-hydroxyprogesterone in four steps (see Supplementary data). Geometry optimizations were carried out with the quantum chemistry program Gaussian 03 using the AM1 semiempirical method or *ab-initio* calculations with the HF/6-31G(d,p) basis set [8].

2.2. Chemistry

2.2.1. 3β,20-Diacetoxy-4-pregnen-11α-ol (**10**)

Imidazole (470 mg, 6.90 mmol) and *t*-butyldimethylsilyl chloride (700 mg, 4.64 mmol) were added successively to a solution of 11α-hydroxyprogesterone (**1**) (390 mg, 1.18 mmol) in anhydrous DMF (4 mL) and the solution was stirred for 3 h at 50 °C under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and then extracted with ether. The organic layer was washed successively with brine and water and dried with sodium sulfate. Evaporation of the solvent followed by flash chromatography (ethyl acetate–hexane 2:8 → 4:6) gave the 11-silyl ether **15** (293 mg, 56%) in addition to recovered starting material (117 mg, 30%); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 5.72 (1H, s, H-4), 4.11 (1H, m, H-11), 2.12 (3H, s, H-21), 1.27 (3H, s, H-19), 0.90 (9H, s, $(CH_3)_3$C–Si), 0.68 (3H, s, H-18), 0.12 (6H, s, $(CH_3)_2$Si); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 209.6 (C-3), 200.3 (C-20), 171.3 (C-5), 124.2 (C-4), 70.2 (C-11), 63.1 (C-17), 58.5 (C-14), 55.3 (C-9), 50.0 (C-12), 43.9 (C-13), 39.6 (C-10), 36.9 (C-1), 34.9 (C-7), 33.8 (C-2), 33.3 (C-6), 31.6 (C-8), 31.1 (C-21), 26.1 (($\boldsymbol{CH_3}$)$_3$C–Si), 24.1 (C-16), 22.7 (C-15), 18.2 (C-19), 18.1 ((CH_3)$_3$**C**–Si), 14.4 (C-18), −3.01 and −3.06 (CH_3–Si).

Sodium borohydride (36.0 mg, 0.95 mmol) was added to a solution of the silyl ether **15** obtained above (262 mg, 0.59 mmol) in dichloromethane (5.3 mL) and methanol (5.3 mL). The reaction mixture was stirred for 60 min at room temperature, acidified (pH 6) with 1M HCl and concentrated to a third of its volume. Water was added to the residue and then extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate and the solvent evaporated under vacuum. The resulting solid was purified by flash chromatography (ethyl acetate–hexane 3:7 → 1:1) to give the 3β,20-diol **16** (225 mg, 85%); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 5.31 (1H, s, H-4), 4.10 (1H, m, H-3), 4.04 (1H, m, H-11), 3.69 (1H, m, H-20), 1.15 (3H, s, H-19), 1.12 (3H, d, J = 7.0 Hz, H-21), 0.88 (9H, s, ((CH_3)$_3$**C**–Si), 0.78 (3H, s, H-18), 0.08 (6H, s, $(CH_3)_2$Si); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 147.5 (C-5), 124.6 (C-4), 70.5 and 70.2 (C-3, C-20), 67.6 (C-11), 59.6 (C-17), 58.2 (C-14), 54.9 (C-9), 51.2 (C-12), 42.7 (C-13), 38.5 (C-10), 36.8 (C-1), 35.1 (C-7), 33.0 (C-6), 32.8 (C-8), 29.3 (C-2), 26.2 (($\boldsymbol{CH_3}$)$_3$C–Si), 25.5 (C-16), 24.4 (C-15), 23.7 (C-21), 19.6 (C-19), 18.2 ((CH_3)$_3$**C**–Si), 13.5 (C-18), −3.01 and −3.06 ((CH_3)$_2$Si).

Acetylation of the 3β,20-diol **16** (220 mg, 0.49 mmol) with acetic anhydride (1.87 mL) and pyridine (1.87 mL) for 24 h at room temperature, gave compound **17** (235 mg, 90%); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 5.26 (1H, s, H-4), 5.22 (1H, m, H-3), 4.77 (1H, m, H-20), 4.03 (1H, m, H-11), 2.05 (6H, s, acetate), 1.16 (3H, s, H-19), 1.14 (3H, d, J = 7.0 Hz, H-21), 0.88 (9H, s, *t*-butyl-Si), 0.67 (3H, s, H-18), 0.08 (6H, s, $(CH_3)_2$Si).

To a solution of **17** (230 mg, 0.43 mmol) in THF (7.5 mL), was added Bu_4NF (319 mg, 1.22 mmol) and the solution was stirred for 4 h at 60 °C. The solvent was evaporated under vacuum and the resulting solid was purified by flash chromatography (ethyl acetate–hexane 2:8 → 3:7) to give 11α-hydroxysteroid **10** (155 mg, 85%). Amorphous solid; IR (KBr) cm^{-1}: 3500, 2937, 2875, 1729, 1680, 1447, 1374, 1247, 1026; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.28 (1H, d, J = 1.3 Hz, H-4), 5.23 (1H, tt, J = 1.9 and 7.5 Hz, H-3), 4.81 (1H, dq, J = 10.8 and 6.0 Hz, H-20), 3.93 (1H, dt, J = 4.9 and 10.5 Hz, H-11), 2.27 (1H, ddd, J = 1.9, 4.9, 13.2 Hz, H-1β), 2.18 (1H, m, H-6β), 2.12 (1H, dd, J = 12.2 and 4.7 Hz, H-12β), 2.05 (1H, m, H-6α), 2.05 (3H, s, 3-acetate), 2.04 (3H, s, 20-acetate), 1.93 (1H, m, H-2α), 1.76 (1H, m, H-16β), 1.73 (1H, m, H-7α), 1.66 (1H, m, H-1α), 1.65 (1H, m, H-15α), 1.64 (1H, m, H-17), 1.61 (1H, m, H-2β), 1.45 (1H, m, H-8), 1.26 (1H, m, H-16α), 1.24 (1H, m, H-12α), 1.20 (1H, s, H-19), 1.15 (3H, d, J = 6.0 Hz, H-21), 1.14 (2H, m, H-14 and H-15β), 0.95 (1H, m, H7β), 0.93 (1H, m, H-9), 0.67 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 171.1 (3-acetate), 170.5 (20-acetate), 148.9 (C-5), 120.6 (C-4), 72.7 (C-20), 70.8 (C-3), 69.3 (C-11), 60.1 (C-9), 54.8 (C-14), 54.7 (C-17), 51.2 (C-12), 42.8 (C-13), 38.7 (C-10), 36.9 (C-1), 35.0 (C-8), 32.9 (C-6), 32.7 (C-7), 25.5 (C-16), 25.2 (C-2), 24.2 (C-15), 21.6 (20-acetate), 21.5 (3-acetate), 19.8 (C-21), 19.6 (C-19), 13.6 (C-18); MS *m/z* (%): 400 (M–H_2O, 2), 358 (9), 166 (18), 124 (23),43 (100); HR MS-ESI: calculated for $C_{25}H_{38}NaO_5$ 441.2612, found 441.2617.

2.2.2. 3β,20-Diacetoxy-5a-pregnan-11α-ol (**11**)

The 11-silyl ether **18** was obtained from compound **3** (300 mg, 0.908 mmol) following the procedure described for compound **15**. The resulting solid was purified by flash chromatography (ethyl acetate–hexane 2.8 → 3:7) to give **18** (222 mg, 55%); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 4.06 (1H, m, H-11), 2.12 (3H, s, H-21), 1.09 (3H, s, H-19), 0.89 (9H, s, $(CH_3)_3$C–Si), 0.64 (3H, s, H-18), 0.10 (6H, s, $(CH_3)_2$Si); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 212.0 (C-3), 200.0 (C-20), 70.3 (C-11), 63.4 (C-17), 59.2 (C-14), 55.8 (C-9), 50.2 (C-12), 47.6 (C-5), 46.2 (C-4), 44.0 (C-13), 39.3 (C-1), 38.5 (C-2), 36.9 (C-10), 34.3 (C-8), 31.5 (C-6), 31.3 (C-21), 29.0 (C-7), 26.5 (($\boldsymbol{CH_3}$)$_3$C–Si), 24.3 (C-16), 22.7 (C-15), 18.2 ((CH_3)$_3$**C**–Si), 14.4 (C-18), 11.5 (C-19), −3.03 and −3.06 (CH_3–Si).

The 3,20-diacetate **20** was obtained from **18** (202 mg, 0.454 mmol), following the procedure described for compound **17**. Compound **20** (165 mg, 83% from **18**); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 4.80 (1H, m, H-3), 4.67 (1H, m, H-20), 4.06 (1H, m,

H-11), 2.05 (6H, s, 3-and 20-acetates), 1.15 (3H, d, J = 7.0 Hz, H-21), 1.09 (3H, s, H-19), 0.88 (9H, s, *t*-butyl-Si), 0.64 (3H, s, H-18), 0.08 (6H, s, CH_3-Si).

To a solution of **20** (163 mg, 0.331 mmol) in THF (5 mL) and acetonitrile (5.5 mL), was added 40% hydrofluoric acid (4.4 mL) and the solution was stirred for 20 min at room temperature. The reaction mixture was neutralized with aqueous potassium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate and the solvent evaporated under vacuum. The resulting solid was purified by flash chromatography (ethyl acetate–hexane 4:6) to give the 11α-hydroxysteroid **11** (108 mg, 85%) as a white solid: mp 151–152 °C (from ethyl acetate–hexane); IR (KBr) cm^{-1}: 3524, 2930, 2871, 1730, 1248, 1026; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 4.80 (1H, dq, J = 10.5 and 6.1 Hz, H-20), 4.68 (1H, tt, J = 5.0 and 11.4 Hz, H-3), 3.87 (1H, dt, J = 5.0 and 10.3 Hz, H-11), 2.37 (1H, dt, J = 13.7 and 3.6 Hz, H-1β), 2.13 (1H, dd, J = 5.1 and 12.4 Hz, H-12β), 2.04 (3H, s, 20-acetate), 2.02 (3H, s, 3-acetate), 1.79 (1H, m, H-4α), 1.75 (1H, m, H-16β), 1.66 (1H, m, H-6α), 1.65 (1H, m, H-17), 1.64 (1H, m, H-15α), 1.63 (2H, m, H-2), 1.53 (1H, m, H-4β), 1.36 (1H, m, H-8), 1.28 (2H, m, H-7), 1.25 (1H, m, H-1α and H-5), 1.24 (1H, m, H-16α), 1.20 (1H, m, H-12α), 1.14 (1H, m, H-14), 1.14 (3H, d, J = 6.2 Hz, H-21), 1.10 (1H, m, H-15β), 0.95 (1H, m, H-6β), 0.95 (1H, s, H-19), 0.76 (1H, t, J = 10.2 Hz, H-9), 0.63 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.7 (3-acetate), 170.5 (20-acetate), 73.4 (C-3), 72.7 (C-20), 69.1 (C-11), 60.5 (C-9), 54.9 (C-14), 54.8 (C-17), 51.3 (C-12), 44.9 (C-5), 42.8 (C-13), 38.5 (C-1), 37.2 (C-10), 34.5 (C-2), 34.4 (C-8), 32.0 (C-6), 29.0 (C-7), 27.7 (C-4), 25.5 (C-16), 24.3 (C-15), 21.6 (20-acetate), 21.5 (3-acetate), 19.8 (C-21), 13.5 (C-18), 12.6 (C-19); MS *m/z* (%): 400 (M–H_2O, 2), 358 (9), 166 (18), 124 (23),43 (100); HR MS-ESI: calculated for $C_{25}H_{40}NaO_5$ 443.2768, found 443.2786.

2.2.3. Representative experimental procedure using irradiation with visible light

Compound **10** (109 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 while irradiating with a 300 W tungsten lamp (5000 lumen) for 20 min at room temperature. The solution was washed with aqueous sodium thiosulfate, dried with sodium sulfate and the solvent was evaporated. The residue was purified by flash chromatography (Florisil, hexane/ethyl acetate 60:40) to give **13** (21.7 mg, 20% yield).

2.2.4. Representative experimental procedure using microwave irradiation

Compound **10** (20.0 mg, 0.048 mmol) was dissolved in recently distilled dichloromethane (4 mL) and DIB (18.4 mg, 0.057 mmol) and iodine (12.7 mg, 0.048 mmol) were added. The reaction mixture was vigorously stirred under microwave irradiation at 300 W (95 °C, 15 psi) for 15 min. The solution was washed with aqueous sodium thiosulfate, dried with sodium sulfate and the solvent was evaporated. The residue was purified by flash chromatography (Florisil, hexane/ethyl acetate 60:40) to give **13** (12.0 mg, 60%).

2.2.5. 3β,20-Diacetoxy-1α,11α-epoxy-4-pregnene (*13*)

White solid: mp 159–160 °C (from ethyl acetate); IR (KBr) cm^{-1}: 2931, 2871, 1729, 1670, 1376, 1250, 1024; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.64 (1H, dd, J = 1.6 and 6.4 Hz, H-4), 5.07 (1H, dt, J = 6.2 and 3.1 Hz, H-3), 4.81 (1H, dq, J = 10.4 and 6.1 Hz, H-20), 4.24 (1H, dd, J = 6.8 and 10.9 Hz, H-1), 3.96 (1H, dt, J = 4.6 and 11.1 Hz, H-11), 2.37 (1H, ddt, J = 1.7, 5.4 and 14.1 Hz, H-6β), 2.32 (1H, m, H-2α), 2.31 (1H, m, H-12β), 2.12 (1H, ddd, J = 1.6, 5.0 and 14.4 Hz, H-6α), 2.02 (3H, s, 20-acetate), 2.01 (3H, s, 3-acetate), 1.98 (1H, s, H-7α), 1.85 (1H, m, H-16β), 1.71 (1H, m, H-17), 1.67 (1H, m, H-15α), 1.65 (1H, m, H-8), 1.58 (1H, ddd, J = 2.9, 10.9 and 13.7 Hz, H-2β), 1.34 (1H, m, H-16α), 1.19 (3H, s, H-19), 1.18 (2H, m, H-14 and H-15β), 1.16 (1H, m, H-12α), 1.14 (3H, d, J = 6.1 Hz, H-21), 1.07 (1H, t, J = 11.9 Hz, H-9), 1.00 (1H, m, H-7β), 0.69 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.6 and 170.5 (3- and 20-acetates), 151.4 (C-5), 115.0 (C-4), 82.0 (C-1), 76.0 (C-11), 72.3 (C-20), 67.5 (C-3), 59.7 (C-9), 57.4 (C-14), 53.3 (C-17), 46.8 (C-13), 44.4 (C-12), 41.8 (C-10), 34.1 (C-2), 34.0 (C-7), 31.1 (C-8), 30.1 (C-6), 26.5 (C-16), 22.5 (C-15), 21.5 (20-acetate), 21.2 (3-acetates), 20.0 (C-21), 19.8 (C-19), 13.9 (C-18); MS, *m/z* (%): 416 (M^+, 0.6), 374 (6), 296 (7), 199 (12), 122 (22), 43 (100); HR MS-DCI: calculated for $C_{25}H_{37}O_5$ 417.2636, found. 417.2641.

2.2.6. 3β,20-Diacetoxy-1α-iodo-5α-pregnan-11α-ol (*14*)

Amorphous solid; IR (KBr) 2929, 2873, 1731, 1372, 1245, 1027 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.63 (1H, t, J = 3.2 Hz, H-1), 5.24 (1H, tt, J = 5.4 and 10.8 Hz, H-3), 4.80 (1H, dq, J = 10.4 and 6.0 Hz, H-20), 3.79 (1H, dq, J = 4,0 and 10.5 Hz, H-11), 2.33 (1H, dddd, J = 2.0, 3.2, 4.8 and 14.4 Hz, H-2α), 2.14 (1H, ddd, J = 3.5, 11.1 and 14.7 Hz, H-2β), 2.12 (1H, dd, J = 4.5 and 12.2 Hz, H-12β), 2.04 (3H, s, 20-acetate), 2.02 (3H, s, 3-acetate), 1.79 (1H, m, H-5), 1.78 (1H, m, H-4α), 1.74 (1H, m, H-16β), 1.66 (1H, q, J = 10.2 Hz, H-17), 1.62 (1H, m, H-15α), 1.61 (1H, m, H-6α), 1.46 (1H, dt, J = 11.4 and 13.2 Hz, H-4β), 1.36 (1H, m, H-7β), 1.32 (1H, dd, J = 12.7 and 14.2 Hz, H-9), 1.30 (1H, m, H-12α), 1.24 (1H, m, H-16α), 1.23 (2H, m, H-8 and H-14), 1.15 (1H, m, H-7α), 1.14 (3H, d, J = 6.4 Hz, H-21), 1.13 (3H, s, H-19), 1.09 (1H, m, H-15β), 0.96 (1H, m, H-6β), 0.65 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.5 and 170.4 (3- and 20-acetates), 72.6 (C-20), 71.4 (C-3), 70.4 (C-11), 59.4 (C-9), 55.1 (C-14), 55.0 (C-1), 54.7 (C-17), 51.2 (C-12), 42.9 (C-13), 41.2 (C-10), 39.3 (C-5), 37.6 (C-2), 35.4 (C-8), 34.4 (C-4), 31.0 (C-6), 29.0 (C-7), 25.4 (C-16), 23.9 (C-15), 21.6 (20-acetate), 21.3 (3-acetate), 19.8 (C-21), 13.8 (C-18), 12.4 (C-19); HR MS-ESI: calculated for $C_{25}H_{39}INaO_5$ 569.1734, found 569.1712.

2.2.7. Cleavage of 1,11-ethers with zinc iodide-acetic anhydride

Procedure A. To a mixture of anhydrous zinc iodide (150 mg, 0.47 mmol) and acetic anhydride (1.0 mL) was added 1α,11α-epoxysteroid **9** (10) (30 mg, 0.072 mmol) and the slurry stirred for 45 min at room temperature, in the dark. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate, sodium thiosulfate, water, and dried with sodium sulfate. The solvent was evaporated and the residue purified by flash chromatography (silica gel, hexane/ethyl acetate 90:10 → 80:20) to give **21** (19.0 mg, 51%) and **22** (8.8 mg, 25%).

Procedure B. To a mixture of anhydrous zinc iodide (150 mg, 0.47 mmol) and acetic anhydride (1.0 mL) was added a solution of 1α,11α-epoxysteroid **9** (30 mg, 0.072 mmol) in dichloromethane (3.0 mL). The reaction mixture was stirred for 40 min at room temperature in the dark followed by work up as above. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate 90:10 → 80:20) to give **21** (4.1 mg, 11%).and **22** (21.4 mg, 61%).

2.2.8. 1β,3α,11α,20-Tetraacetoxy-5β-pregnane (*21*)

White solid: mp 145–146 °C (from ethyl acetate–hexane); IR (KBr) 2935, 2873, 1743, 1449, 1372, 1245, 1077, 1027, 960 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.32 (1H, dd, J = 2.0 and 3.7 Hz, H-1), 5.04 (1H, tt, J = 5.5 and 11.1 Hz, H-3), 4.98 (1H, dt, J = 4.9 and 10.7 Hz, H-11), 4.76 (1H, dq, J = 10.9 and 6.0 Hz, H-20), 2.33 (1H, dd, J = 4.9 and 12.2 Hz, H-12β), 2.07 (3H, s, 11-acetate), 2.05 (3H, s, 3-acetate), 2.04 (3H, s, 20-acetate), 1.99 (3H, s, 1-acetate),

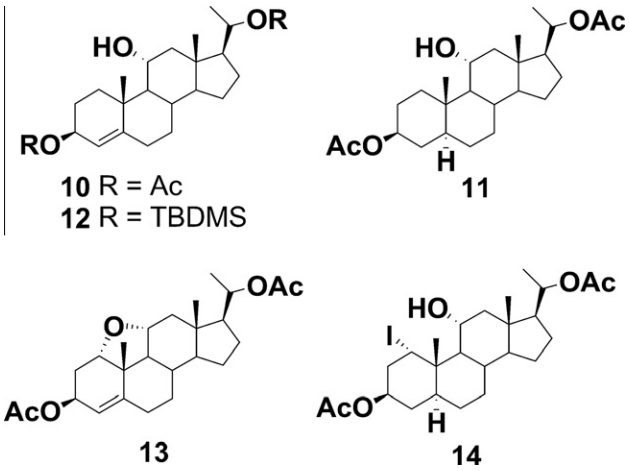


Fig. 2. Structures of compounds **10**–**14**.

2.02 (1H, m, H-5), 2.00 (1H, m, H-2β), 1.96 (1H, m, H-2α), 1.89 (1H, t, *J* = 10.6 Hz, H-9), 1.86 (1H, br q, *J* = 12.5 Hz, H-4α), 1.76 (1H, m, H-16β), 1.75 (1H, m, H-6β), 1.70 (1H, m, H-4β), 1.65 (1H, m, H-15α), 1.61 (1H, q, *J* = 9.8 Hz, H-17), 1.54 (1H, dq, *J* = 3.5 and 11.1 Hz, H-8), 1.46 (1H, ddt, *J* = 2.7, 13.3 and 3.8 Hz, H-7β), 1.33 (1H, br d, *J* = 13.8 Hz, H-6α), 1.26 (1H, m, H-14), 1.25 (2H, m, H-7α and H-16α), 1.18 (1H, dd, *J* = 11.1 and 12.2 Hz, H-12α), 1.14 (3H, d, *J* = 6.2 Hz, H-21), 1.13 (1H, m, H-15β), 1.00 (3H, s, H-19), 0.69 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.6 (20-acetate), 170.5 (3-acetate), 170.4 (1-acetate), 170.0 (11-acetate), 76.8 (C-1), 72.7 (C-20), 71.7 (C-11), 70.2 (C-3), 54.82 (C-14), 54.78 (C-17), 45.8 (C-12), 45.3 (C-9), 42.6 (C-13), 39.2 (C-10), 36.5 (C-5), 34.7 (C-8), 32.0 (C-4), 30.9 (C-2), 26.2 (C-6), 25.6 (C-7), 25.5 (C-16), 24.2 (C-15), 21.5 (11-acetate), 2 × 21.4 (1- and 3-acetates), 21.1 (20-acetate), 19.8 (C-21), 18.2 (C-19), 13.3 (C-18); HR MS-ESI: calculated for $C_{29}H_{44}NaO_8$ 543.2928, found 543.2949.

2.2.9. 3α,11α,20-Triacetoxy-1β-iodo-5β-pregnane (**22**)

White solid: mp 212–213 °C (from ethyl acetate–hexane); IR (KBr) 2935.3, 2878, 1735, 1447, 1368, 1242, 1025, 954 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.48 (1H, ddt, *J* = 5.3, 11.0 and 8.0 Hz, H-3), 5.04 (1H, t, *J* = 3.3 Hz, H-1), 4.97 (1H, dt, *J* = 5.1 and 10.5 Hz, H-11), 4.76 (1H, dq, *J* = 10.8 and 6.0 Hz, H-20), 2.36 (1H, dd, *J* = 5.1 and 12.3 Hz, H-12β), 2.27 (2H, dd, *J* = 3.2 and 8.2 Hz, H-2), 2.17 (1H, t, *J* = 10.6 Hz, H-9), 2.11 (1H, ddd, *J* = 4.1, 6.6 and 13.1 Hz, H-5), 2.06 (3H, s, 20-acetate), 2.00 (3H, s, 11-acetate), 1.99 (3H, s, 3-acetate), 1.87 (1H, dt, *J* = 11.5 and 13.0 Hz, H-4α), 1.76 (1H, m, H-16β), 1.75 (1H, m, H-6β), 1.70 (1H, m, H-4β), 1.65 (1H, m, H-15α), 1.61 (1H, q, *J* = 9.5 Hz, H-17), 1.59 (1H, m, H-8), 1.43 (1H, ddt, *J* = 13.5, 2.4 and 4.0 Hz, H-7β), 1.33 (1H, br d, *J* = 14.1 Hz, H-6α), 1.27 (1H, m, H-14), 1.26 (1H, m, H-16α), 1.25 (3H, s, H-19), 1.25 (1H, m, H-7α), 1.18 (1H, dd, *J* = 10.9 and 12.3 Hz, H-12α), 1.14 (3H, d, *J* = 6.2 Hz, H-21), 1.13 (1H, m, H-15β), 0.67 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.4, 170.3 (3- and 20-acetates), 169.5 (11-acetate), 72.8 (C-20), 72.7 (C-3), 72.2 (C-11), 54.7 (C-17), 54.6 (C-14), 50.7 (C-1), 45.6 (C-12), 44.0 (C-9), 42.4 (C-13), 40.0 (C-10), 38.6 (C-5), 36.8 (C-2), 36.7 (C-8), 31.9 (C-4), 27.3 (C-19), 26.6 (C-6), 25.5 (C-16), 25.4 (C-7), 24.3 (C-15), 21.7 (11-acetate), 21.4 (3-acetate), 21.3 (20-acetate), 19.7 (C-21), 13.3 (C-18); HR MS-ESI: calculated for $C_{27}H_{41}INaO_6$ 611.1840, found. 611.1834.

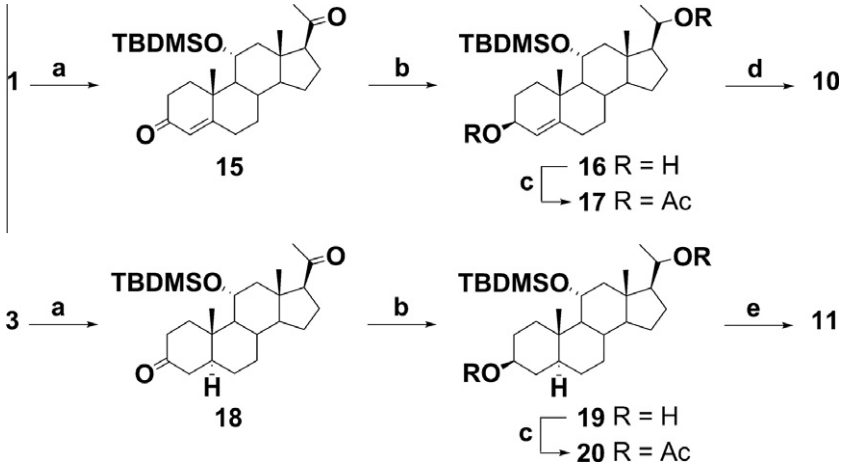
Table 1
Photolysis with visible light or microwave irradiation of 11α-hydroxysteroids in the presence of DIB/iodine in dichloromethane.[a]

Entry	Steroid	Conditions (time min)	Products (yield)
1	**8**	Photolysis (20)[b]	**9** (89%)[d]
2	**8**	Microwave irradiation 200 W (10)[b]	**9** (90%)
3	**3**	Photolysis (20)[b]	**6** (22%); **7** (66%)[d]
4	**3**	Microwave irradiation 200 W (10)[b]	**7** (20%)
5	**3**	Microwave irradiation 300 W (10)[b]	**7** (68%)
6	**11**	Photolysis (30)[b]	**14** (24%)
7	**11**	Microwave irradiation 300 W (15)[b]	**14** (25%)
8	**10**	Photolysis (20)[b]	**13** (20%)
9	**10**	Photolysis (30)[b]	**13** (30%)
10	**10**	Photolysis (20)[c]	**13** (30–50%)[e]
11	**10**	Microwave irradiation 300 W (15)[b]	**13** (60%)
12	**10**	Microwave irradiation 300 W (15)[c]	**13** (50%)
13	**12**	Microwave irradiation 300 W (30)[b]	Complex mixture[f]
14	**12**	Photolysis (30)[b]	Complex mixture[f]
15	**6**	Microwave irradiation 300 W (30)[b]	Complex mixture[f]

[a] Photolysis under irradiation with a 300 W tungsten lamp (5000 lm) at room temperature. Microwave irradiation in a CEM Discover microwave system at constant power of either 200 W (71 °C, 12 psi) or 300 W (95 °C, 15 psi). 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 (1:2.4:2).
[d] Data taken from Ref. [5].
[e] Reaction yields were not reproducible.
[f] Reaction mixture consisted mainly of fragmentation products.

2.2.10. 1α,3β,11α,20-Tetraacetoxy-4-pregnene (**23**)

Amorphous solid; IR (KBr) 2940, 2873, 1734, 1663, 1446, 1373, 1246, 1117, 1026 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.61 (1H,



Scheme 1. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 50 °C; (b) $NaBH_4$, MeOH, CH_2Cl_2, 25 °C; (c) Ac_2O, py, 25 °C; (d) Bu_4NF/THF 60 °C; (e) HF 40%, THF, acetonitrile, 25 °C.

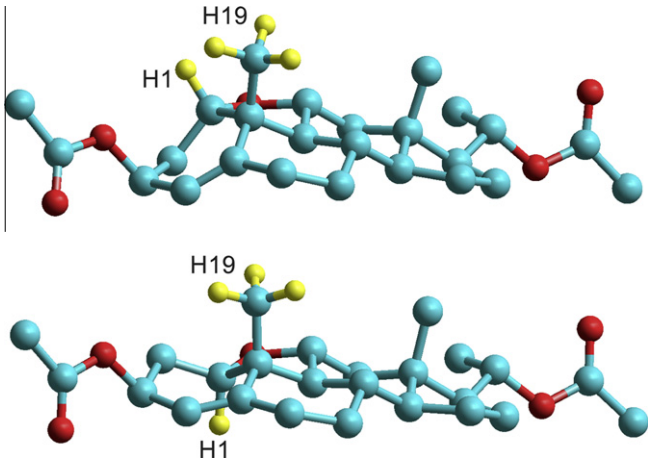


Fig. 3. AM1 calculated structures of 1α,11α-epoxypregnene **13** (a) and its 1β,11α isomer (b) showing the relative positions of H-1 and H-19.

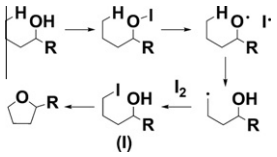


Fig. 4. Proposed mechanism for the hypoiodite reaction [9].

dd, J = 5.9 and 1.6 Hz, H-1), 5.41 (1H, br s, $W_{1/2}$ = 4.7 Hz, H-4), 5.34 (1H, tdd, J = 2.5, 6.0 and 8.9 Hz, H-3), 5.01 (1H, dt, J = 5.2 and 10.5 Hz, H-11), 4.77 (1H, dq, J = 10.6 and 6.2 Hz, H-20), 2.36 (1H, dd, J = 12.3 and 5.1 Hz, H-12β), 2.26 (1H, ddt, J = 2.3, 4.7 and 11.4 Hz, H-6β), 2.14 (1H, ddt, J = 1.0, 13.0 and 5.9 Hz, H-2α), 2.08 (3H, s, 3-acetate), 2.07 (3H, s, 11-acetate), 2.06 (1H, m, H-6α), 2.02 (3H, s, 1-acetate), 2.00 (3H, s, 20-acetate), 1.94 (1H, ddd, J = 1.8, 9.2 and 13.1 Hz, H-2β), 1.84 (1H, br d, J = 12.6 Hz, H-7β), 1.75 (1H, m, H-16β), 1.73 (1H, m, H-8), 1.65 (1H, m, H-15α), 1.61 (1H, t, J = 10.6 Hz, H-9), 1.60 (1H, q, J = 9.7 Hz, H-17), 1.26 (1H, m, H-16α), 1.22 (1H, m, H-14), 1.15 (1H, m, H-15β), 1.14 (1H, m, H-12α), 1.14 (3H, d, J = 6.1 Hz, H-21), 1.09 (3H, s, H-19), 1.09 (1H, m, H-7α), 0.71 (3H, s, H-18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.8, 170.7 (1- and 3-acetates), 170.4 (20-acetate), 170.2 (11-acetate), 146.9 (C-5), 119.1 (C-4), 73.5 (C-1), 72.7 (C-20), 71.6 (C-11), 68.0 (C-3), 54.7 (C-17), 54.5 (C-14), 54.2 (C-9), 45.4 (C-12), 42.5 (C-13), 42.3 (C-10), 35.1 (C-8), 34.1 (C-7), 32.1 (C-6), 28.6 (C-2), 25.4 (C-16), 24.3 (C-15), 21.6 (11-acetate), 2 × 21.4 (3 and 20-acetates), 21.2 (1-acetate), 19.8 (C-21), 15.9 (C-19), 13.3 (C-18); HR MS-ESI: calculated for $C_{29}H_{42}NaO_8$ 541.2772, found. 541.2793.

3. Results and discussion

The readily available 11α-hydroxypregnanes **3, 8, 10** and **11** were chosen to compare both methodologies, photolysis with visible light and microwave irradiation, for the remote functionalization reaction (see Figs. 1 and 2 for structures). Compounds **3** and **8** were obtained from 11α-hydroxyprogesterone as described previously [5]. Compounds **10** and **11** were prepared from **1** and **3**, respectively in 4 steps (Scheme 1), by protection of the 11α-hydroxy group as the *tert*-butyldimethylsilyl ether (to give **15** and **18**) followed by reduction of the 3,20-diketone with $NaBH_4$ (to **16** and **19**) and acetylation of the resulting 3,20-diol with acetic anhydride-pyridine (to give **17** and **20**). Compound **11** was obtained by cleavage of the TBDMS ether **20** using 40% hydrofluoric acid. In the case of silyl ether **17**, treatment under the same conditions resulted in the elimination of the 3-acetate; therefore in this case Bu_4NF/THF was used for the deprotection of the 11α-hydroxy group to give compound **10**.

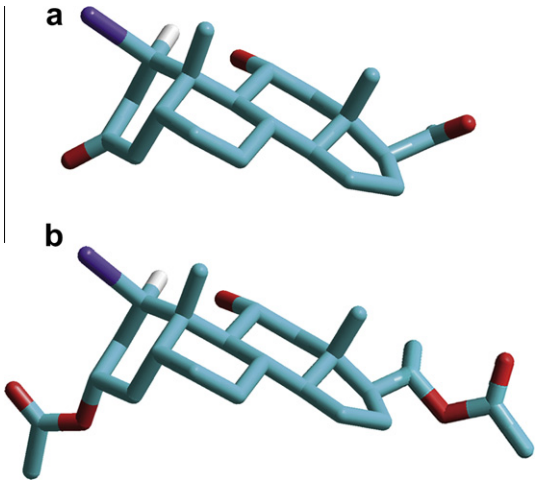


Fig. 5. HF/6-31G(d,p) calculated structures for the most stable 1-iodo intermediates derived from the 5β-pregnanes **2** (a) and **8** (b).

The remote functionalization reaction on compounds **3** and **8** gave similar results with both methodologies (Table 1, entries 1–5), although in the case of compound **3** a higher microwave potency was required (Table 1, entries 2 and 5). When the reaction was attempted on the 3β-acetate **11** (Table 1, entries 6–7) the 1-iodosteroid **14** was obtained in low yield together with fragmentation products but the corresponding 1,11-epoxysteroid was not detected.

In the case of the Δ^4 steroid **10** both the 1α,11α- and the 1β,11α-epoxysteroid may result (Fig. 3), however the 1α,11α-epoxysteroid **13** was the only cyclization product formed as determined by NMR spectroscopy (see below). Irradiation with visible light resulted in low yields that could not be significantly improved by increasing the reaction time (Table 1, entries 8 and 9) or a different steroid/DIB/iodine ratio (entry 10), longer reaction times resulted in extensive decomposition. When the reaction was carried out with microwave irradiation, a 60% yield of the 1α,11α-epoxysteroid **13** was obtained and the Δ^1 derivative was not detected as a byproduct (entry 11). In this case, changing the steroid/DIB/iodine ratio gave a lower yield (entry 12).

The ^{1}H NMR spectrum of **13** showed a double doublet at δ 4.24 (J = 6.8 and 10.9 Hz) assigned to H-1 and a double triplet at δ 3.96 (J = 4.6 and 11.1 Hz) assigned to H-11, consistent with the presence of a 1α,11α-epoxy functionality. The β orientation of H-1was confirmed by the correlation observed between H-1 (δ 4.24) and H-19 (δ 1.19) in the NOESY spectrum, in agreement with the 2.56 Å distance predicted by AM1 calculations between those hydrogens. No NOE correlation between H-1α and H-19 is expected in the 1β,11α-epoxysteroid (Fig. 3).

The above results and those obtained previously with compounds **1** and **2** [5] indicate that the outcome of the reaction is heavily dependent not only in the type of A/B ring fusion but also on the nature and orientation of the C-3 substituent. To have a better insight on the factors influencing the reaction we analyzed the stability and preferred conformations of the possible 1-iodo intermediates (**I** in Fig. 4) derived from the 11α-hydroxysteroids **1**–**3**, **8**, **10** and **11** [9]. The geometries of the intermediate 1-iodo-11α-alcohols were optimized using *ab initio* methods (HF/6-31G(d,p)); in the case of the 11α-hydroxy-5β-pregnanes **2** and **8** the most stable intermediate had the iodine at C-1 in an axial (β) orientation (Fig. 5). This arrangement can result in either elimination or

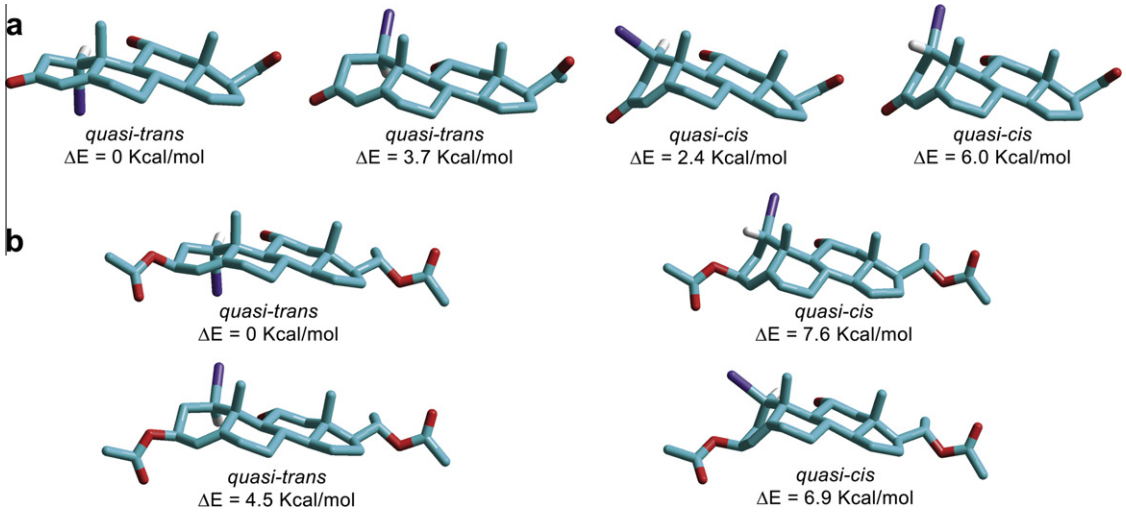


Fig. 6. HF/6-31G(d,p) calculated structures and relative energies, for the possible 1-iodo intermediates (*quasi–cis* and *quasi–trans* conformers) corresponding to the Δ^4-pregnenes **1** (a) and **10** (b).

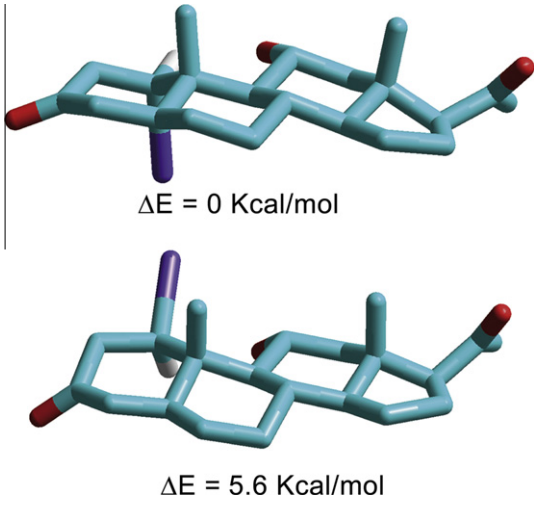
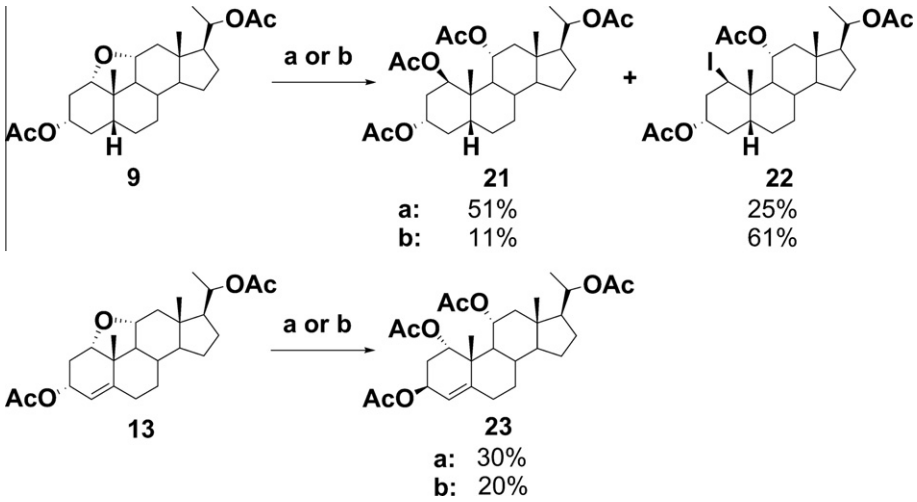


Fig. 7. HF/6-31G(d,p) calculated structures and relative energies, for the possible 1-iodo intermediates derived from 5α-pregnane **3**. See supporting information (Fig. S1) for the analogous intermediates derived from **11**.

intramolecular substitution by the hydroxyl at C-11, to give the cyclized product. Thus, for compound **8**, the 1α,11α-epoxysteroid **9** (Table 1, entries 1,2), was obtained as the major product, while in the case of compound **2** the presence of the 3-keto group would favor the elimination reaction to give the α,β-unsaturated steroid **5** [5].

In the 11α-hydroxy-Δ^4-pregnenes **1** and **10**, the conformational equilibrium of ring A (*quasi–cis* vs. *quasi–trans* A/B fusion) results in two possible conformers for each 1-iodo-11α-hydroxy intermediate (Fig. 6). In the 3-ketosteroid **1** the most stable intermediates (1α-iodo *quasi–trans and* 1β-iodo *quasi–cis* conformers) have the iodine at C-1 in an axial orientation leading to the elimination product **4** [5]. The 3β-acetate in compound **10** stabilizes the *quasi–trans* conformers, but intramolecular cyclization can only take place via the 1β-iodo *quasi–cis* conformer that would be better accessible under the high energy conditions provided by microwave irradiation (Table 1, entries 11–12). No cyclized product was observed when the reaction was carried out with the 3β-*t*-butyldimethylsilyl analogue **12**, either under photolysis with visible light or microwave irradiation (Table 1, entries 13 and 14), this result is consistent with the destabilizing effect of an axial bulky *t*-butyldimethylsilyloxy group on the 1β-iodo *quasi–cis* conformer.



Scheme 2. Reagents and conditions: (a) ZnI_2/Ac_2O, 45 min, 25 °C; (b) $ZnI_2/Ac_2O/CH_2Cl_2$, 40 min, 25 °C. Yields correspond to isolated products purified by flash chromatography on Florisil (ethyl acetate/hexane).

In the case of the 11α-hydroxy-5α-pregnanes **3** and **11**, neither the 1α-iodo nor the 1β-iodo intermediates allows for an intramolecular SN2 attack on C-1 (Fig. 7). In spite of this, the 1,11-epoxysteroid **7** was the major product from the reaction on the 3-ketosteroid **3** (Table 1, entries 3 and 5) even though, the most stable iodosteroid derived from **3** (with an axial 1α-iodine) has the adequate orientation to give the elimination product **6**. Furthermore, under microwave irradiation no elimination product was detected. With the 3β-acetate **11**, the reaction does not proceed further and a low yield of the 1α-iodosteroid **14** results, confirming that intramolecular cyclization does not take place on this intermediate (Table 1, entries 6 and 7). The fact that cyclization of the 5α reduced steroid only occurred in the presence of a C-3 carbonyl suggests some involvement of this functional group in this case, however attempts to cyclize the elimination product **6** were unsuccessful both under acid (*p*-TsOH,CH_2Cl_2) or basic (MeO^-/MeOH) conditions [5]. No cyclization was observed either, upon treatment of **6** with DIB/I_2 and microwave irradiation (Table 1, entry 15).

Besides the interesting biological activities displayed by 1,11-epoxypregnanes [6], these compounds provide a way of introducing a substituent at a non-functionalized C-1 of the steroid nucleus. In particular, we prepared compounds **21** and **22** by cleavage of the 1α,11α-oxygen bridge in compound **9** using ZnI_2/Ac_2O or ZnI_2/Ac_2O/CH_2Cl_2 [10] (Scheme 2). When the reaction was attempted on compound **13**, the 1-iodosteroid was not detected and only the 1α-acetoxy derivative **23** was obtained in low yield, probably due to rearrangements of the homoallylic carbocation at C-1.

Overall, our results show that photolysis with visible light may be advantageously replaced by microwave irradiation to prepare 1,11-oxygen bridges using Suarez reagent, especially in the case of sensitive substrates.

Acknowledgements

The authors acknowledge the financial support of the Agencia Nacional de Promoción Científica y Tecnológica (PICT-2006 00727), CONICET-Argentina (PIP 0579) and Universidad de Buenos Aires (UBACYT X026).

Appendix A. Supplementary data

HF/6-31G(d,p) calculated structures and relative energies, for the possible 1-iodo intermediates derived from **11**, experimental procedure for the preparation of compound **12** and ^1H and ^{13}C NMR spectra of compounds **10**, **11**, **13**, **14** and **21**–**23**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.steroids.2011.07.016.

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