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Norrish–Prins reaction as a key step in the synthesis of 14β-hydroxy-5α (or 5β or $\Delta^{5,6}$)-pregnane derivatives

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ABSTRACT

Numerous bioactive glycosteroids are characterized by aglycones bearing a 14β-hydroxy pregnane skeleton like boucerin and isoramanone. In general, the syntheses of the latter are achieved by acidic hydrolysis of the corresponding glycosteroids. These aglycones were also obtained by a combined Norrish type I–Prins reaction starting from the corresponding 12-keto-pregnane derivatives. However, for the Norrish–Prins reaction, no reports describe the influence of the A/B ring junction (cis or trans or $\Delta^{5,6}$ double bond) or the influence of the substitution pattern at position 20. Herein, we describe the use of Norrish type I–Prins reactions to synthesize isoramanone and boucerin derivatives and their A/B cis and trans analogs. The influence of the parameters mentioned above is also presented. These studies showed that the A/B ring junction has little influence on the Norrish type I–Prins reaction but that the substitution pattern at position 20 is important. The presence of a dioxolane group induced not only the formation of the desired 14β-hydroxy pregnane derivatives in the highest yields but also the formation of new spiro derivatives.

1. Introduction

In a Norrish type-I reaction, the UV-induced α-cleavage of a carbonyl compound leads to an acyl-alkyl diradical as the primary photoproduct that evolves toward an aldehyde and an alkene [1]. On the other hand, the acid catalyzed condensation of an alkene with an aldehyde is known as a Prins reaction [2]. Starting from hecogenin acetate **1**, Bladon et al. showed that the Norrish type I reaction gave lumihecogenin acetate **3** [3]. Relevant extensions of this pioneering work were achieved by Chinn [4], Welzel [5], Winterfeld [6] and Fuchs [7] who first used Norrish type I reactions to prepare aldehyde **3** via the diradical intermediate **2**. Under acidic conditions, aldehyde **3** afforded the 14β-hydroxy derivative **4,** resulting from a Prins reaction, and the $\Delta^{14,15}$-derivative **5**, resulting from an ene reaction (Scheme 1).

Welzel et al. showed that combining the photolysis with an acidic treatment of compounds **6** (or **7**) promoted the formation of ene products **8** (**9**) and a mixture of 5, 6-dihydro-boucerin derivatives **10**–**13**. The ratio of the latter was related to the substitution pattern of compound **3** at position 20 (Scheme 2) [8].

To the best of our knowledge, no studies dealing with the influence of the A/B ring junction (cis or trans or $\Delta^{5,6}$ double bond) or the influence of the substitution pattern at position 20 on the outcome of the combined Norrish–Prins reaction have been described. We wish to report our results concerning the synthesis of isoramanone (or digipurpurogenin II) [9a,b] and boucerin [10] derivatives, and their A/B cis and trans analogs using Norrish type I–Prins reactions (Fig. 1). Isoramanone and boucerin represent the aglycones of numerous bioactive glycosteroids and therefore their synthesis is of interest [9b–f].

2. Experimental

2.1. General

Melting points were measured on a Stuart Scientific melting point apparatus (SMP 3) and are uncorrected. Reactions were carried out under argon with magnetic stirring and degassed solvents. Et_2O and THF were distilled from Na/benzophenone. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck $60F_{254}$) and the spots were visualized under UV lamp (254 or 365 nm) and sprayed with phosphomolybdic acid solution (25 g phosphomolybdic acid, 10 g cerium sulfate, 60 mL H_2SO_4, 940 mL H_2O) followed by heating on a hot plate. For column chromatography, silica gel (Merck Si 60 40–60 μm) was used. IR spectra were recorded on Bruker Alpha (ATR) spectrophotomer. ^1H NMR spectra were recorded at 300 MHz (Bruker AC-300) and ^{13}C NMR spectra at 75 MHz (Bruker AC-300) using the signal of the

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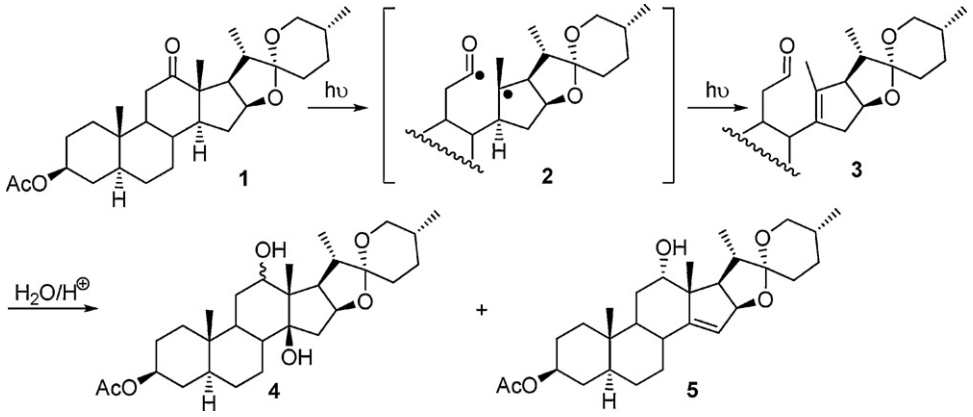
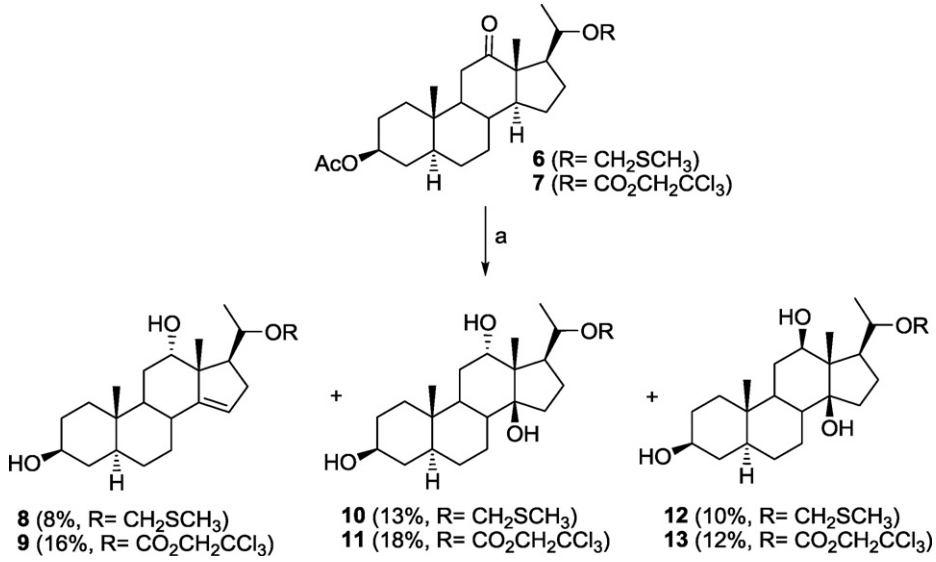


Scheme 1. Norrish-Prins reaction starting from hecogenin acetate.



Scheme 2. Reagents and reaction conditions: (a) i: hυ, CH_2Cl_2, 1 h, 25 °C; ii: AcOH/H_2O/CF_3CO_2H (2.5/1/0.6), 4 h, 10 °C.

residual non-deuterated solvent as internal reference. Significant ^{1}H NMR data are tabulated in the following order: chemical shift (δ) expressed in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants in hertz, number of protons. High-resolution mass spectra (HRMS) were performed on a Agilent 6520 Accurate Mass Q-TOF.

2.2. General procedure for the Norrish type I–Prins (NP) reaction

A solution of 12-keto derivative (**14**–**16**, **19**, **20**, **24**, **30**, **32**, **33**) in CH_2Cl_2 was deoxygenated with argon for 15 min and irradiated with a high pressure mercury lamp (Philips HPK 125) for 15 min in a refrigerated quartz vessel. The solvent was evaporated under reduced pressure to afford the corresponding crude seco aldehyde. To a solution of the latter in THF was added a solution of AcOH/H_2O/CF_3COOH (2.5/1/0.6). After 2 h stirring at r.t., the reaction mixture was diluted with CH_2Cl_2, washed with water and with sat. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (petroleum ether/EtOAc (8:2–6:4) to afford the resulting products.

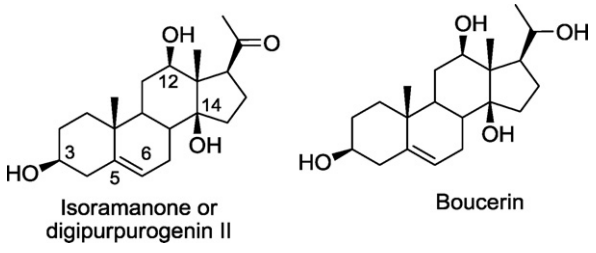


Fig. 1. Isoramanone and boucerin, aglycones of numerous bioactive glycosteroids.

2.3. NP reaction starting from 3β,20R-bis(acetoxy)-5α-pregnan-12-one (**14**), leading to compounds **34**, **36**, **38** and **40**

Norrish type I reaction: **14** (1.00 g, 2.39 mmol); CH_2Cl_2 (280 mL). Prins reaction: THF (1.1 mL), AcOH/H_2O/CF_3COOH (2.5/1/0.6, 11 mL).

3β,20R-bis(acetoxy)-5α-12α-hydroxy-pregn-14-ene (**34**): as a white solid (175 mg, 26% yield, mp 86–90 °C). IR (ATR): 3577, 1731, 1714. ^{1}H NMR ($CDCl_3$): 5.24 (s, 1H, H-15); 4.95 (dq, 1H, J = 6.1–10.8 Hz, H-20); 4.67 (tt, 1H, J = 4.9–11.2 Hz, H-3α); 3.70 (t, 1H, J = 2.9 Hz, H-12β); 2.74 (td, 1H, J = 8.2–10.8 Hz, H-17α); 2.25 (ddd, 1H, J = 2.6–8.2–15.1 Hz, H-16); 2.02 (s, 3H, CH_3, Ac); 2.01 (s, 3H, CH_3, Ac); 1.95–0.90 (m, 17H); 1.22 (d, 3H, J = 6.0 Hz, CH_3, H-

21); 0.84 (s, 3H, CH_3); 0.83 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.7 (C=O, OAc); 170.5 (C=O, OAc); 151.6 (C, C-14); 119.2 (CH, C-15); 73.5 (CH, C-12); 72.9 (CH, C-3); 72.6 (CH, C-20); 51.3 (C, C-13); 46.5 (CH); 45.2 (CH); 44.1 (CH); 36.5 (CH_2); 35.1 (C, C-10); 34.5 (CH); 33.9 (CH_2); 32.4 (CH_2); 29.5 (CH_2); 28.8 (CH_2); 28.1 (CH_2); 27.3 (CH_2); 21.5 (CH_3); 21.4 (CH_3); 19.6 (CH_3); 17.2 (CH_3); 17.2 (CH_3); 11.7 (CH_3). HRMS (ESI) *m/z*: $C_{25}H_{38}NaO_5$ [M+Na$^+$] calcd. 441.2611, found 441.2623. $[\alpha]_D^{20}$: +46.5 (*c*. 0.016, $CHCl_3$).

3β,20R-bis(acetoxy)-5α-12α-hydroxy-pregn-8-ene (**36**): as a white solid (77 mg, 11%, mp 120–123 °C). IR (ATR): 3504, 1715. ^1H NMR ($CDCl_3$): 4.90 (dq, 1H, *J* = 6.2–10.1 Hz, H-20) ; 4.71 (tt, 1H, *J* = 4.9–11.3 Hz, H-3α) ; 3.77 (s, 1H, H-12β) ; 2.45–2.10 (m, 4H); 2.05 (s, 3H, CH_3, Ac); 2.02 (s, 3H, CH_3, Ac); 1.90–1.00 (16H, m); 1.22 (d, 3H, *J* = 6.3 Hz, CH_3, H-21); 0.82 (s, 3H, CH_3); 0.71 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.7 (C=O, OAc); 170.3 (C=O, OAc); 137.2 (C=C); 127.1 (C=C); 73.4 (CH, C-12); 72.5 (CH, C-3); 71.8 (CH, C-20); 47.1 (CH); 46.9 (C, C-13); 44.4 (CH); 43.9 (CH); 36.6 (C, C-10); 36.0 (CH_2); 34.1 (CH_2); 29.2 (CH_2); 28.5 (CH_2); 27.4 (CH_2); 26.2 (CH_2); 25.9 (CH_2); 24.3 (CH_2); 21.5 (CH_3); 21.4 (CH_3); 19.7 (CH_3); 19.5 (CH_3); 12.9 (CH_3). HRMS (ESI) *m/z*: $C_{25}H_{38}NaO_5$ [M+Na$^+$] calcd. 441.2611, found 441.2622. $[\alpha]_D^{20}$: +25 (*c*. 0.01, $CHCl_3$).

3β,20R-bis(acetoxy)-5α-12α-14β-dihydroxy-pregnane (**38**): as a white solid (61 mg, 9%, mp 152–153 °C). IR (ATR): 3402, 1730. ^1H NMR ($CDCl_3$): 4.90 (dq, 1H, *J* = 6.1–9.5 Hz, H-20); 4.68 (tt, 1H, *J* = 4.9–11.3 Hz, H-3α); 3.65 (t, 1H, *J* = 3.5 Hz, H-12β); 2.40 (q, 1H, *J* = 9.0 Hz); 2.02 (s, 3H, CH_3, Ac); 2.01 (s, 3H, CH_3, Ac); 1.95–0.95 (m, 21H); 1.22 (d, 3H, *J* = 6.0 Hz, CH_3, H-21); 0.92 (s, 3H, CH_3); 0.82 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.7 (C=O, OAc), 170.4 (C=O, OAc), 85.6 (C, C-14), 76.2 (CH, C-12), 74.2 (CH, C-3), 73.5 (CH, C-20), 50.3 (C, C-13), 47.6 (CH), 44.2 (C), 42.7 (CH), 41.2 (CH), 36.7 (CH_2), 35.5 (C, C-10), 33.8 (CH_2), 33.4 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 21.6 (CH_3), 21.4 (CH_3), 19.4 (CH_3), 15.9 (CH_3), 12.0 (CH_3). HRMS (ESI) *m/z*: $C_{25}H_{40}NaO_6$ [M+Na$^+$] calcd. 459.2717, found 459.2722. $[\alpha]_D^{20}$: +32 (*c*. 0.009, $CHCl_3$).

3β,20R-bis(acetoxy)-5α-12β-14β-dihydroxy-pregnane (**40**): as a white solid (106 mg, 15%, mp 81–84 °C). IR (ATR): 3435, 1713. ^1H NMR ($CDCl_3$): 4.95–4.75 (m, 1H, H-20); 4.75–4.60 (m, 1H, H-3α); 3.28 (dd, 1H, *J* = 3.7–11.9 Hz, H-12α); 2.04 (s, 3H, CH_3, Ac); 2.01 (s, 3H, CH_3, Ac); 1.98–0.70 (m, 22H); 1.21 (d, 3H, *J* = 6.0 Hz, CH_3, H-21); 0.88 (s, 3H, CH_3); 0.81 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.7 (C=O, OAc); 170.2 (C=O, OAc); 86.1 (C, C-14); 77.1 (CH, C-12); 73.7 (CH, C-3); 73.4 (CH, C-20); 60.4 (CH_2); 52.6 (CH); 51.6 (C, C-13); 46.3 (CH); 44.3 (CH); 41.3 (CH); 36.8 (CH_2); 35.6 (CH_2); 33.7 (C, C-10); 32.1 (CH_2); 29.7 (CH_2); 28.4 (CH_2); 27.7 (CH_2); 27.3 (CH_2); 21.4 (CH_3); 19.0 (CH_3); 14.2 (CH_3); 12.1 (CH_3); 7.9 (CH_3). HRMS (ESI) *m/z*: $C_{25}H_{40}NaO_6$ [M+Na$^+$] calcd. 459.2717, found 459.2723. $[\alpha]_D^{20}$: +6 (*c*. 0.033, $CHCl_3$).

*2.4. NP reaction starting from 3β-acetoxy-5α-pregnan-12,20-dione (**15**), leading to compounds **42***

Norrish type I reaction: **15** (402 mg, 1.07 mmol); CH_2Cl_2 (230 mL). Prins reaction: THF (2.0 mL), AcOH/H_2O/CF_3COOH (2.5/1/0.6, 10 mL).

3β-Acetoxy-5α-12β-14β-dihydroxy-pregnan-20-one (**42**): as a white solid (83 mg, 20%, mp 93–95 °C). IR (ATR): 3434, 1728, 1692. ^1H NMR ($CDCl_3$): 4.65 (tt, 1H, *J* = 4.9–11.5 Hz, H-3α) ; 3.53 (t, 1H, *J* = 6.6 Hz, H-17α) ; 3.26 (dd, 1H, *J* = 4.2–11.7 Hz, H-α) ; 2.23 (s, 3H, CH_3, H-21) ; 2.10–0.60 (m, 21H); 1.99 (s, 3H, CH_3, Ac); 0.87 (s, 3H, CH_3); 0.80 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 218.1 (C=O, C-20) ; 170.8 (C=O, OAc) ; 85.2 (C, C-14) ; 73.8 (CH, C-12) ; 73.4 (CH, C-3) ; 56.8 (CH) ; 55.2 (C, C-13) ; 46.4 (CH); 44.4 (CH); 39.2 (CH); 36.9 (CH_2); 35.6 (C, C-10); 33.9 (CH_2); 33.7 (CH_2); 33.0 (CH_3); 29.8 (CH_2); 28.3 (CH_2); 27.8 (CH_2); 27.3 (CH_2); 24.7 (CH_2); 21.4 (CH_3); 12.1 (CH_3); 8.4 (CH_3). HRMS (ESI) *m/z*: $C_{23}H_{37}O_5$ [M+H$^+$] calcd. 393.2563, found 393.2623. $[\alpha]_D^{20}$: +16 (*c*. 0.031, $CHCl_3$).

*2.5. NP reaction starting from 3β-acetoxy-5α-cyclic 20-(ethylene acetal)-pregnan-12-one (**16**) leading to compounds **15**, **42, 47***

Norrish type I reaction: **16** (800 mg, 1.91 mmol); CH_2Cl_2 (250 mL). Prins reaction: THF (3.5 mL), AcOH/H_2O/CF_3COOH (2.5/1/0.6, 18 mL).

3β-Acetoxy-5α-pregnan-12,20-dione (**15**): as a white solid (69 mg, 10%, mp 189–192 °C). IR(ATR): 1723, 1699. ^1H NMR ($CDCl_3$): 4.68 (tt, 1H, *J* = 4.9–11.2 Hz, H-3α); 3.30 (t, 1H, *J* = 9.3 Hz, H-17α); 2.48 (t, 1H, *J* = 13.2 Hz, H-11); 2.30–2.05 (m, 2H); 2.26 (s, 3H, CH_3, Ac); 2.02 (s, 3H, CH_3, Ac); 1.90–0.95 (15H, m); 0.94 (s, 3H, CH_3); 0.91 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 212.7 (C=O, C-12); 209.1 (C=O, C-20); 169.0 (C=O; OAc); 72.5 (CH, C-3); 57.5 (C, C-13), 56.7 (CH, C-17); 55.5 (CH); 53.6 (CH); 43.8 (CH); 37.4 (CH_2); 35.7 (CH_2); 35.5 (C); 34.1 (CH_2); 33.1 (CH_2); 30.7 (CH); 30.6(CH_3); 27.5 (CH_2); 26.5 (CH_2); 23.4 (CH_2); 21.9 (CH_2), 20.7 (CH_3); 12.9 (CH_3); 11.2 (CH_3). HRMS (ESI) *m/z*: $C_{23}H_{35}O_4$ [M+H$^+$] calcd. 375.2530, found 375.2547. $[\alpha]_D^{20}$: +135 (*c*. 0.016, $CHCl_3$).

3β-Acetoxy-5α-12β-14β-dihydroxy-pregnan-20-one (**42**) (231 mg, 31% yield) is described above.

3β-Acetoxy-12α-hydroxy-5α-12,14α-cyclo-12,13-secopregna-13(17)-20-one (**47**): as a white solid (138 mg, 19%, mp 139–140 °C). IR (ATR): 3415, 1726, 1666, 1611. ^1H NMR ($CDCl_3$): 4.70 (tt, 1H, *J* = 5.1–11.1 Hz, H-3α); 4.17–4.02 (m, 1H, H-12β); 2.80–2.40 (m, 2H); 2.30–0.70 (m, 20H); 2.22 (s, 3H, CH_3, H-21); 2.02 (s, 3H, CH_3, Ac); 1.95 (t, 3H, *J* = 2.1 Hz, CH_3, H-18); 0.81 (s, 3H, CH_3, H-19). ^{13}C NMR ($CDCl_3$): 198.7 (C=O, C-20); 170.6 (C=O, OAc); 154.2 (C=C); 137.7 (C=C); 78.6 (CH, C-12); 73.5 (CH, C-3); 66.2 (C, C-14); 51.4 (CH); 44.6 (CH); 43.3 (CH); 37.2 (CH_2); 35.5 (C, C-10); 33.4 (CH_2); 32.5 (CH_2); 30.9 (CH_2); 30.4 (CH_3); 28.7 (CH_2); 27.0 (CH_2); 25.8 (CH_2); 22.2 (CH_2); 21.4 (CH_3); 12.2 (CH_3); 11.3 (CH_3). HRMS (ESI) *m/z*: $C_{23}H_{35}O_4$ [M+H$^+$] calcd. 375.2457, found 375.2537. $[\alpha]_D^{20}$: +19 (*c*. 0.007, $CHCl_3$).

*2.6. NP reaction starting from 3β,20R-bis(acetoxy)-5β-pregnan-12-one (**19**) leading to compounds **35**, **39** and **41***

Norrish type I reaction: **19** (264 mg, 0.63 mmol), CH_2Cl_2 (200 mL). Prins reaction: THF (1.0 mL), AcOH/H_2O/CF_3COOH (2.5/1/0.6, 4.3 mL).

3β,20R-bis(acetoxy)-5β-12α-hydroxy-pregn-14-ene (**35**): as a white solid (76 mg, 28%). IR (ATR): 3573, 1731, 1707. ^1H NMR ($CDCl_3$): 5.27 (s, 1H, H-15); 5.04 (t, 1H, *J* = 2.7 Hz, H-3α); 5.03–4.95 (m, 1H, H-20); 3.71 (t, 1H, *J* = 2.4 Hz, H-12β); 2.75 (td, 1H, *J* = 8.1–10.8 Hz); 2.26 (dddd, 1H, *J* = 1.5–2.7–8.1–14.7 Hz); 2.20–0.70 (m, 15H); 2.04 (s, 3H, CH_3, Ac); 2.02 (s, 3H, CH_3, Ac); 1.23 (d, 3H, *J* = 6.0 Hz, CH_3, H-21); 0.97 (s, 3H, CH_3); 0.85 –s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.5 (C=O, 2OAc); 152.2 (C=C, C-14); 119.0 (C=CH, C-15); 73.0 (CH, C-12); 72.6 (CH, C-3); 70.7 (CH, C-20); 51.4 (C, C-13); 46.8 (CH); 37.2 (CH); 36.4 (C, C-10); 34.7 (CH); 32.3 (CH_2); 31.4 (CH_3); 30.4 (CH_2); 29.1 (CH_2); 26.1 (CH_2); 25.0 (CH_2); 23.7 (CH_2); 23.3 (CH_3); 21.6 (CH_3); 19.7 (CH_3); 17.3 (CH_3). HRMS (ESI) *m/z*: $C_{25}H_{38}NaO_5$ [M+Na$^+$] calcd. 441.2611, found 441.2623. $[\alpha]_D^{20}$: +35 (*c*. 0.011, $CHCl_3$).

3β,20R-bis(acetoxy)-5β-12α-hydroxy-pregn-8-ene (**39**): as a white solid (40 mg, 15%). IR (ATR): 3469, 1722. ^1H NMR ($CDCl_3$): 5.09 (1H, t, *J* = 2.7 Hz, H-3α); 4.94–4.82 (1H, m, H-20); 3.78 (1H, t, *J* = 3.0 Hz, H-12β); 2.60–0.70 (20H, m); 2.04 (3H, s, CH_3, Ac); 2.03 (3H, s, CH_3, Ac); 1.22 (3H, d, *J* = 6.0 Hz, CH_3, H-21); 0.85 (3H, s, CH_3); 0.81 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 170.7 (C=O, OAc); 170.3 (C=O, OAc); 136.4 (C=C); 127.8 (C=C); 72.5 (CH); 71.8 (CH); 70.5 (CH);

47.2 (CH); 46.8 (C, C-13); 37.5 (CH); 36.3 (C, C-10); 30.8 (CH); 30.2 (CH_2); 30.1 (CH_2); 26.5 (CH_2); 26.1 (CH_2); 26.0 (CH_2); 25.3 (CH_2); 24.3 (CH_2); 24.2 (CH_2); 21.5 (CH_3); 19.7 (CH_3); 19.4 (CH_3). $[\alpha]_D^{20}$: +36 (*c*. 0.02, $CHCl_3$).

3β,20R-bis(acetoxy)-5Hβ-12β,14β-dihydroxy-pregnane (**41**): as a white solid (42 mg, 15%). IR (ATR): 3485, 1714. ^{1}H NMR ($CDCl_3$): 5.05 (1H, s, H-3α); 4.92–4.76 (1H, m, H-20); 3.29 (1H, dd, *J* = 3.7–11.9 Hz, H-12α); 2.20–0.80 (22H, m); 2.03 (3H, s, CH_3, Ac); 2.02 (3H, s, CH_3, Ac); 1.21 (3H, d, *J* = 3.0 Hz, CH_3, H-21); 0.95 (3H, s, CH_3); 0.87 (3H, s, CH_3). 13C NMR (CDCl3): 170.7 (C=O, OAc); 170.2 (C=O, OAc); 86.3 (C, C-14); 77.3 (CH); 73.7 (CH); 70.3 (CH); 52.7 (C, C-13); 51.7 (CH); 41.5 (CH); 36.8 (CH); 35.0 (C, C-10); 32.4 (CH); 32.1 (CH_2); 30.4 ($2CH_2$); 28.4 (CH_2); 26.3 (CH_2); 26.1 (CH_2); 25.0 (CH_2); 23.6 (CH_3); 21.5 (CH_3); 21.4 (CH_3); 19.0 (CH_3); 8.0 (CH_3). $[\alpha]_D^{20}$: +12 (*c*. 0.03, $CHCl_3$).

*2.7. NP reaction starting from 3β-acetoxy-5β-cyclic 20-(ethylene acetal) pregnan-12-one (**20**) leading to compounds **24**, **43** and **48***

Norrish type I reaction: **20** (201 mg, 0.48 mmol), CH_2Cl_2 (150 mL). Prins reaction: THF (1 mL), $AcOH/H_2O/CF_3COOH$ (2.5/1/0.6, 6.5 mL).

3β-Acetoxy-5β-pregnan-12,20-dione (**24**): as a white solid (10 mg, 5%, mp 150–153 °C). IR (ATR): 1722, 1702. ^{1}H NMR ($CDCl_3$): 5.03 (t, 1H, *J* = 2.1 Hz, H-3α); 3.29 (t, 1H, *J* = 9.8 Hz, H-17α); 2.43 (t, 1H, *J* = 12.5 Hz, H-11); 2.23 (s, 3H, CH_3, H-21); 2.15–0.75 (m, 19H); 2.02 (s, 3H, CH_3, Ac); 1.03 (s, 3H, CH_3); 0.92 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 213.3 (C=O); 209.6 (C=O); 170.5 (C=O, OAc); 70.1 (CH, C-3); 58.4 (C, C-13); 57.7 (CH); 54.3 (CH); 42.7 (CH); 37.8 (CH_2); 36.8 (CH); 35.5 (C, C-10); 35.0 (CH); 31.3 (CH_3); 30.6 (CH_2); 30.5 (CH_2); 26.3 (CH_2); 25.8 (CH_2); 24.8 (CH_2); 24.1 (CH_2); 23.2 (CH_3); 22.7 (CH_2); 21.4 (CH_3); 13.5 (CH_3). HRMS (ESI) *m*/*z*: $C_{23}H_{35}O_4$ [M+H$^+$] calcd. 375.2457, found 375.2550. $[\alpha]_D^{20}$: +150 (*c*. 0.016, $CHCl_3$).

3β-Acetoxy-5β-12β,14β-dihydroxy-pregnan-20-one (**43**): as a white solid (29 mg, 15%). IR (ATR): 3426, 1729, 1692. ^{1}H NMR ($CDCl_3$): 5.05 (s, 1H, H-3β) ; 3.55 (t, 1H, *J* = 6.3 Hz, H-17α) ; 3.29 (dd, 1H, *J* = 3.9–11.7 Hz, H-12α); 2.25 (s, 3H, CH_3, H-21); 2.20–0.80 (m, 21H); 2.04 (s, 3H, CH_3, Ac); 0.96 (s, 3H, CH_3); 0.88 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 218.1 (C=O, C-20); 170.8 (C=O, OAc); 85.4 (C, C-14); 74.0 (CH, C-12); 70.5 (CH, C-3); 56.8 (CH, C-17); 55,3 (C, C-13); 39.4 (CH); 36.9 (CH); 35.0 (C, C-13); 34.1 (CH_2); 33.1 (CH); 32.3 (CH_3); 30.5 (CH_2); 29.8 (CH_2); 26.2 (CH_2); 25.0 (CH_2); 24.7 (CH_2); 23.7 (CH_3); 21.6 (CH_3); 21.5 (CH_2); 8.4 (CH_3). HRMS (ESI) *m*/*z*: $C_{23}H_{37}O_5$ [M+H$^+$] calcd. 393.2563, found 393.2624. $[\alpha]_D^{20}$: +24 (*c*. 0.022, $CHCl_3$).

3β-Acetoxy-12α-hydroxy-5β-12,14α-cyclo-12,13-secopregna-13(17)-20-one (**48**): as a white solid (45 mg, 25%). IR (ATR): 3408, 1730, 1707, 1673. ^{1}H NMR ($CDCl_3$): 5.05 (s, 1H, H-3α); 4.15–4.05 (m, 1H, H-12β); 2.70–2.55 (m, 1H); 2.30–0.80 (m, 19H); 2.20 (s, 3H, CH_3, H-21); 2.03 (s, 3H, CH_3, Ac); 1.94 (t, 3H, *J* = 1.8 Hz, CH_3, H-18); 0.94 (s, 3H, CH_3, H-19). ^{13}C NMR ($CDCl_3$): 198.3 (C=O, C-20); 170.7 (C=O, OAc); 154.5 (C=C); 137.6 (C=C); 76.0 (CH, C-12); 70.4 (CH, C-3); 66.7 (C, C-14); 43.6 (CH); 37.6 (CH); 36.2 (CH); 34.7 (C, C-10); 32.5 (CH_2); 31.7 (CH_2); 31.0 (CH_2); 30.6 (CH_2); 30.5 (CH_3); 27.0 (CH_2); 25.1 (CH_2); 22.5 (CH_2 + CH_3); 21.5 (CH_3); 20.6 (CH_2); 12.2 (CH_3). HRMS (ESI) *m*/*z*: $C_{23}H_{35}O_4$ [M+H$^+$] calcd. 375.2457, found 375.2527. $[\alpha]_D^{20}$: +25 (*c*. 0.028, $CHCl_3$).

*2.8. NP reaction starting from 3β-acetoxy-5β-pregnan-12,20-dione (**24**) leading to compound **43***

Norrish type I reaction: **24** (377 mg, 1.00 mmol), CH_2Cl_2 (200 mL). Prins reaction: THF (1.5 mL), $AcOH/H_2O/CF_3COOH$ (2.5/1/0.6, 6.5 mL).

3β-Acetoxy-5β-12β,14β-dihydroxy-pregnan-20-one (**43**): as a white solid (52 mg, 10%). (described above).

*2.9. NP reaction starting from 3β,20R-bis(acetoxy)-preg-5-ene-12-one (**30**) leading to compounds **44** and **45***

Norrish type I reaction: **30** (184 mg, 0.44 mmol), CH_2Cl_2 (150 mL). Prins reaction: THF (0.5 mL), $AcOH/H_2O/CF_3COOH$ (2.5/1/0.6, 5.0 mL).

3β,20R-bis(acetoxy)-12α-hydroxy-pregnan-5,14-diene (**44**): as a white solid (32 mg, 17%, mp 117–119 °C). IR (ATR): 3487, 1725, 1710. ^{1}H NMR ($CDCl_3$): 5.44 (m, 1H, H-6); 5.32 (d, 1H, *J* = 1.5 Hz, H-15); 4.98 (dq, 1H, *J* = 6.0–11.1 Hz, H-20); 4.61 (m, 1H, H-3α); 3.76 (s, 1H, H-12β); 2.76 (dt, 1H, *J* = 8.3–10.6 Hz); 2.50–0.70 (m, 15H); 2.04 (s, 3H, CH_3, Ac); 2.03 (s, 3H, CH_3, Ac); 1.22 (d, 3H, *J* = 6.0 Hz, CH_3, H-21); 1.03 (s, 3H, CH_3); 0.89 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.5 (2C=O, OAc); 150.6 (C=C); 139.0 (C=C); 122.2 (C=CH); 120.9 (C=CH); 76.6 (CH, C-12); 72.7 (CH, C-3); 72.6 (CH, C-20); 51.4 (C, C-13); 46.4 (CH); 42.2 (CH); 38.0 (CH_2); 36.6 (CH_2); 32.5 (CH_2); 30.3 (CH_2); 29.4 (CH); 28.4 (CH_2); 27.6 (CH_2); 21.5 (CH_3); 21.4 (CH_3); 19.7 (CH_3); 18.9 (CH_3); 17.0 (CH_3). HRMS (ESI) *m*/*z*: $C_{25}H_{36}NaO_5$ [M+Na$^+$] calcd. 439.2455, found 439.2460. $[\alpha]_D^{20}$: +8 (*c*. 0.017, $CHCl_3$).

3β,20R-bis(acetoxy)-12β,14β-dihydroxy-pregn-5-ene (**45**): as a white solid (22 mg, 12%, mp 131–133 °C). IR (ATR): 3461, 1715. ^{1}H NMR ($CDCl_3$): 5.43 (m, 1H, H-6); 4.87 (dq, 1H, *J* = 5.8–9.7 Hz, H-20); 4.60 (tt, 1H, *J* = 5.2–10.9 Hz, H-3α); 3.34 (dd, 1H, *J* = 3.9–11.7 Hz, H-12α); 2.50–0.60 (m, 19H); 2.03 (s, 3H, CH_3, Ac); 2.02 (s, 3H, CH_3, Ac); 1.22 (d, 3H, *J* = 6.0 Hz, H-21); 1.01 (s, 3H, CH_3); 0.92 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.6 (C=O, OAc); 170.2 (C=O, OAc); 138.4 (C=C, C-5); 122.4 (C=CH, C-6); 86.5 (C, C-14); 76.3 (CH, C-12); 73.7 (CH, C-3); 73.6 (CH, C-20); 52.4 (C, C-13); 51.5 (CH); 43.4 (CH); 37.9 (CH_2); 37.0 (CH); 36.9 (CH_2); 32.6 (CH_2); 28.4 (CH_2); 27.6 (CH_2); 27.1 (CH_2); 25.8 (CH_2); 21.5 (C, C-10); 21.4 ($2CH_3$); 19.4 (CH_3); 19.0 (CH_3); 7.87 (CH_3). HRMS (ESI) *m*/*z*: $C_{25}H_{38}NaO_6$ [M+Na$^+$] calcd. 457.2561, found 457.2569. $[\alpha]_D^{20}$: −4 (*c*. 0.011, $CHCl_3$).

*2.10. NP reaction starting from 3β-acetoxy-pregn-5-ene-12,20-dione (**32**) leading to compounds **46***

Norrish type I reaction: **32** (114 mg, 0.31 mmol), CH_2Cl_2 (150 mL). Prins reaction: THF (0.5 mL), $AcOH/H_2O/CF_3COOH$ (2.5/1/0.6, 2.5 mL).

3β-Acetoxy-12β,14β-dihydroxy-pregn-5-ene-20-one (**46**): as a white solid (16 mg,, 13%, mp 140–142 °C). ^{1}H NMR ($CDCl_3$): 5.42 (m, 1H, H-6); 4.65–4.50 (m, 1H, H-3α); 4.37 (s, 1H, OH); 3.61 (t, 1H, *J* = 6.3 Hz, H-17α); 3.35 (dd, 1H, *J* = 4.2–11.7, H-12α); 2.40–2.15 (m, 3H); 2.27 (s, 3H, CH_3, H-21); 2.10–0.80 (m, 14H); 2.03 (s, 3H, CH_3, Ac,); 1.01 (s, 3H, CH_3, H-18); 0.92 (s, 3H, CH_3, H-19). ^{13}C NMR ($CDCl_3$): 218.0 (C=O, C-20); 170.6 (C=O, OAc); 137.8 (C=C, C-5); 123.1 (C=CH, C-6); 85.5 (C, C-14); 73.6 (CH, C-12); 73.4 (CH, C-3); 56.9 (CH, C-17); 55.0 (C, C-13); 43.3 (CH, C-9); 37.8 (CH_2, C-1); 37.0 (CH_2, C-4); 36.8 (C, C-10); 35.6 (CH_3, C-21); 34.5 (CH_2, C-15); 33.1 (CH, C-8); 29.9 (CH_2, C-11); 27.6 (CH2, C-2); 27. (CH_2, C-7); 24.4 (CH_2, C-16); 21.4 (CH_3, OAc); 19.3 (CH_3, C-19); 8.3 (CH_3, C-18). HRMS (ESI) *m*/*z*: $C_{23}H_{34}NaO_5$ [M+Na$^+$] calcd. 413.2298, found 413.2308. $[\alpha]_D^{20}$: +145 (*c*. 0.01, $CHCl_3$).

*2.11. NP reaction starting from 3β-acetoxy-12-keto, cyclic 20-(ethylene acetal) pregn-5-ene (**33**) leading to compounds **32**, **46** and **49***

Norrish type I reaction: **33** (895 mg, 2.15 mmol), CH_2Cl_2 (280 mL). Prins reaction: THF (4.0 mL), $AcOH/H_2O/CF_3COOH$ (2.5/1/0.6, 20.0 mL).

3β-Acetoxy-pregn-5-ene-12,20-dione (**32**): as a white solid (153 mg, 19%, mp 192–194 °C). IR (ATR): 1729, 1703. ^1H NMR ($CDCl_3$): 5.42–5.40 (m, 1H, H-6); 4.59 (tt, 1H, *J* = 4.6–11.4 Hz, H-3α); 3.34 (t, 1H, *J* = 9.6 Hz, H-17α); 2.62 (t, 1H, *J* = 13.2 Hz, H-11); 2.50–2.00 (m, 4H); 2.26 (s, 3H, CH_3, H-21); 2.03 (s, 3H, CH_3, Ac); 2.00–0.80 (m, 12H); 1.12 (s, 3H, CH_3); 0,98 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 213.0 (C=O); 209.4 (C=O); 170.2 (C=O, OAc); 139.2 (C=C, C-5); 121.9 (C=CH, C-6); 73.1 (CH, C-3); 57.6 (C, C-13); 57.4 (CH); 54.0 (CH); 527 (CH); 52.7 (CH); 37.6 (CH_2); 37.4 (CH_2); 37.2 (C, C-10); 36.4 (CH_2); 31.1 (2CH + CH_2); 27.3 (CH_2); 24.0 (CH_2); 22.4 (CH_2); 21.2 (CH_3); 18.7 (CH_3); 13.2 (CH_3). HRMS (ESI) *m*/*z*: $C_{23}H_{33}O_4$ [M+H$^+$] calcd. 373.2301, found 373.2376. $[\alpha]_D^{20}$: +55 (*c*. 0.009, $CHCl_3$).

3β-Acetoxy-12β,14β-dihydroxy-pregn-5-ene-20-one (**46**): 210 mg, 25% yield (described above).

3β-Acetoxy-12α-hydroxy-12,14α-cyclo-12,13-secopregna-5,13(17)-diene-20-one (**49**): as a white solid (118 mg, 15%, mp 116–117 °C). IR (ATR): 3430, 1729, 1666, 1608. ^1H NMR ($CDCl_3$): 5.36 (d, 1H, *J* = 4.8 Hz, H-6); 4.58 (tt, 1H, *J* = 4.8–11.4 Hz, H-3α); 4.14 (dt, 1H, *J* = 8.2–9.7 Hz, H-12β); 2.80–0.80 (m, 17H); 2.22 (s, 3H, CH_3, H-21); 2.02 (s, 3H, CH_3, Ac); 1.96 (t, 3H, *J* = 2.1 Hz, CH_3, H-18); 1.04 (s, 3H, CH_3, H-19). ^{13}C NMR ($CDCl_3$): 198.7 (C=O, C-20); 170.5 (C=O, OAc); 153.7 (C=C); 140.5 (C=C); 137.9 (C=C); 122.6 (C=CH); 76.5 (CH, C-12); 73.7 (CH, C-3); 65.7 (C, C-14); 48.3 (CH); 39.9 (CH); 37.9 (CH_2); 37.7 (CH_2); 37.2 (C, C-10); 32.4 (CH_2); 30.5 (CH); 30.3 (CH_2); 27.4 (CH_2); 25.9 (CH_2); 21.8 (CH_2); 21.4 (CH_3); 18.0 (CH_3); 12.1 (CH_3). $[\alpha]_D^{20}$: −12 (*c*. 0.006, $CHCl_3$).

3. Results and discussion

Before presenting the Norrish type I–Prins reactions, we described the synthesis of the 12-keto pregnane derivatives bearing A/B trans, A/B cis and $\Delta^{5,6}$ ring junctions with different substituents at position 20 (carbonyl, acetoxy and dioxolane groups).

3.1. Synthesis of the starting material for the Norrish–Prins reactions

3.1.1. A/B trans ring junction

Hecogenin acetate **1** was used as the starting material for the synthesis of pregnane analogs bearing an A/B trans ring junction and an acetate, a carbonyl or a dioxolane group at position 20. First, hecogenin acetate was transformed into the 12-keto pregnane analogs **14** and **15** bearing a A/B trans ring junction [11]. For the pregnane analog **16** bearing a dioxolane group at position 20, the regioselective protection of the diketo derivative **15** was impossible. Indeed, the usual protection reaction condition (pTsOH, ethylene glycol) led to an inseparable mixture of compounds. Thus, to synthesize compound **16**, we transformed hecogenin acetate **1** into the keto derivative **17** [12]. After protection of the keto group as a dioxolane, the resulting compound was treated with potassium hydroxide to give diol **18**. Regioselective protection of the 3β-hydroxy group followed by a Dess–Martin periodinane oxidation gave the desired dioxolane derivative **16** (Scheme 3) [13].

3.1.2. A/B cis ring junction

For the synthesis of pregnane analogs bearing an A/B cis ring junction, 3α,12α-bis(acetoxy), 5β, pregnan-20-one was used as the starting material. Compound **19** was obtained according to a known literature procedure [14]. To prepare the A/B cis pregnane analog **20** bearing a dioxolane group at position 20, we transformed 3α,12α-bis (acetoxy), 5β, pregna-20-one into the ketoderivative **21** which was then subjected to a Mitsunobu reaction to yield the 3β-benzoate derivative **22** [15]. Protection of the keto group followed by a double saponification afforded the diol **23**. Finally, a regioselective protection of the 3β-hydroxy group and oxidation of the 12α-hydroxy group yielded the desired compound **20** (Scheme 4).

The synthesis of the A/B cis pregnane analog **24** bearing a carbonyl group at position 20 was achieved starting from desoxycholic acid **25,** which was first transformed into compound **26** according to a known literature procedure [14]. Deprotection of the benzoate group followed by a reprotection of the resulting hydroxy as an acetate yielded the desired A/B cis pregnane analog **24** (Scheme 5).

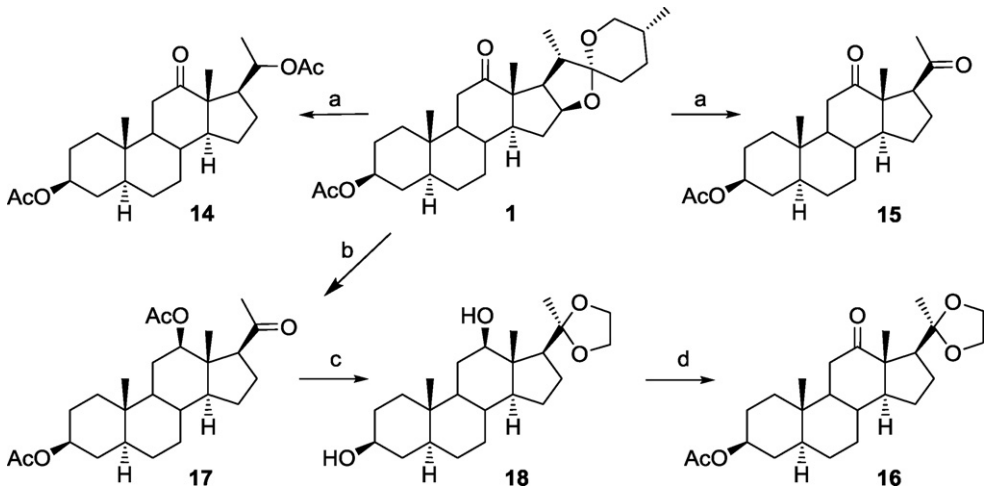
3.1.3. A/B $\Delta^{5,6}$ ring junction

Pregnenolone analogs bearing either an acetate or a carbonyl group at position 20 are precursors of derivatives of isoramanone and boucerin. These analogs were prepared starting from the diketo derivative **27** [16]. Addition of acetyl chloride to the latter gave the dienol acetate **28** [17] which led to the triol **29** after sodium borohydride reduction [18] followed by a KOH promoted saponification reaction. A regioselective protection of the 3β-and 17β-hydroxyl groups followed by Jones oxidation [19] of the 12α-hydroxy group afforded the desired compound **30**. On the other hand, the dioxolane **31** was obtained by successive protection of the carbonyl group as a dioxolane, sodium borohydride reduction and KOH saponification of the dienol acetate **28**. Finally, the deprotection of the dioxolane, followed by a regioselective protection of the 3β-hydroxy as an acetate and an oxidation of the 12α-hydroxy group gave the desired compound **32** (Scheme 6). The corresponding dioxolane derivative **33** was obtained by a regioselective protection of the 3β-hydroxy group of **31** before a Dess–Martin oxidation.

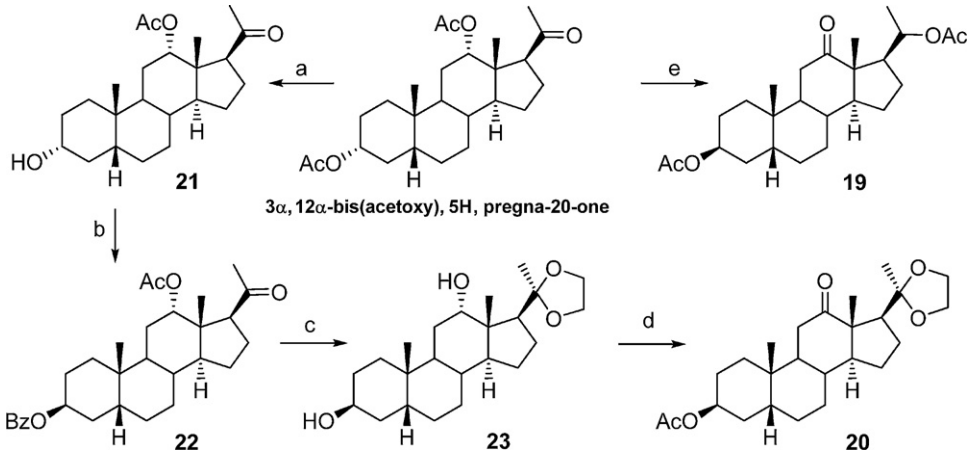
3.2. Norrish–Prins reactions

At this stage, nine different compounds **14**–**16**, **19**, **20**, **24**, **30**, **32**, **33** were suitable for a combined Norrish type I–Prins reaction. The photolysis was carried out in a water refrigerated quartz vessel using a high pressure mercury lamp Philips HPK 125 for 15 min. Longer reaction times led to decomposition, as shown by TLC analysis of the crude reaction mixture. The Prins reaction was carried out directly on the product of the photolysis, using a 2.5/1/0.6 $AcOH/H_2O$/TFA mixture. It was possible to isolate the Norrish type I products, i.e. the aldehydes **16a**, **20a** and **33a** (Scheme 7); however these products were unstable. Furthermore, the overall yield of the Norrish–Prins reaction did not increase when the Prins reaction was carried out on the purified Norrish type I product (Table 1).

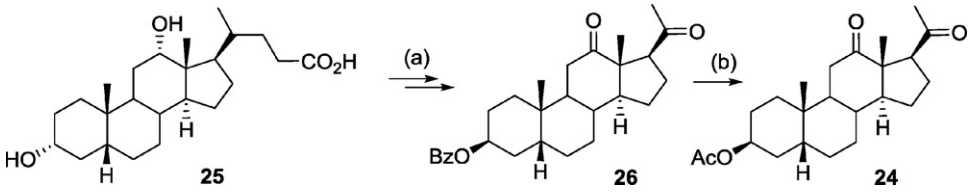
The expected 12α (or 12β),14β-dihydroxy derivatives **38**–**46** were always obtained in 10–31% yield starting from the corresponding 12-keto derivatives **14**–**16**, **19**, **20**, **24**, **30**, **32**, **33** (entries 1–9). On the other hand, products **34**, **36** and **35**, **39** [the structure of compound **36** was confirmed by X-ray analysis (Fig. 2)] resulting from a Conia-ene rearrangement were isolated as major products starting from 20-acetoxy derivatives **14** and **19** (entries 1 and 4). Welzel et al. also noticed the formation of Conia ene derivatives [20]; however these authors never observed the formation of the $\Delta^{8,14}$ derivatives. Starting from protected preganolone derivatives **16**, **20** and **33**, products **15** (10%), **24** (<5%) and **32** (10%) resulting from a deprotection reaction of the dioxolane group were isolated. Surprisingly, spiro derivatives **47** (19%), **48** (25%) and **49** (15%) were also isolated (entries 3, 6 and 9). The structure of the spiro derivative **47** was confirmed by X-ray analysis (Fig. 3). The overall yields ranged from 10% to 60%. The lowest yields were obtained starting from 20-keto derivatives **15**, **24** and **32** (entries 2, 5 and 7) and the



Scheme 3. Reagents and reaction conditions: (a) see Ref. [11]; (b) see Ref. [12]; (c) i: ethylene glycol, trimethyl orthoformate cat, CH_2Cl_2, 23 h, reflux (90%); ii: KOH, MeOH, 16 h, reflux (83%); (d) i: Ac_2O, DMAP cat, Py, CH_2Cl_2, 19 h, 25 °C (70%); ii: Dess–Martin periodinane, CH_2Cl_2, 1 h, 25 °C (80%).



Scheme 4. Reagents and reaction conditions: (a) K_2CO_3, MeOH, 1 h, 25 °C (83%); (b) C_6H_5COOH, $P(C_6H_5)_3$, $EtO_2C–N{=}N–CO_2Et$, THF, 15 h, 25 °C (quant.); (c) i: ethylene glycol, pTsOH cat., toluene, 2 h 30, reflux (76%); ii: KOH, MeOH, 2 h, reflux (25%); (d) i: Ac_2O, DMAP cat, Py, CH_2Cl_2, 7 h, 25 °C (53%); ii: Dess–Martin periodinane, CH_2Cl_2, 50 min, 25 °C (97%); (e): see Ref. [14].



Scheme 5. Reagents and reaction conditions: (a) see Ref. [14]; (b) i: KOH, MeOH, 2 h, reflux (quant.); ii: Ac_2O, DMAP cat, Py, CH_2Cl_2, 6 h, reflux (60%).

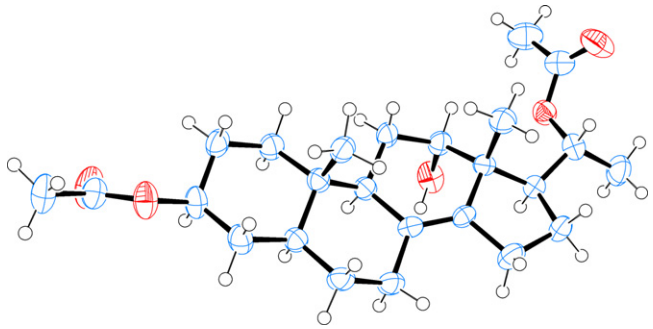
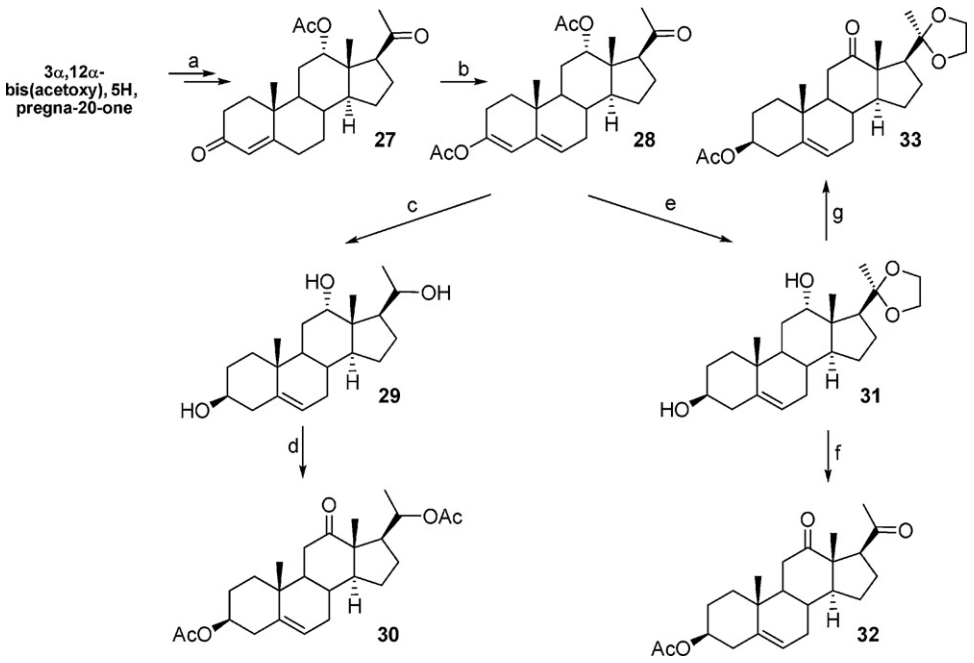


Fig. 2. ORTEP drawing of compound **36** ($\Delta^{8,14}$ isomer) with thermal ellipsoids at the 30% probability level [21].

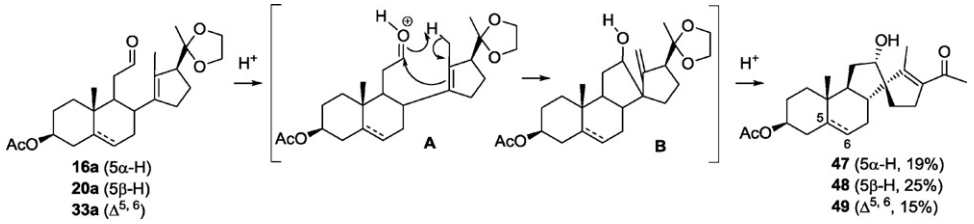
highest yields starting from dioxolane derivatives **16**, **20** and **33** (entries 3, 6 and 9).

The formation of the spiro derivatives **47**–**49** could be explained as follows: after formation of the Norrish type I products (i.e. aldehydes **16a**, **20a** and **33a**), acidic treatment gave intermediate **A** that evolved toward intermediate **B** according to a Conia ene reaction. Deprotection of the dioxolane group and isomerisation of the exo cyclic double bond yielded the spiro derivatives **47**, **48** and **49** (Scheme 7).

However, this explanation does not account for the fact that the formation of spiro derivatives was not observed starting from compounds **14**, **19**, **30** and **15**, **24**, **32** bearing respectively an acetate group or a carbonyl group at position 20. To explain these results, we postulate that an acidic acetal hydrolysis takes place to give



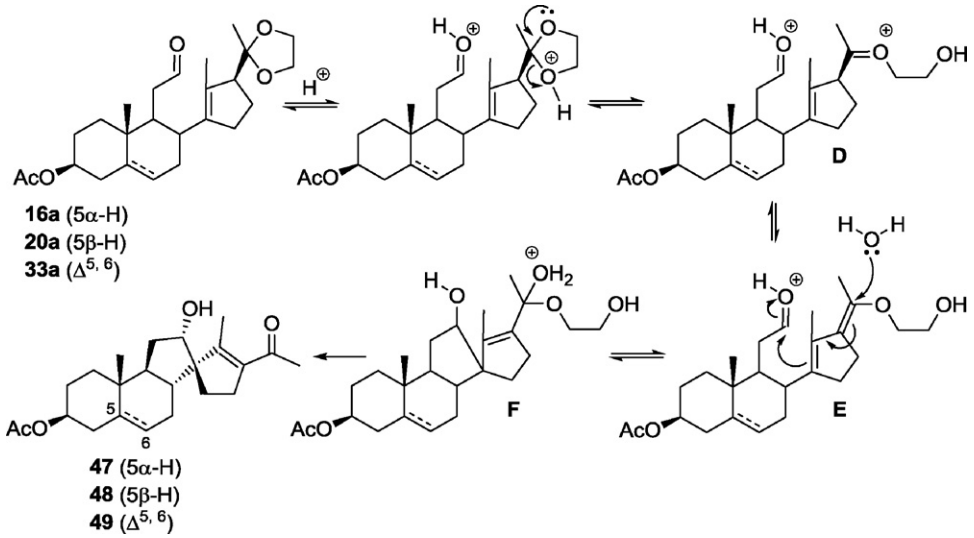
Scheme 6. Reagents and reaction conditions: (a) see Ref. [16]; (b) Ac_2O, AcCl, 1 h, reflux (85%); (c) i: $NaBH_4$, THF/MeOH (1/1), 0–25 °C, 19 h, ii: KOH, MeOH, 2 h, reflux (overall yield: quant.); (d) Ac_2O, DMAP, py, CH_2Cl_2, 7 h, 25 °C (63%); ii: CrO_3, acetone, 45 min, 25 °C (81%); (e) i: ethylene glycol, PPTS, toluene, 3 h 30, reflux (quant.), ii: $NaBH_4$, THF/MeOH (1/1), 1 h 30, 25 °C, iii: KOH, MeOH, 4 h, reflux (ii + iii: 60%); (f) i: oxalic acid, SiO_2, CH_2Cl_2, 1 h, 25 °C (quant.), ii: Ac_2O, DMAP cat, Py, CH_2Cl_2, 4 h 30, 25 °C (28%), iii: CrO_3, acetone, 30 min, 25 °C (53%); (g) i: Ac_2O, DMAP cat, Py, CH_2Cl_2, 3 h, 25 °C (80%), ii: Dess–Martin periodinane, CH_2Cl_2, 1 h, 25 °C (99%).



Scheme 7.

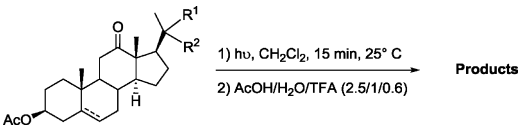
intermediate **D** (Scheme 8). The latter is in equilibrium with the dienol **E** which, after the addition of water, leads to intermediate **F** that is a direct precursor of the spiro derivatives **47**, **48** and **49**. Thus, the formation of spiro derivatives did not occur starting from compounds **14**, **19**, **30** and **15**, **24**, **32**, because the formation of a type **E** intermediate cannot occur (Scheme 8).

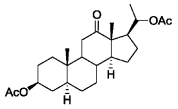
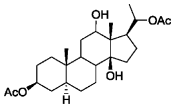
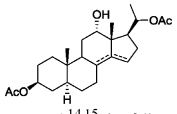
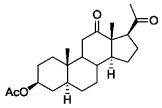
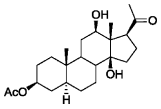
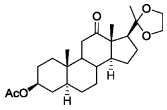
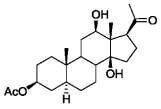
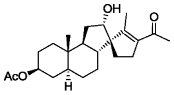
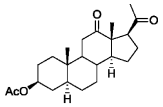
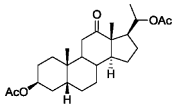
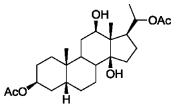
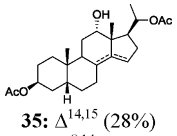
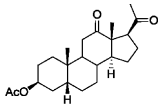
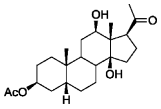
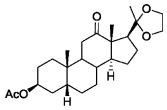
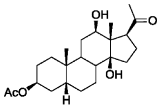
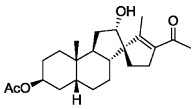
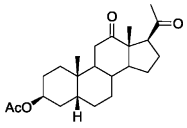
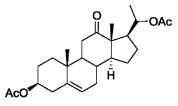
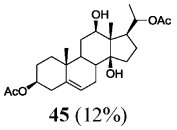
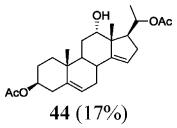
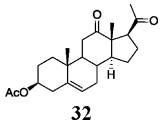
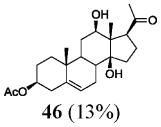
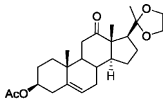
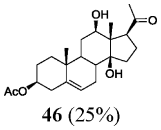
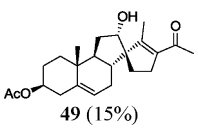
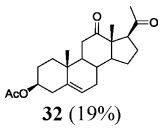
Three findings are clear from these results. First it is possible to run a Norrish–Prins reaction starting from pregnenolone deriva-



Scheme 8.

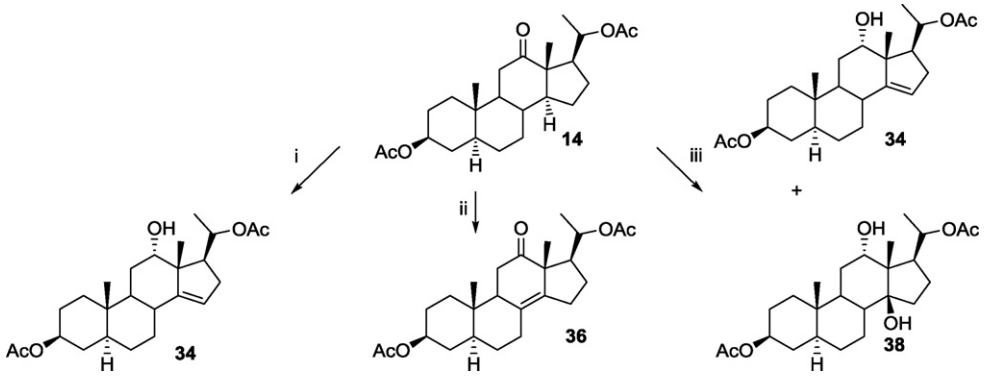
Table 1
Norrish–Prins reaction.



Entry	Starting material	Products		
		14β-Hydroxy derivatives	Spiro derivatives	Other products
1	 **14**	 **38**: 12α-OH (9%) **40**: 12β-OH (15%)	–	 **34:** $\Delta^{14,15}$ (26%) **36:** $\Delta^{8,14}$ (11%)
2	 **15**	 **42** (20%)	–	–
3	 **16**	 **42** (31%)	 **47** (19%)	 **15** (10%)
4	 **19**	 **41** (15%)	–	 **35:** $\Delta^{14,15}$ (28%) **39:** $\Delta^{8,14}$ (15%)
5	 **24**	 **43** (10%)	–	–
6	 **20**	 **43** (15%)	 **48** (25%)	 **24** (<5%)
7	 **30**	 **45** (12%)	–	 **44** (17%)
8	 **32**	 **46** (13%)	–	–
9	 **33**	 **46** (25%)	 **49** (15%)	 **32** (19%)

tives, this being reported for the first time. Second, the A/B ring junction (trans, cis or $\Delta^{5,6}$) has little influence on the unfolding of the Norrish–Prins reaction but the substitution pattern at position 20 is of importance. The best results were achieved starting from dioxolane derivatives **16**, **20** and **33**. Finally, the unexpected formation of spiroderivatives, which is also reported for the first time, is closely related to the substitution pattern at position 20 and takes place exclusively starting from dioxolane derivatives.

The influence of an acidic medium on the Prins reaction was studied by treating the crude reaction mixture resulting from the



Scheme 9. Reagents and reaction conditions: i: (a) hυ, CH_2Cl_2, 15 min, 25 °C; (b) BF_3, Et_2O, toluene, 25 min, 0 °C [**34** (17%)]; ii: (a) hυ, CH_2Cl_2, 15 min, 25 °C; (b) $SnCl_4$, CH_2Cl_2, 1.5 h, 25 °C (30%); iii: (a) hυ, CH_2Cl_2, 15 min, 25 °C; (b) HBF_4, Et_2O, 40 min, 25 °C [**34** (38%), **38** (10%)].

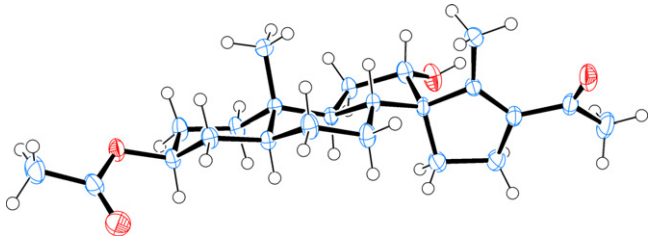


Fig. 3. ORTEP drawing of spiro derivative **47** with thermal ellipsoids at the 30% probability level [22].

Norrish type I reaction of compound **14** with different Lewis acids like BF_3. Et_2O and $SnCl_4$. Conia ene products **34** and **36** were exclusively obtained. However, in the presence of HBF_4, the 14β-hydroxy derivative **38** was isolated as a minor product (10%) in addition to the Conia ene product **34** (38%). It is also reasonable to postulate that compounds **34, 36** could arise from a Lewis acid-promoted water elimination starting from compound **38**. Thus, the use of this type of Lewis acids must be avoided to obtain 14β-hydroxy pregnane derivatives (Scheme 9).

4. Conclusion

Starting from 12-keto pregnane derivatives, we synthesized isoramanone and boucerin derivatives and the synthesis of their A/B cis and trans analogs by using as a key step a combined Norrish type I–Prins reaction. The yields ranged from 10 to 31%. The A/B ring junction clearly has little influence on the Norrish type I–Prins reaction. However, the substitution pattern at position 20 is important. The presence of a dioxolane group in position 20 induced not only the formation of 14β-hydroxy pregnane derivatives in the highest yields but also the formation of new spiro derivatives. The access to numerous 14β-hydroxy pregnane derivatives now allows the synthesis of numerous aglycones and analogs that are present in *Hoodia gordonii* [16] or in *Caralluma* for example [23]. The synthesis of the latter is currently underway in our laboratory and the results will be reported in due course.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.steroids.2011.05.004.

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[22] CCDC-796190 contains the supplementary crystallographic data for the spiro-derivative **47**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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