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Stereoselective catalytic hydrogenation of Δ^7-6-ketosteroids in the presence of sodium nitrite

Apichart Suksamrarn,* Tanud Tanachatchairatana and Chana Sirigarn

Department of Chemistry, Faculty of Science, Ramkhamhaeng University, Bangkok 10240, Thailand

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Abstract—Catalytic hydrogenation with Pd–C as a catalyst in the presence of sodium nitrite is a simple, convenient and high yielding stereoselective reduction of olefinic function of Δ^7-6-ketosteroids to the corresponding dihydro analogues.

1. Introduction

In search of steroids and ecdysteroids with new biological activities, we would like to modify structures of these compounds for biological activity testing and 20-hydroxyecdysone (**1**), the arthropod moulting hormone obtainable in a large quantity from *Vitex glabrata*,[1] was chosen for a starting material. Our initial aim was to reduce **1** and related ecdysteroids to the corresponding 7,8-dihydro analogues. It is well-known that reduction of Δ^7-6-ketosteroids to the corresponding saturated ketones is not a facile process and, in general, this has been accomplished by treatment with lithium in liquid ammonia.[2,3] The method, however, presents drawbacks concerning complicated experimental procedure and difficulty in the control of overreduction of the keto function and this led to decrease in chemical yields of the products.[4–6] Another reducing agent, sodium dithionite in the presence of a phase transfer catalyst, has recently been reported to effect selective reduction of 7-en-6-one system.[7] This method has nevertheless suffered from the overreduction problem, unless precise conditions are exercised. It is known that ecdysteroids are susceptible to experimental conditions employed. For example, dehydration across C-14 and C-15 easily occurred even in mild acidic condition,[8,9] whereas in basic condition C-5 epimerization[10–12] and C-9 hydroxylation[13] were reported. Any reduction conditions selected for ecdysteroids should therefore be mild enough not to cause side reactions to occur.

2. Results and discussion

Catalytic hydrogenation[14] was the first reduction method we chose to investigate, since in practice it is convenient to perform and the conditions are relatively mild. However, we found that hydrogenation of 20-hydroxyecdysone (**1**)[1] in ethanol, with 10% Pd–C as a catalyst, gave disappointing results; at least seven components including 30–40% of the starting ecdysteroid **1** were present on TLC. Ponasterone A (**2**), prepared by catalytic hydrogenation of a mixture of stachysterone C 2,3:20,22-diacetonide and 25,26-dide-hydroponasterone A 2,3:20,22-diacetonide[15] followed by deacetonation, has also been used in the experiment and similar result was obtained. We therefore searched for a reagent to prevent or minimize overreduction and/or undesired products. A number of inorganic salts of metal ions with low oxidation state have been chosen and we eventually found that catalytic hydrogenation in the presence of sodium nitrite ($NaNO_2$) smoothly reduced **1** to the corresponding dihydro analogue **3** in 96% yield. The reaction was clean and only a trace of a less polar product was detected by TLC. Cerium(III) chloride ($CeCl_3$)[16] gave a similar result, but the reaction proceeded much slower. The best result was obtained when approximately three folds (w/w) of 10% Pd–C was used and about 20 equiv. of 25% aqueous $NaNO_2$ was added. The reaction proceeded very sluggishly when solid $NaNO_2$ was employed.

The structure of **3** was established by comparisons of spectroscopic (IR, ^{1}H, ^{13}C NMR and mass spectra) data with those of the parent compound **1** and was confirmed by 1D and 2D NMR techniques. Thus the IR absorption frequency has changed from the conjugated keto group at 1655 cm^{-1} in **1** to the saturated keto group at 1699 cm^{-1} in **3**. The absence of the olefinic H-7 signal around δ 5.8–6.2 in the ^{1}H NMR spectrum of **3** indicated that the Δ^7 in **1** was hydrogenated. The negative ion FABMS of **3** with *m*/*z* of 481, which corresponded to $[M-H]^-$, and the elemental analysis were in agreement with structure **3**. Assignments of ^{1}H and ^{13}C NMR signals in C_5D_5N were accomplished by COSY, DEPT, HMQC and HMBC experiments. The ^{1}H NMR

Keywords: catalytic hydrogenation; ecdysteroids; Δ^7-6-ketosteroids; sodium nitrite.

* Corresponding author. Tel.: +66-2-3191900; fax: +66-2-3108381; e-mail: apichart@ram1.ru.ac.th

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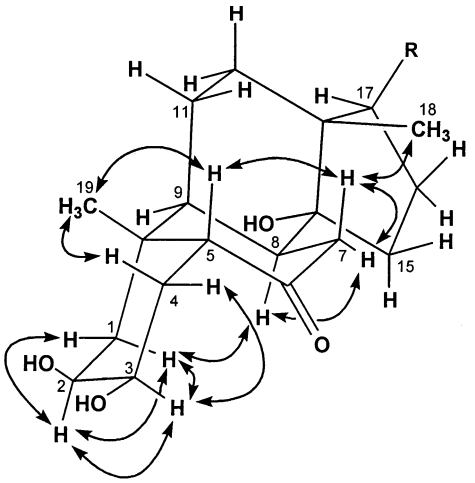


Figure 1. NOE correlations of compound **3**.

spectra of **3** were also recorded in CD_3OD in order to obtain information of some signals which were obscured in C_5D_5N, especially those of H-4, H-5 and H-7α. The splitting patterns and coupling constants of H-7α, H-7β and especially H-8 in the ^1H NMR spectra indicated that H-8 was *cis* to H-9 as indicated in **3**. The alternative *trans* H-8 and H-9 relationship as shown in **4** was ruled out, since in the latter case large coupling constants between H-8 and H-7α, and H-8 and H-9 should be expected. Since previous reports indicated that C-5 epimerization of ecdysteroids could take place very readily in some cases,[17,18] it was therefore necessary to establish the stereochemistry at the 5-position of the product. If H-5 was in β-orientation as that of the starting ecdysteroid **1**, NOE enhancement between 19-Me and H-5 should be observed. A molecular model of **3** (see Fig. 1) revealed the proximity of 19-Me and H-5. Thus, irradiation of 19-Me signal caused NOE enhancement of H-5 and upon irradiation of the H-5 signal resulted in NOE enhancement of the 19-Me. The alternative 5α-analogue (i.e. structure **5**) was therefore not possible. Further NOE experiments (see Fig. 1) also confirmed structure **3**. The ^1H NMR signal in CD_3OD of H-5 appeared as a broad singlet, with $W_{1/2}$ value of 10 Hz, thus confirming the stereochemistry as shown in Fig. 1. It was noteworthy that an alternative three-dimensional structure of 5β-ecdysteroid could be drawn as shown in Fig. 2. However it was ruled out by the following key NOE correlations. Irradiation of H-8 caused enhancements of H-1α and H-7α signals. The stereochemical arrangement as indicated in **4** should not give rise to NOE interaction between H-8 and H-1α.

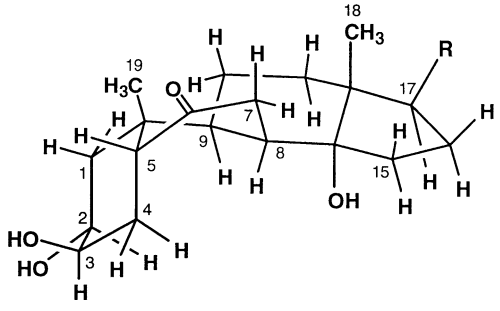
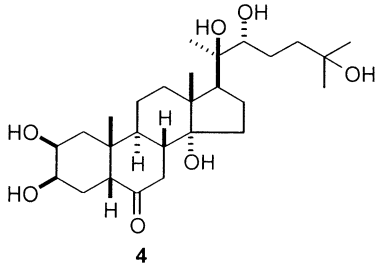


Figure 2. Alternative three-dimensional structure of compound **3**.

Irradiation of H-7β resulted in enhancements of H-5, H-7α and 18-Me signals. NOE enhancement should not be observed for H-5 of structure **4**. NOE correlation between H-7β and 18-Me needed special attention; this interaction occurred only when H-8 was in the α-orientation. It should be noted that, unlike the starting ecdysteroid **1**, H-2 and H-3 of the product **3** are respectively in equatorial and axial orientations, and that the C and D-rings of **3** are perpendicular to the B-ring (see Fig. 1).



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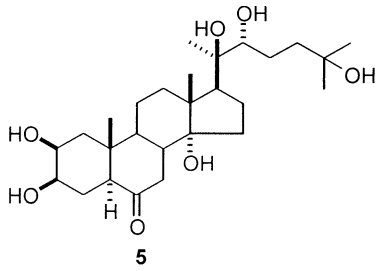

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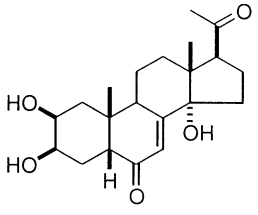
To test for generalization of our reduction method, the ecdysteroid **2** was subjected to hydrogenation under the same conditions and 7,8-dihydroponasterone A (**6**) was obtained in 93% yield. The structure of **6** was confirmed by the same analogy to that of compound **3**. Similarly, pterosterone (**7**),[19] the 24-hydroxy analogue of **2**, was hydrogenated to the dihydro analogue **8** in 88% yield. Poststerone (**9**),[20] the 20-keto analogue of compound **1**, was also hydrogenated to 7,8-dihydropoststerone (**10**) in 86% yield (see Scheme 1).



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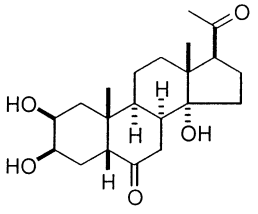

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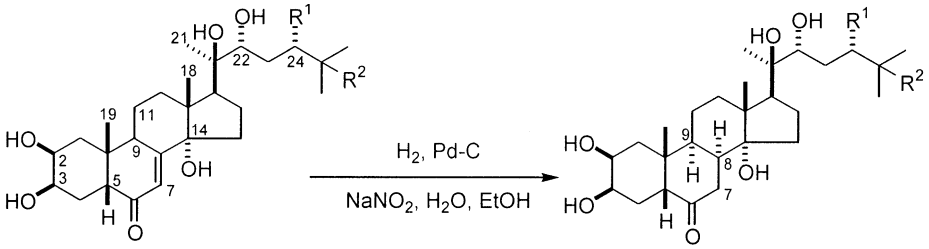
Since the 7-en-6-one system is relatively more sterically hindered, in the presence of a side-chain double bond this latter isolated olefinic function was preferentially reduced to the corresponding dihydro analogue and the reduction was completed before hydrogenation of Δ^7 has taken place.

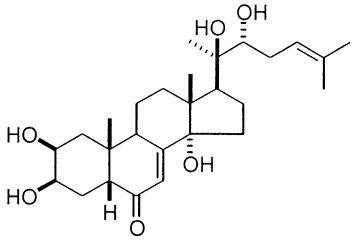


1 R^1 = H, R^2 = OH
2 R^1 = R^2 = H
7 R^1 = OH, R^2 = H

3 R^1 = H, R^2 = OH
6 R^1 = R^2 = H
8 R^1 = OH, R^2 = H

Scheme 1. Catalytic hydrogenation of ecdysteroids.

Thus, in the presence of $NaNO_2$, stachysterone C (**11**)[21] was reduced to ponasterone A (**2**) in 90% yield. Longer reduction time (see Table 1) converted **11** to the tetrahydro analogue **6** in 86% yield. Similarly, 25,26-didehydroponasterone A (**12**)[21] was hydrogenated to compound **2** in high yield.



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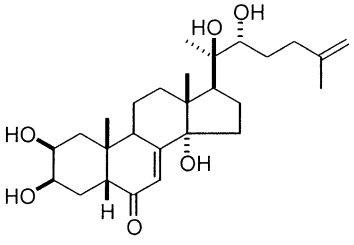

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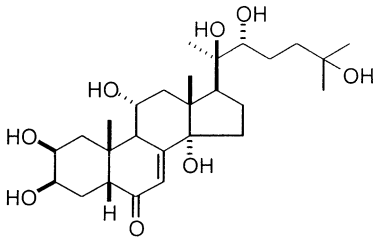
Prolonged hydrogenation of **12** also yielded compound **6** in high yield. In order to see whether the method could selectively reduced the Δ^{25} in the presence of the Δ^{24} olefinic function, a 2:3 mixture of compounds **11/12** was subjected to catalytic hydrogenation in the presence of $NaNO_2$ and progress of the reaction was monitored by TLC examinations. It was found that the side-chain double bond of compound **12** was first reduced, followed by that of compound **11**. It should be noted that the time interval between completion of side-chain reduction and the beginning of conjugate reduction of the Δ^7-keto system was sufficient to obtain only the side-chain reduction product **2**. Without $NaNO_2$, attempts to selectively reduce Δ^{25} in the presence of the Δ^{24} olefinic bond were unsuccessful; it was apparent that both side-chain double bonds had been reduced at approximately the same time. The hydrogenation results are summarized in Table 1.

Table 1. Catalytic hydrogenation of Δ^7-6-ketosteroids in EtOH using Pd–C in the presence of $NaNO_2$

Entry	Compound	Product	Time	Yield (%)[a]
1	**1**	**3**	3 h	96
2	**2**	**6**	2.5 h	93
3	**7**	**8**	2 h	88
4	**9**	**10**	2.5 h	86
5	**11**	**2**	25 min	90
6	**11**	**6**	3 h	86
7	**12**	**2**	20 min	91
8	**12**	**6**	3 h	88

Starting material:10% Pd–C was 1:3 (w/w). 20 equiv. of 25% aq $NaNO_2$ has been used throughout the experiments.
[a] Isolated yield.

The method, however, has some limitations. We found that turkesterone (**13**),[1] an 11α-hydroxy ecdysteroid, was converted to the unexpected product **1** presumably through the dehydration intermediate **14** followed by hydrogenation of the γ,δ-conjugated olefinic function. The intermediacy of **14** was supported by performing reaction in the presence of solid $NaNO_2$, instead of aq $NaNO_2$, and the dehydration product **14** was obtained in 72% yield. The structure of **14** was deduced from the spectroscopic data. Thus the absence of the carbinol resonance and the presence of the olefinic signal of H-11 in the ^1H NMR spectrum, as well as the high resolution FAB mass spectrum which exhibited the $[M-H]^-$ at *m/z* 477.2844 were consistent with the structure. The finding was not surprising, since it was known that



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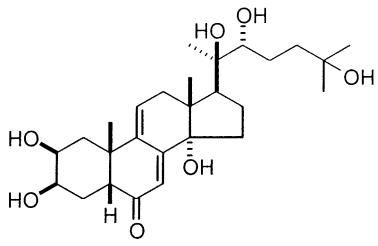

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11α-hydroxy ecdysteroids was dehydrated very readily under relatively mild conditions.[22]

The mechanistic implication of this reaction has not been investigated. However, the results indicated that $NaNO_2$ did not just act as a retarder of hydrogenation reaction, since the reaction products from both methods were different.

In conclusion, we have provided a method for stereoselective catalytic hydrogenation of olefinic function in a Δ^7-6-keto system of 5β-steroids, the H-8 of which was in the α-orientation and the H-5β configuration was preserved. The procedure was simple, convenient, high yielding and no special precautions were required.

3. Experimental

3.1. General experimental procedures

Melting points were determined on an Electrothermal melting point apparatus and were uncorrected. IR spectra were recorded in KBr on a Perkin–Elmer FT-IR Spectrum BX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. Mass spectra were measured on a Finnigan MAT 90 instrument. Column chromatography and TLC were carried out using Merck's silica gel 60 (<0.063 mm) and precoated silica gel 60 F_{254} plates, respectively. Spots on TLC were visualized under UV light and by spraying with anisaldehyde–H_2SO_4 reagent followed by heating.

3.1.1. Catalytic hydrogenation of compound 1. To a solution of compound **1** (150 mg, 0.312 mmol) in EtOH (5 mL) was added 10% Pd–C (450 mg, 0.422 mmol) and 25% aq $NaNO_2$ solution (1.8 mL, 6.521 mmol) and the mixture hydrogenated at atmospheric pressure for 3 h, using a hydrogen balloon. The mixture was filtered through a short acidic alumina column; the residue was washed with EtOH and the solvent evaporated. The crude product was purified by short silica column chromatography to afford 7,8-dihydro-20-hydroxyecdysone (**3**) (145 mg, 0.300 mmol or 96%), colourless needles (from MeOH), mp 153–155°C; (Found: C, 62.32; H, 9.91. $C_{27}H_{46}O_7{\cdot}2H_2O$ requires C, 62.52; H, 9.72%); IR ν_{max} 3429, 2963, 1699, 1382, 1323, 1273, 1225, 1152, 1128, 1064, 950 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 1.35 (s, 2×3H, 26-Me and 27-Me), 1.53 (s, 3H, 18-Me), 1.54 (s, 3H, 21-Me), 1.56 (1H, H-15a),[a] 1.68 (s, 3H, 19-Me), 1.70 (1H, H-1β),[a] 1.85 (1H, H-1α),[a] 2.08 (1H, H-16a),[a] 2.10 (1H, H-15b),[a] 2.20 (1H, H-4β),[a] 2.46 (1H, H-16b),[a] 2.53 (1H, H-9),[a] 2.54 (dd, J=14.6, 4.5 Hz, 1H, H-7α), 2.56 (2H, H-4α and H-5),[a] 2.72 (dt, J=14.6, 4.5 Hz, 1H, H-8), 2.92 (t, J=14.6 Hz, 1H, H-7β), 2.96 (dd, J=9.4, 8.5 Hz, 1H, H-17), 3.86 (br d, J=9.4 Hz, 1H, H-22), 4.27 (m, $W_{1/2}$=9 Hz, 1H, H-2), 4.32 (m, $W_{1/2}$=20 Hz, 1H, H-3), [a] obscured signal; ^{1}H NMR (400 MHz, CD_3OD) δ 1.14 (s, 3H, 21-Me), 1.17 (s, 2×3H, 18-Me and 26-Me), 1.18 (s, 3H, 27-Me), 1.37 (s, 3H, 19-Me), 1.45 (1H, H-1β),[b] 1.65 (1H, H-1α),[b] 1.77 (1H, H-4β),[b] 1.78 (1H, H-24a),[b] 2.00 (1H, H-4α),[b] 2.24 (dd, J=14.4, 4.4 Hz, 1H, H-7α), 2.30 (t, J=9.3 Hz, 1H, H-17), 2.36 (dt, J=14.4, 4.4 Hz, 1H, H-8), 2.51 (br s, $W_{1/2}$=10 Hz, 1H, H-5), 2.77 (t, J=14.4 Hz, H-7β), 3.28 (1H, H-22),[b] 3.75 (m, $W_{1/2}$=20 Hz, 1H, H-3), 3.90 (m, $W_{1/2}$=10 Hz, 1H, H-2), [b] obscured signal; ^{13}C NMR (100 MHz, C_5D_5N) δ 19.1 (C-18), 19.2 (C-11), 21.2 (C-21), 21.6 (C-16), 26.6 (C-4), 27.5 (C-23), 27.7 (C-19), 30.0 (C-26), 30.2 (C-27), 31.7 (C-15), 34.4 (C-12), 39.7 (C-10), 40.4 (C-1), 41.6 (C-9), 41.8 (C-7), 42.6 (C-24), 43.6 (C-8), 48.0 (C-13), 50.3 (C-17), 51.7 (C-5), 67.5 (C-3), 69.6 (C-25), 70.5 (C-2), 76.9 (C-20), 77.6 (C-22), 83.9 (C-14), 212.4 (C-6); ^{13}C NMR (100 MHz, CD_3OD) δ 19.1 (C-18), 19.7 (C-11), 20.5 (C-21), 21.5 (C-16), 26.5 (C-4), 27.3 (C-23), 27.7 (C-19), 28.9 (C-26), 29.6 (C-27), 31.8 (C-15), 34.8 (C-12), 40.2 (C-10), 40.7 (C-1), 41.7 (C-9), 42.1 (C-7), 42.4 (C-24), 43.9 (C-8), 48.5 (C-13), 50.6 (C-17), 52.3 (C-5), 68.2 (C-3), 70.8 (C-2), 71.3 (C-25), 78.0 (C-20), 78.5 (C-22), 85.5 (C-14), 215.1 (C-6); HMBC correlations (C_5D_5N): H-2 (C-3, C-4, C-10), H-7β (C-6, C-8, C-14), H-8 (C-6, C-9, C-13), H-17 (C-12, C-13, C-14, C-16, C-18, C-21), 18-Me (C-12, C-13, C-14, C-17), 19-Me (C-5, C-9, C-10), 21-Me (C-17, C-20), H-22 (C-20, C-21, C-23, C-24), 26-Me (C-24, C-25, C-27), 27-Me (C-24, C-25, C-26); HMBC correlations (CD_3OD): H-1 (C-2), H-2 (C-3, C-10), H-4α (C-3, C-6), H-4β (C-2, C-6), H-5 (C-3, C-6, C-10), H-7α (C-8, C-14), H-7β (C-6, C-8, C-14), H-8 (C-6, C-9, C-13, C-14), H-17 (C-13, C-14, C-16), 18-Me (C-12, C-13, C-14, C-17), 19-Me (C-5, C-9, C-10), 21-Me (C-17, C-20), H-22 (C-20, C-21, C-23), 26-Me (C-24, C-25, C-27), 27-Me (C-24, C-25, C-26); FABMS (negative ion mode) m/z 481 $[M-H]^-$.

3.2. Catalytic hydrogenation of compounds 2, 7 and 9

Compounds **2**, **7** and **9** were separately subjected to catalytic hydrogenation in similar manner to that of compound **1**, using conditions indicated in entries 2–4 to give, respectively, compounds **6**, **8** and **10**.

3.2.1. 7,8-Dihydroponasterone A (6). 14 mg (0.030 mmol, 93%) from 15 mg (0.032 mmol) of **2**. Colourless needles (from acetone), mp 201–203°C; IR ν_{max} 3438, 2953, 1701, 1383, 1064 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 0.79 (d, J=6.5 Hz, 3H, 26-Me), 0.81 (d, J=6.5 Hz, 3H, 27-Me), 1.54 (s, 2×3H, 18-Me and 21-Me), 1.67 (s, 3H, 19-Me), 2.55 (dd, J=14.6, 4.5 Hz, 1H, H-7α), 2.73 (dt, J=14.6, 4.5 Hz, 1H, H-8), 2.90 (t, J=9.1 Hz, H-17), 2.93 (t, J=14.6 Hz, H-7β), 3.79 (br d, J=9.7 Hz, 1H, H-22), 4.27 (m, $W_{1/2}$=9 Hz, 1H, H-2), 4.33 (m, $W_{1/2}$=20 Hz, 1H, H-3); HRFABMS (negative ion mode) m/z 465.3217 $[M-H]^-$ (calcd for $C_{27}H_{46}O_6-H$, 465.3216).

3.2.2. 7,8-Dihydropterosterone (8). 11.5 mg (0.023 mmol, 88%) from 13 mg (0.027 mmol) of **7**. Amorphous; IR ν_{max} 3418, 2925, 1697, 1465, 1383, 1064 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 0.99 (d, J=6.7 Hz, 3H, 26-Me), 1.00 (d, J=6.7 Hz, 3H, 27-Me), 1.52 (s, 3H, 18-Me), 1.55 (s, 3H, 21-Me), 1.67 (s, 3H, 19-Me), 2.55 (dd, J=14.5, 4.3 Hz, 1H, H-7α), 2.73 (ddd, J=14.5, 4.3, 4 Hz, 1H, H-8), 2.88 (t, J=8.9 Hz, H-17), 2.92 (t, J=14.5 Hz, H-7β), 3.92 (m, $W_{1/2}$=17 Hz, 1H, H-24), 4.12 (br d, J=9.6 Hz, 1H, H-22), 4.28 (m, $W_{1/2}$=8 Hz, 1H, H-2), 4.32 (m, $W_{1/2}$=20 Hz, 1H, H-3); HRFABMS (negative ion mode) m/z 481.3161 $[M-H]^-$ (calcd for $C_{27}H_{46}O_7-H$, 481.3165).

3.2.3. 7,8-Dihydropoststerone (10). 9.5 mg (0.026 mmol,

86%) from 11 mg (0.030 mmol) of **9**. Colourless prisms (from acetone), mp 215–217°C; IR ν_{max} 3518, 3398, 3347, 3178, 2951, 2882, 1707, 1691, 1440, 1355, 1332, 1272, 1206, 1172, 1072, 1050 cm^{-1}; ^1H NMR (400 MHz, C_5D_5N) δ 0.92 (s, 3H, 18-Me), 1.66 (s, 3H, 19-Me), 2.09 (s, 3H, 21-Me), 2.46–2.57 (m, 4H) and 2.69–2.74 (m, 2H) (two sets of overlapping signals, H-4α, H-5, H-7α, H-7β, H-8 and H-9), 3.60 (br d, J=8.4 Hz, H-17), 4.28 and 4.30 (two partially overlapping signals, H-2 and H-3); HRFABMS (negative ion mode) m/z 363.2173 $[M-H]^-$ (calcd for $C_{21}H_{32}O_5-H$, 363.2171).

3.3. Catalytic hydrogenation of compounds 11 and 12

Compound **11** and **12** were similarly hydrogenated under conditions indicated in Table 1 (entries 5–8). The products obtained were identical to authentic compounds **2** and **6** by TLC and ^1H NMR comparisons.

3.4. Catalytic hydrogenation of compound 13

Compound **13** (20 mg, 0.040 mmol) was subjected to catalytic hydrogenation in similar manner to that of compound **1** for 1 h to yield the unexpected product **1** (13 mg, 0.027 mmol or 67%) as colourless crystals (from MeOH–EtOAc), mp 240–241°C (lit.[1] 240–242°C). Spectroscopic (^1H NMR and mass spectra) data were consistent with those of authentic **1**.[1]

3.4.1. Catalytic hydrogenation of compound 13 in the presence of solid $NaNO_2$. The above procedure was repeated, using solid $NaNO_2$ in place of aq $NaNO_2$ and the reaction time was 24 h to yield the dehydration product **14** as colourless needles (from MeOH–EtOAc), mp 243–244°C (9 mg (0.018 mmol, 72%) from 13 mg (0.026 mmol) of **13**); IR ν_{max} 3379, 2963, 2923, 1660, 1648, 1617, 1465, 1383, 1370, 1148, 1051, 925 cm^{-1}; ^1H NMR (400 MHz, C_5D_5N) δ 1.24 (s, 2×3H, 18-Me and 19-Me), 1.36 (s, 2×3H, 26-Me and 27-Me), 1.57 (s, 3H, 21-Me), 3.05–3.10 (m, 2H, H-5 and H-17), 3.88 (br d, J=9.4 Hz, 1H, H-22), 4.15 (m, 1H, H-2), 4.17 (m, $W_{1/2}$=7 Hz, 1H, H-3), 6.20 (br s, 1H, H-7), 6.35 (br d, J=6.4 Hz, 1H, H-11); HRFABMS (negative ion mode) m/z 477.2844 $[M-H]^-$ (calcd for $C_{27}H_{42}O_7-H$, 477.2852).

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