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Stereoselective reduction of arteannuin B and its chemical transformations

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Respectfully dedicated to Professor Richard R. Schmidt on the occasion of his 68th birthday

Abstract—Absolute stereochemistry of dihydroarteannuin B **5** obtained by the reduction of arteannuin B **3** with Ni_2B, $NaBH_4$ or $CdCl_2$–Mg–MeOH–H_2O has been established by 2D NMR and single crystal X-ray diffraction studies. Some experiments aimed at the synthesis of dihydrodeoxyarteannuin B [C-4, 5 double bond isomer of **11**] are also discussed.

1. Introduction

The major secondary metabolites of the Chinese antimalarial plant *Artemisia annua* are artemisinin **1**, artemisinic acid **2** and arteannuin B **3** (Fig. 1). Of these three, only artemisinin **1** is the biologically active component and has been converted into several other derivatives, which are more effective and are now under clinical use.[1,2] Artemisinic acid **2** has been chemically converted into artemisinin **1** in 40% yield in a two-step synthesis.[3] Lansbury et al.[4] have reported the chemical conversion of arteannuin B **3** to artemisinin **1**. Our attempts[5] for the same conversion led to a novel rearranged product and during the course of our investigations we carried out some other reactions which are described herein including the determination of the relative stereochemistry of the C-13 methyl in dihydroarteannuin B **5**.

2. Results and discussion

In an earlier publication, nickel boride reduction of arteannuin B **3** has been shown to furnish[5] the dihydroarteannuin B **5**. The stereochemistry of the C-13 methyl was assigned as α mainly on the basis of its chemical shifts in $CDCl_3$ and C_6D_6, and also by comparison of coupling constants.[6] Lansbury et al.[4] has assigned the β-stereochemistry to the C-13 methyl group of dihydroarteannuin B, obtained by hydrogenation of arteannuin B **3** with Wilkinson's catalyst [$Rh(PPh_3)_3Cl$]. Our compound was different from Lansbury et al.[4] in respect of its NMR behaviour and mp. Reaction of **5** with $BF_3{\cdot}Et_2O$–Ac_2O furnishes the rearranged product **4** whose X-ray analysis[5] does confirm the absolute stereochemistry of **5**. Nevertheless, in view of the epimerization possible under these acidic conditions ($BF_3{\cdot}Et_2O$–Ac_2O), it was considered

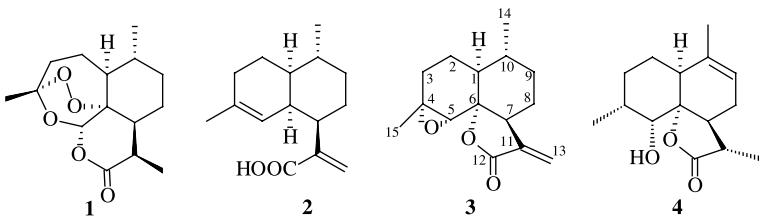

Figure 1. Major secondary metabolites (**1–3**) of *A. annua*.

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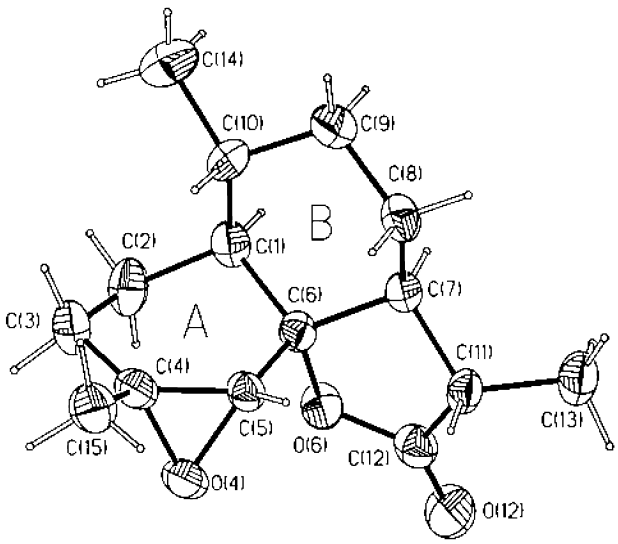


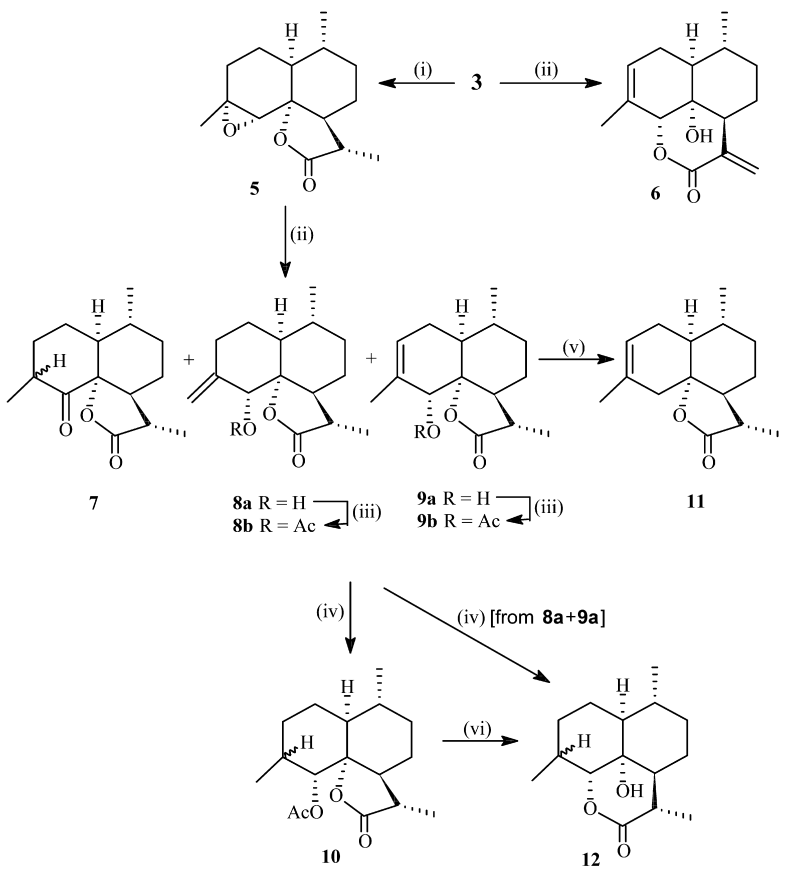
Figure 2. A perspective view of dihydroarteannuin B **5** with numbering scheme. Thermal ellipsoids were drawn with 40% probability. H-atoms are represented as spheres of an arbitrary size.

desirable to ascertain the stereochemistry of product **5** by single crystal X-ray analysis. This would settle the conflicting reports[7,8] appearing in the literature about the configuration of the C-13 methyl of dihydroarteannuin B **5**.

A perspective view of the molecule **5** is shown in Figure 2, which clearly illustrates the relative configuration at all chiral centers. Two six-membered rings are *cis*-fused at the C(1)–C(6) bond, as is an epoxide ring at C(4)–C(5). The γ-lactone ring is *trans*-fused at C(6)–C(7) and bears an α-oriented methyl group attached to C(11). The C(10) methyl group is also α-oriented, while the C(4) methyl group is β. Due to the fusion with the epoxide ring, the six-membered A ring is flattened at C(4) and C(5), and its conformation can be described as an intermediate between C(1), C(2) half-chair and C(1) sofa. The six-membered B ring adopts the chair conformation slightly distorted towards C(7) sofa form. The confirmation of the two rings closely resembles the conformation found in arteannuin B **3**.[9–11] The saturated γ-lactone ring adopts C(7) envelope conformation which seems to be characteristic for 11,13-dihydro derivatives of arteannuin B.[12] In arteannuin B **3** and isoarteannuin B,[13] the conformation of α-methylene γ-lactone ring is close to C(7), C(6) half-chair form.

Reduction of arteannuin B **3** with $NaBH_4$ or $CdCl_2$–Mg–MeOH–H_2O[14,15] furnished the dihydroarteannuin B **5** (Scheme 1) in almost quantitative yield, which was found to be identical (mp, mixed mp, TLC, co-TLC, IR and NMR) with the authentic sample of **5**.[5]

We now describe some experiments (Scheme 1) which were carried out to synthesize dihydrodeoxyarteannuin B [C-4, 5 double bond isomer of **11**] for its eventual transformation to artemisinin **1** using Lansbury et al.'s method.[4] Thus, it was decided to create a double bond between C-4, C-5 through bromohydrin formation. However, the reaction of arteannuin B **3** with HBr in THF at room temperature



Scheme 1. *Reagents and conditions*: (i) $NaBH_4$, MeOH, room temperature; (ii) HBr, THF, room temperature; (iii) Ac_2O, py, room temperature; (iv) Pd–C (10%), EtOH, H_2, 50 psi; (v) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, diglyme, room temperature (for **9b**); (vi) KOH–MeOH (10%) room temperature.

furnished a product, which was identified as **6**, mp 186–187°C (EtOAc–hexane) by direct comparison (TLC, co-TLC, mp, mixed mp and ^{1}H NMR) with the authentic sample.[14] The reaction of dihydroarteannuin B **5** with HBr in THF at room temperature furnished a mixture of three products, which were separated by preparative TLC (10% EtOAc–hexane). The less polar minor product was identified as the ketone **7** (mixture of C-4 epimers) by spectral data. The more polar major product was found to be a mixture of two products (≈85:15, single spot on TLC) as indicated by its ^{1}H NMR spectrum. Acetylation of this mixture with Ac_2O–Py led to the isolation of two products after preparative silica gel TLC (20% EtOAc–hexane, double run).

The more polar minor product was identified as **8b**, mp 86–87°C (EtOAc–hexane) by its spectral analysis. The IR spectrum gave strong absorption bands at 1780 and 1736 cm^{-1}. In the ^{1}H NMR spectrum, a singlet at δ 5.85 for one proton was assigned to 5-H; the two singlets at δ 4.90 and 4.67 each for one proton represented the exomethylene protons. The mass spectrum gave the molecular ion peak at *m*/*z* 292. The ^{13}C NMR spectrum gave seventeen peaks in the fully decoupled spectrum as demanded by structure **8b**. In the DEPT edited spectrum, there were 4×C, 5×CH, 5×CH_2, and 3×CH_3 which is in full accord with the assigned structure. The signals at δ 179.6 and 169.0 were responsible for the two carbonyl groups of the lactone and the acetate moieties, respectively. The signals at δ 141.8 and 86.6 were assigned to C-4 and C-6, respectively. The signal at δ 108.4 was assigned to C-15 and at δ 72.6 to C-5.

The less polar major product was identified as the acetate **9b** by direct comparison (TLC, co-TLC, mp, mixed mp, NMR and MS) with its authentic sample.[5]

Hydrogenation of **9b** over 10% Pd–C in dry EtOH at 50 psi furnished the dihydro derivative **10**, mp 65–67°C (EtOAc–hexane) which was found to be a mixture (vide ^{1}H and ^{13}C NMR) of C-4 epimers in the ratio of ≈1:5. Similarly, hydrogenation of **8b** under the above mentioned conditions gave the dihydro derivative **10**, mp 65–67°C (EtOAc–hexane) which was also found to be a mixture of C-4 epimers in the same ratio (i.e. ≈1:5) as that obtained from compound **9b**. In the ^{1}H NMR spectrum, 5-H appeared as doublet (J=5.7 Hz) at δ 5.39 for the major compound. For the minor compound, 5-H appeared as a doublet (J=11.1 Hz) at δ 5.26. The acetate methyl for the major compound appeared as a sharp singlet at δ 2.04, 13-CH_3, 15-CH_3 and 14-CH_3 appeared as doublets (J=6.0–7.0 Hz) at δ 1.13, 1.07 and 0.91 respectively, whereas, the corresponding doublets of these protons for the minor compound were not clearly discernible. The ^{13}C NMR spectrum also indicated that it is a mixture of C-4 epimers in the ratio of ≈1:5 by displaying seventeen signals for the major product. The corresponding seventeen signals for the minor compound were not clearly discernible being partially masked by the signals of the major isomer. In the DEPT edited spectrum, there were 3×C, 6×CH, 4×CH_2, and 4×CH_3 in full accord with the assigned structure. The two signals at δ 179.6 and 169.3 represented the two carbonyl groups of lactone and acetate, respectively. The carbons of the lactone and acetate oxygen appeared at δ 85.8 and 71.8, respectively. The mass spectrum gave the molecular ion peak at *m*/*z* 294.

It has been reported[16] that the reaction of Ni_2B with allylic acetate furnishes the corresponding olefin by reductive removal of the acetate, which in certain cases is attended by double bond migration. Reaction of the acetate **9b** with Ni_2B in diglyme furnished a single product, which was identified as **11** on the basis of spectral data. In the ^{1}H NMR spectrum, the signals due to the acetate methyl as well as the proton of the acetate were missing. A multiplet at δ 5.35 was assigned to 3-H and the C-15 methyl appeared as a broad singlet at δ 1.50. The mass spectrum gave the molecular ion peak at *m*/*z* 234. However, in compound **11**, the double bond could not be isomerised to C-4,5-position under various acidic reaction conditions viz. acidic alumina, oxalic acid in EtOH/reflux, *p*-TsOH in benzene etc.

Alkaline hydrolysis of the acetate **10** with 10% KOH–MeOH furnished the rearranged alcohol **12** in quantitative yield. The IR spectrum gave strong absorption bands at 3468 and 1714 cm^{-1}. In the ^{1}H NMR spectrum, a doublet (J=7 Hz) at δ 4.50 was assigned to 5-H; three doublets (J=7 Hz each) at δ 1.26, 1.10 and 0.90 were assigned to 13-CH_3, 15-CH_3 and 14-CH_3, respectively. The mass spectrum gave the molecular ion peak at *m*/*z* 252.

Hydrogenation of the mixture [(**8a**+**9a**) obtained in the reaction of HBr with **5**] over 10% Pd–C in dry EtOH at 50 psi also furnished **12** as the only product.

3. Conclusions

Reduction of arteannuin B **3** with Ni_2B,[5] $NaBH_4$ or $CdCl_2$–Mg–MeOH–H_2O[14,15] furnishes the same product, dihydro-arteannuin B **5** in which the relative stereochemistry of the C-13 methyl has been established by single crystal X-ray diffraction studies.

4. Experimental

4.1. General

All melting points were determined in open capillaries and are uncorrected. IR spectra were recorded as thin films unless otherwise stated on Perkin–Elmer 1710 FT-IR spectrophotometer. The NMR spectra were recorded on a Varian FT-80 (80 MHz) or a Bruker WM-400 (400 MHz) or a Bruker DRX-300 (300 MHz) in $CDCl_3$ unless stated with TMS as internal standard. Chemical shifts are expressed as δ in ppm. Mass spectra were recorded under electron impact at 70 eV on JEOL JMS D-100 spectrometer. Fast Atom Bombardment Mass Spectroscopy (FABMS) were carried out with JEOL SX 102/DA-6000 mass spectrometer using *m*-nitrobenzyl alcohol as matrix at an accelerating voltage of 10 kV. Optical rotations were recorded on JASCO DIP-180 digital polarimeter. Elemental analysis was carried out on HERAEUS CHN-O-RAPID elemental analyzer. For preparative TLC, Si gel G (E. Merck, India) was used. Sodium borohydride used was purchased from Aldrich Chemical Company Inc., USA. All the solvents were

purified before use. THF was distilled over $LiAlH_4$ before use. Hexane refers to the fraction bp 65–70°C. Work up reaction mixtures were dried over anhydrous Na_2SO_4.

The two-dimensional NMR experiments were carried out with the sample dissolved in $CDCl_3$ on a Bruker DRX-300 spectrometer (300 MHz). All the 2D NMR experiments were carried out using standard Bruker software. Assignments of ^{13}C signals have been made on the basis of comparison with other compounds in this series except where it has been mentioned by HMQC and HMBC NMR experiments.

4.2. X-Ray crystallographic study of (5)

$C_{15}H_{22}O_3$, MW=250.33; orthorhombic; crystal size: 0.55×0.40×0.25 mm; $P2_12_12_1$; a=9.451(2) Å, b=10.520(3) Å, c=13.841(3) Å; V=1376.1(5) Å^3; Z=4; D_x=1.208 mg/m^3; absorption coefficient: 0.082 mm^{-1}; F(000)=544. Single crystals of dihydroarteannuin B **5** were obtained from EtOAc–hexane solution. The reflection intensities were measured on a four-circle KM-4 (KUMA Diffraction)[17] diffractometer equipped with graphite monochromator using Mo K_α radiation. The cell constants and the orientation matrix obtained from a least-squares fit of 85 centered reflections with θ in the range 8.07 to 18.21°. The reflections were measured using ω–2θ scan technique for θ from 1 to 27°, with the scan rate depending directly on the net count for rapid pre-scans on each reflections and a scan range in ω of 1.0°. Index ranges: $0\leq h\leq 12$, $0\leq k\leq 13$, $0\leq l\leq 17$. Background measurements were estimated from 68-step profile. The intensities were corrected for Lorentz and polarization effects but not for absorption [μ (Mo K_α) 0.082 mm^{-1}]. The structure was solved by direct methods with SHELXS-86[18] and refined with SHELXL-93.[19] Heavy atoms (C, O, N) were refined anisotropically. The positions of the H-atoms attached to the C-atoms were calculated at standardized distances of 0.96 Å. All H-atoms were refined using a riding model with isotropic temperature factors 30% higher than the isotropic equivalent for the atom to which the H-atom was bonded. The function minimized was $\sum[w(F_o^2-F_c^2)^2]$ with $w=1/[\sigma^2(F_o)^2+(\alpha P)^2+bP]$ where $P=(F_o^2+2F_c^2)/3$, α=0.083 and b=0. Convergence was attained at R=0.042 for 899 observed reflections [$F_o\geq 4\sigma(F_o)$] and $wR2$=0.148 for all 1740 reflections and 164 refined parameters. The final difference map showed minima and maxima ranging from −0.16 to 0.19 eÅ^{-3}. Siemens Stereochemical Workstation was used to prepare drawings.[20,21]

4.2.1. Dihydroarteannuin B (5). To a stirred solution of **3** (100 mg, 0.40 mmol) in dry MeOH (4 mL) at room temperature, $NaBH_4$ (100 mg, 2.65 mmol) was added slowly over a period of 15 min and monitored the reaction on TLC. After 1 h when reaction was complete, H_2O (200 mL) was added and extracted with CH_2Cl_2 (3×100 mL), dried (Na_2SO_4) and evaporated to dryness to give dihydroarteannuin B **5** (90 mg, 89%) as colourless orthorhombic crystals, mp 179–181°C (EtOAc–hexane); [Found: C, 71.92; H, 8.80. $C_{15}H_{22}O_3$ (250.33) requires C, 71.97; H, 8.86%]; R_f (20% EtOAc–*n*-hexane) 0.55; $[\alpha]_D^{25}=-58.5°$ (*c*, 0.4, $CHCl_3$); ν_{max}(KBr) 1768 cm^{-1}; δ_H (300 MHz, $CDCl_3$, assignment by ^1H–^1H COSY) 2.85 (1H, s, 5-H), 2.68 (1H, m, 11-H), 1.95 (1H, m, 8-H_a), 1.87 (1H, m, 9-H_a), 1.85 (2H, m, 3-H), 1.79 (1H, m, 7-H), 1.74 (1H, m, 2-H_a), 1.71 (1H, m, 8-H_b), 1.58 (1H, m, 1-H), 1.52 (1H, m, 10-H), 1.50 (1H, m, 2-H_b), 1.38 (3H, brs, 15-CH_3), 1.24 (3H, d, J=7 Hz, 13-CH_3), 1.20 (1H, m, 9-H_b), 0.97 (3H, d, J=7 Hz, 14-CH_3). Irradiation of signal at δ 1.24 (3H, d, J=7 Hz, 13-CH_3) collapsed the multiplet at δ 2.68 into a doublet (J=14 Hz); δ_H (400 MHz, C_6D_6) 2.45 (1H, s, 5-H), 2.14 (1H, m, 11-H), 1.09 (3H, brs, 15-CH_3), 1.02 (3H, d, J=7 Hz, 13-CH_3), 0.63 (3H, d, J=7 Hz, 14-CH_3); δ_C (75.5, $CDCl_3$, assignment by DEPT, HMQC and HMBC NMR experiments) 178.31 (C-12), 80.81 (C-6), 57.93 (C-5), 57.79 (C-4), 54.69 (C-2), 44.42 (C-1), 32.61 (C-11), 34.51 (C-9), 30.50 (C-10), 24.35 (C-3), 22.76 (C-15), 22.65 (C-8), 18.36 (C-13), 16.14 (C-2), 12.75 (C-14); *m/z* (EI) 250 (M^+), 208, 179, 164, 151, 135, 121, 107, 93, 81, 67, 55, 43.

4.3. Reaction of (3) with HBr

To a stirred solution of **3** (100 mg, 0.40 mmol) in freshly distilled THF (4 mL) at room temperature, 48% HBr (0.5 mL) was added and the reaction was monitored by TLC. After 3 h when the reaction was complete, reaction mixture was quenched with H_2O (200 mL) and extracted with CH_2Cl_2 (3×100 mL). The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated to give a residue which showed a single spot on TLC and was purified by preparative TLC (20% EtOAc–hexane) to furnish a solid (80 mg, 80%) which was identified as **6**, mp 186–187°C (EtOAc–hexane, reported[14] mp 182–184°C) on the basis of TLC, co-TLC, mp, mixed mp and ^1H NMR with the authentic sample.[14]

4.4. Reaction of (5) with HBr

A solution of **5** (100 mg, 0.40 mmol) in freshly distilled THF (4 mL) was stirred at room temperature for 5 min and 48% HBr (0.3 mL) was added to it. The reaction mixture was monitored on TLC and after 7 h when the reaction was complete the reaction mixture was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3×100 mL). The CH_2Cl_2 extract was washed with dilute solution of $NaHCO_3$, H_2O, dried (Na_2SO_4) and evaporated to give a yellowish coloured semi-solid which on TLC (10% EtOAc–hexane) showed two spots. These were isolated by preparative TLC (10% EtOAc–hexane) to give 18 mg of the less polar minor product as colourless oil, which was identified as **7** by spectral data. The more polar major product showed two spots on TLC moving very close to each other, which could not be separated on Si gel TLC. The ^{13}C NMR spectrum of this major product indicated that it is a mixture of two alcohols in the ratio of ≈85:15. It was therefore, acetylated as such.

4.5. Acetylation

To a solution of 100 mg of the major product (mixture of two alcohols) in dry pyridine (1.0 mL), Ac_2O (2.0 mL) was added and the reaction mixture was left at room temperature for overnight. The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×150 mL), dried (Na_2SO_4) and evaporated under vacuum. The traces of pyridine were removed by co-distillation with toluene to

afford a residue, which on TLC (20% EtOAc–hexane) showed two spots and these were isolated by preparative TLC (20% EtOAc–hexane, double run). The less polar major product was obtained as a solid (83 mg), mp 120–122°C (EtOAc–hexane) and was identified as the acetate **9b** by direct comparison (TLC, co-TLC, mp, mixed mp, ^{1}H NMR and MS) with its authentic sample.[5] The more polar minor product **8b** was also obtained as a colourless solid (10 mg), mp 86–87°C (EtOAc–hexane).

4.5.1. Ketone (7). Colourless oil; [Found: C, 71.92; H, 8.82. $C_{15}H_{22}O_3$ (250.33) requires C, 71.97; H, 8.86%]; R_f (10% EtOAc–*n*-hexane) 0.75; ν_{max}($CHCl_3$) 2928, 1778, 1723 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.95 (1H, m, 4-H), 2.83 (1H, m, 11-H), 1.16 (3H, d, *J*=7 Hz, 13-CH_3), 0.98 (3H, d, *J*=7 Hz, 15-CH_3), 0.90 (3H, d, *J*=7 Hz, 14-CH_3). Irradiation of signal at δ 1.16 (3H, d, *J*=7 Hz, 13-CH_3) collapsed the multiplet at δ 2.83 (11-H) into a doublet (*J*=13.4 Hz); δ_H (200 MHz, C_6D_6) 2.81 (1H, m, 11-H or 4-H), 2.04 (1H, m, 11-H or 4-H), 1.06 (3H, d, *J*=7 Hz, 13-CH_3), 0.95 (3H, d, *J*=7 Hz, 15-CH_3), 0.62 (3H, d, *J*=7 Hz, 14-CH_3); *m*/*z* (EI) 250 (M^+), 222, 207, 192, 179, 165 (100), 151, 137, 123, 109, 95, 81, 69, 55, 42.

4.5.2. Acetate (8b). Colourless crystals, mp 86–87°C (EtOAc–hexane); [Found: C, 69.80; H, 8.24. $C_{17}H_{24}O_4$ (292.37) requires C, 69.84; H, 8.27%]; R_f (20% EtOAc–*n*-hexane) 0.30; ν_{max} (KBr) 1780 (CO of lactone), 1736 cm^{-1} (CO of acetate); δ_H (400 MHz, $CDCl_3$) 5.85 (1H, s, 5-H), 4.90 (1H, s, 15-H_a), 4.67 (1H, s, 15-H_b), 2.60 (1H, m, 11-H), 2.15 (3H, s, OCOCH_3), 1.18 (3H, d, *J*=7 Hz, 13-CH_3), 0.98 (3H, d, *J*=7 Hz, 14-CH_3); δ_C (100.6 MHz, $CDCl_3$, assignment by DEPT NMR experiment) 179.6 (s, C-12), 169.0 (s, O*C*OCH_3), 141.8 (s, C-4), 108.4 (t, C-15), 86.6 (s, C-6), 72.6 (d, C-5), 56.2 (d), 50.8 (d), 38.9 (d), 35.5 (t), 30.8 (d), 28.9 (t), 23.8 (t), 22.9 (t), 21.1 (q, OCO*C*H_3), 19.9 (q), 15.2 (q); *m*/*z* (EI) 292 (M^+), 250, 233, 232, 204, 177, 176, 151 and 69.

4.5.3. Hydrogenation of (9b). A solution of **9b** (100 mg, 0.34 mmol) in dry EtOH (25 mL) was hydrogenated in the presence of 10% Pd–C (300 mg) in a Parr shaker type hydrogenator with H_2 pressure at 50 psi for 5 h and the reaction was monitored on TLC. After 5 h when no starting material was left in the reaction mixture, catalyst was filtered out and the solvent evaporated to furnish **10** (98 mg, 97%) as colourless crystals, mp 65–67°C (EtOAc–hexane); [Found: C, 69.32; H, 8.86. $C_{17}H_{26}O_4$ (294.39) requires C, 69.36; H, 8.90%]; R_f (20% EtOAc–*n*-hexane) 0.40; ν_{max}(KBr) 1780 (CO of lactone), 1739 cm^{-1} (CO of acetate); δ_H (300 MHz, $CDCl_3$) 5.39 (1H, d, *J*=5.7 Hz, 5-H of major), 5.26 (1H, d, *J*=11.1 Hz, 5-H of minor), 2.52 (1H, m, 4-H or 11-H), 2.26 (1H, m, 4-H or 11-H), 2.04 (3H, s, OCOCH_3), 1.13 (3H, d, *J*=6.9 Hz, 13-CH_3), 1.07 (3H, d, *J*=7.2 Hz, 15-CH_3), 0.91 (3H, d, *J*=6.0 Hz, 14-CH_3); δ_C (75.5 MHz, $CDCl_3$, assignment by DEPT NMR experiment) 179.6 (s, C-12), 169.3 (s, O*C*OCH_3), 85.8 (s, C-6), 71.8 (d, C-5), 57.3 (d), 50.5 (d), 38.9 (d), 35.5 (t), 32.0 (d), 30.4 (d), 24.7 (t), 22.6 (t), 21.4 (q, OCO*C*H_3), 19.8 (q), 17.9 (t), 15.4 (q), 14.0 (q); *m*/*z* (EI) 294 (M^+), 266, 252, 238, 234, 220, 219, 206, 192 (100), 178, 165, 161, 109, 103, 83, 69, 54, 43; *m*/*z* (FAB) 295 $[M + H]^+$, 251, 235.

4.6. Hydrogenation of (8b)

A solution of **8b** (50 mg, 0.17 mmol) in dry EtOH (25 mL) and 10% Pd–C (200 mg) was hydrogenated as discussed above. After 3 h when no starting material was left, the reaction was worked up as given above to furnish **10** (48 mg, 96%).

4.7. Reaction of (9b) with Ni_2B

To solution of **9b** (100 mg, 0.34 mmol) in dry diglyme (3 mL), $NiCl_2{\cdot}6H_2O$ (400 mg, 1.69 mmol) was added and the reaction mixture was stirred at room temperature. After 5 min, $NaBH_4$ (200 mg, 5.26 mmol) was added in portions over a period of 30 min and the reaction was monitored by TLC. After 2 h of addition of $NaBH_4$, reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL), dried (Na_2SO_4) and evaporated to dryness. The residue after preparative TLC (10% EtOAc–hexane) furnished **11** (12 mg, 15%) as gum and **9b** (86 mg) was obtained as unreacted starting material.

4.7.1. Compound (11). Gum; [Found: C, 76.84; H, 9.43. $C_{15}H_{22}O_2$ (234.34) requires C, 76.88, H, 9.46%]; R_f (20% EtOAc–*n*-hexane) 0.45; ν_{max}($CHCl_3$) 1747 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 5.35 (1H, brs, 3-H), 1.50 (3H, brs, 15-CH_3), 1.20 (3H, d, *J*=7 Hz, 13-CH_3), 0.90 (3H, d, *J*=7 Hz, 14-CH_3); *m*/*z*(EI) 234 (M^+), 219, 206 and 204.

4.7.2. Alkaline hydrolysis of (10). To a solution of **10** (100 mg, 0.34 mmol) in MeOH (5 mL), 10% KOH–MeOH (0.5 mL) was added and the reaction mixture was stirred at room temperature monitoring on TLC. After 7 h when no starting material was left, it was diluted with 3% HCl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3×100 mL), washed with dilute solution of $NaHCO_3$, H_2O, dried (Na_2SO_4) and evaporated to furnish a residue which on purification by preparative TLC (20% EtOAc–hexane) furnished **12** (84 mg, 98%) as colourless oil; [Found: C, 71.34; H, 9.56. $C_{15}H_{24}O_3$ (252.35) requires C, 71.39; H, 9.59%]; R_f (20% EtOAc–*n*-hexane) 0.35; ν_{max}($CHCl_3$) 3468, 1714 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 4.50 (1H, d, *J*=8 Hz, 5-H), 1.26 (3H, d, *J*=7 Hz, 13-CH_3), 1.10 (3H, d, *J*=7 Hz, 15-CH_3), 0.90 (3H, d, *J*=7 Hz, 14-CH_3); *m*/*z* (EI) 252 (M^+), 234, 223, 195, 177, 160, 124, 109, 96, 84, 69, 55, 42.

4.8. Hydrogenation of the mixture of (8a) and (9a)

A solution of **8a** and **9a** (100 mg, mixture of two alcohols) in dry EtOH (25 mL) was hydrogenated in the presence of 10% Pd–C (200 mg) with H_2 pressure set at 50 psi as discussed above. After 7 h when no starting material was left, catalyst was filtered out and the solvent evaporated to furnish **12** (98 mg, 97%) as colourless oil, which was identified on the basis of comparison with the authentic sample (TLC, co-TLC, IR, NMR and MS).

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21. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-181880. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].