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Enantiospecific synthesis and confirmation of the relative and absolute stereostructure of 11-hydroxyguaiadienes

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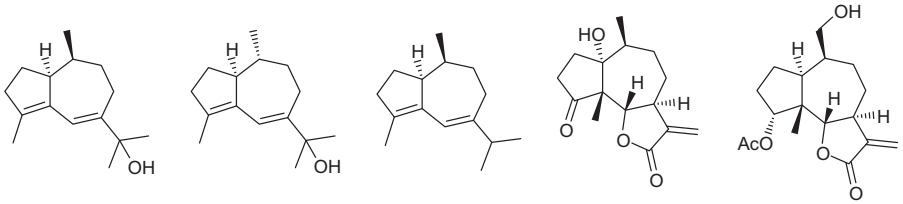
ABSTRACT

Enantiospecific total synthesis of two epimeric sesquiterpenes 11-hydroxyguaiadienes has been accomplished starting from the readily available monoterpene (*R*)-limonene, which confirmed the structure and absolute configuration of the natural products.

1. Introduction

Guaianes constitute a large group among various bicyclo[5.3.0]decane containing sesquiterpenes and are present in plant, liverwort as well as marine sources.[1] Hydroxyguaianes are interesting oxygenated sesquiterpene natural products isolated from plant and marine sources. In 1977, Bohlmann et al. reported[2] the isolation of 11-hydroxyguaiadiene **1a** from the roots of *Parthenium hysterophorus* along with guaiadiene **2** and pseudoguaianolides **3** and **4**. The structure of 11-hydroxyguaiadiene **1a** was established on the basis of the spectroscopic data, in particular, analysis of europium induced shifts in the ^{1}H NMR spectrum. In 2000, Nkunya et al. during their phytochemical analysis of the root bark of *Lettowianthus stellatus* Diels (Annonaceae), a plant which grows in the coastal rainforests of Kenya and Tanzania, reported[3] the isolation of the epimeric 11-hydroxyguaiadiene **1b** along with several known sesquiterepenes and aporphinoid alkaloids. The structure of 11-hydroxyguaiadiene **1b** was deduced on the basis of detailed 1 and 2D NMR studies (IR, HRMS, ^{1}H and ^{13}C NMR, homonuclear COSY, HMQC, and HMBC experiments).



1a **1b** **2** **3** **4**

There has been no report on the synthesis of 11-hydroxyguaiadiene **1b** and only one report[4a] on the synthesis of 11-hydroxyguaiadiene **1a**. In 1996, Lee and Yoon reported the synthesis of **1a** along with clavukerin A from limonene oxide, employing an 8-*endo trig* radical cyclization and intramolecular aldol condensation as the key steps. However, the authors reported[4b] that the specific rotation of the synthetic sample did not match the value reported[2] for the natural product **1a**, resulting in ambiguity over its structure. In continuation of our interest in the synthesis of natural products[5] starting from the readily available monoterpene (*R*)-limonene **5**, and in order to solve the ambiguity regarding the structures of 11-hydroxyguaiadienes **1a** and **1b**, and also to establish their absolute configuration, the synthesis of both hydroxyguaiadienes **1a** and **1b** was undertaken.

2. Results and discussion

It was thought (Scheme 1) that the synthesis of the isomeric hydroxyguaiadienes **1a** and **1b** could be achieved by starting from the C-6 epimeric hydroxy ketones **6a** and **6b**, whose synthesis from (*R*)-limonene **5** was recently accomplished in our laboratory, enroute to aciphyllenes,[5f] by employing a type II carbonyl ene reaction[6] of aldehyde **7** as the key step.

The synthetic sequences are depicted in Schemes 2–4. The synthesis of the key intermediate hydroxyketones **6a** and **6b** has been carried out employing the methodology developed in our laboratory.[5f] Thus, a four step conversion of (*R*)-limonene **5** generated the bromide **8**, which on coupling with ethyl acetoacetate generated ketoester **9**. The keto ester **9** was then transformed into

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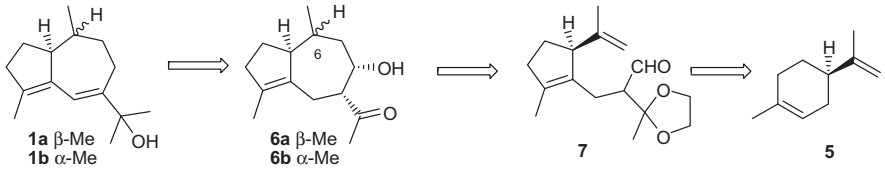
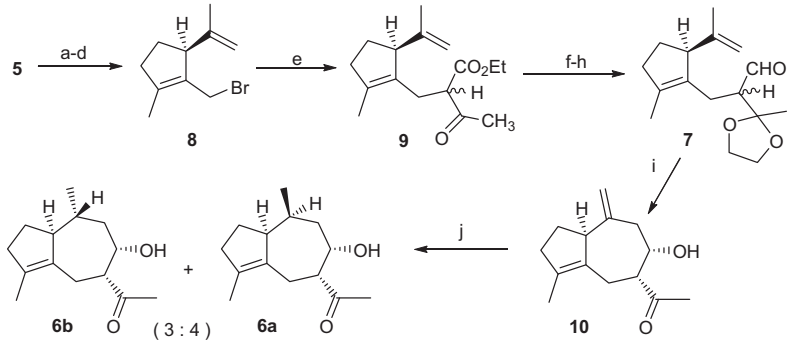
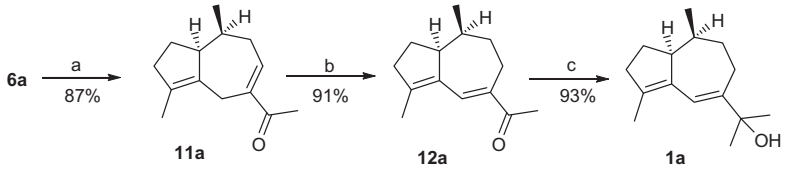


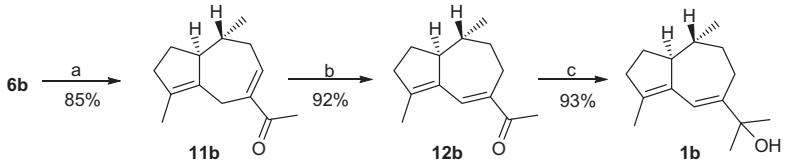
Scheme 1.



Scheme 2. Reagents: (a) O_3/O_2, CH_2Cl_2–MeOH; Me_2S; (b) piperidine, AcOH, C_6H_6; (c) $NaBH_4$, MeOH; (d) PBr_3, py, Et_2O; (e) $MeCOCH_2COOEt$, K_2CO_3, acetone; (f) $(CH_2OH)_2$, *p*-TSA, C_6H_6; (g) LAH, Et_2O; (h) IBX, DMSO; (i) $BF_3{\cdot}Et_2O$, CH_2Cl_2; (j) H_2, $(Ph_3P)_3RhCl$, EtOAc.



Scheme 3. Reagents: (a) MsCl, Et_3N, CH_2Cl_2, rt, 6 h; (b) $RhCl_3{\cdot}H_2O$, EtOH; (c) MeMgCl, THF.



Scheme 4. Reagents: (a) MsCl, Et_3N, CH_2Cl_2, rt, 6 h; (b) $RhCl_3{\cdot}H_2O$, EtOH; (c) MeMgCl, THF.

aldehyde **7** in three steps. A boron trifluoride diethyl etherate mediated type II carbonyl ene reaction of aldehyde **7** generated hydroxy ketone **10** in a stereoselective manner. Hydrogenation of the exomethylene group in **10** using Wilkinson catalyst generated a mixture of hydroxy ketones **6a** and **6b**. The stereochemistries of the secondary methyl group as well as the other stereogenic centers in **6a** and **6b** were confirmed by single crystal X-ray diffraction analysis[5f] of the minor isomer **6b**.

It was seen that it required three steps for the conversion of hydroxyketones **6a**,**b** into 11-hydroxyguaiadienes **1a**,**b**, via dehydration, isomerisation of the resultant olefin, and nucleophilic addition of the fifteenth carbon. Firstly, the sequence was carried out with the major hydroxy ketone **6a** to generate hydroxyguaiadiene **1a**. The reaction of the β-hydroxy ketone **6a** with an excess of methanesulphonyl chloride and triethylamine in anhydrous methylene chloride at rt furnished enone **11a** in 87% yield. After exploring various reagents (acidic as well as basic) for the isomerisation of the double bond in the bicyclic dienone **11a**, rhodium chloride[7] was found to be suitable. Thus, refluxing a solution of the bicyclic enone **11a** with a catalytic amount of rhodium chloride hydrate in ethanol for 24 h furnished dienone **12a** in 91% yield. A shift in the carbonyl absorption band to 1661 cm^{-1} due to the dienone in the IR spectrum and in the ^1H NMR spectrum, the absence of signals due to the diallylic methylene, and presence of a downfield singlet at δ 7.34 due to the β-olefinic proton of the dienone established the structure of the bicyclic dienone **12a**, which was further confirmed by the 14 lines in the ^{13}C NMR spectrum. The regioselective Grignard reaction of the enone with methylmagnesium chloride furnished the 6β,7α-11-hydroxyguaiadiene **1a** in 93% yield, whose structure was established from its spectroscopic data. Comparison of the ^1H and ^{13}C NMR spectra of the sample obtained herein in deuterochloroform with those reported[4a] by Lee and Yoon, for their synthetic sample, revealed that both were identical. Moreover, the ^1H NMR spectrum of the compound obtained in the present study in a 1:1 mixture of deuterochloroform and hexadeuterobenzene was found to be identical to that reported by Bohlmann et al. for the natural product. The synthetic hydroxyguaiadiene **1a** also had a specific rotation $\{[\alpha]_D^{26} = -34.7$ (*c* 1.0, $CHCl_3)\}$ value comparable to that reported for the natural product {lit.[2] $[\alpha]_D^{24} = +34.0$ (*c* 2.5, $CHCl_3)\}$ but with an opposite sign, thus establishing

the absolute configuration of the natural hydroxyguaiadiene **1a** as (6*S*,7*S*).

After successfully accomplishing the synthesis of 6β,7α-isomer **1a**, synthesis of the diastereomeric 11-hydroxyguaiadiene **1b** was also carried out in a similar manner. Thus, reaction of the β-hydroxy ketone **6b** with an excess of methanesulphonyl chloride and triethylamine in methylene chloride at rt furnished the enone **11b** in 85% yield. Isomerisation of the double bond in the enone **11b** with rhodium chloride hydrate in ethanol furnished the dienone **12b** in 92% yield. Regioselective Grignard reaction of the enone **12b** with methylmagnesium chloride in anhydrous THF furnished (6*R*,7*S*)-11-hydroxyguaiadiene **1b** in 93% yield, whose structure was established from its spectral data. It was further confirmed by comparing the ^{1}H and ^{13}C NMR spectra of the synthetic material **1b**, recorded in hexadeuterobenzene, with those of the natural compound reported[3] by Nkunya et al. The optical rotation of the synthetic hydroxyguaiadiene **1b**, $[\alpha]_D^{26} = -55.1$ (*c* 1.1, $CHCl_3$), was found to be identical to that of the natural product **1b** including the sign of rotation, {lit.[3] $[\alpha]_D^{21} = -55.0$ (*c* 0.25, $CHCl_3$)}, thereby establishing the absolute configuration of the natural product **1b** as (6*R*,7*S*).

3. Conclusion

The enantioselective total synthesis of both the isomers of 11-hydroxyguaiadienes **1a** and **1b** has been accomplished. The present sequence, in addition to the complete stereostructure, has also established the absolute configuration of the natural products.

4. Experimental

IR spectra were recorded on a Jasco FTIR 410 and Perkin Elmer FTIR spectrum BX and GX spectrophotometers. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Brucker Avance 400 spectrometer. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 and Jasco P-1020 polarimeters and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical thin-layer chromatography (TLC) were performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Acme's silica gel G containing 13% calcium sulfate as binder and various combinations of ethyl acetate–hexane and methylene chloride–hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapor. Acme's silica gel (100–200 mesh) was used for column chromatography.

4.1. 1-[(6*S*,7*S*)-6,10-Dimethylbicyclo[5.3.0]deca-1(10),2-dien-3-yl]ethanone 12a

To a magnetically stirred solution of enone[5f] **11a** (22 mg, 0.11 mmol) in ethanol (1 mL) was added $RhCl_3{\cdot}H_2O$ (6 mg) and refluxed for 24 h. Ethanol was then removed under reduced pressure and the reaction mixture was filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:19) as eluent first furnished the unreacted starting material **11a** (11 mg). Further elution of the column with CH_2Cl_2–hexane (1:9) gave the conjugated dienone **12a** (10 mg, 91%, based on starting material consumed) as pale blue oil. $[\alpha]_D^{22} = -103.7$ (*c* 0.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2956, 2922, 2874, 2856, 1661 (C=O), 1623, 1434, 1382, 1356, 1260, 1219; ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.34 (1H, s, H-2′), 3.16 (1H, br s, H-7′), 2.65-2.25 (2H, m), 2.38 (3H, s, CH_3C=O), 2.20–1.70 (4H, m), 1.89 (3H, s, olefinic-CH_3), 1.70–1.50 (3H, m), 0.76 (3H, d, *J* 6.9 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 199.9 (C, C=O), 148.1 (C), 140.0 (C), 134.7 (C), 134.6 (CH, C-2′), 51.6 (CH, C-7′), 38.6 (CH_2), 34.5 (CH_2), 34.3 (CH, C-6′), 26.8 (CH_2), 25.9 (CH_3, CH_3C=O), 23.0 (CH_2), 15.2 (CH_3), 13.7 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412, found: 227.1417.

4.2. 2-[(6*S*,7*S*)-6,10-Dimethylbicyclo[5.3.0]deca-1(10),2-dien-3-yl]propan-2-ol 1a

To a cold (0 °C), magnetically stirred solution of the dienone **12a** (10 mg, 0.05 mmol) in anhydrous THF (0.5 mL) was added methylmagnesium chloride (3.0 M in THF, 0.25 mL, 0.75 mmol) and stirred for 4 h at rt. The reaction was quenched with aq NH_4Cl (3 mL) and extracted with ether (3 × 3 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished 11-hydroxyguaiadiene **1a** (10 mg, 93%) as colorless oil. $[\alpha]_D^{26} = -34.7$ (*c* 1.0, $CHCl_3$); {lit.[2] $[\alpha]_D^{24} = +34.0$ (*c* 2.5, $CHCl_3$)}; IR (neat): ν_{max}/cm^{-1} 3376 (OH), 2965, 2924, 2871, 2855, 1606, 1462, 1377, 1250, 1159, 942; ^{1}H NMR [400 MHz, (1:1) $CDCl_3$+C_6D_6]: δ 6.43 (1H, s, H-2′), 3.16 (1H, br s, H-7′), 2.35 (1H, dd, *J* 16.9 and 7.7 Hz), 2.25 (1H, dd, *J* 8.8 and 1.3 Hz), 2.14 (1H, ddd, *J* 11.2, 8.4 and 2.8 Hz), 2.05–1.80 (2H, m), 1.75 (3H, s, olefinic-CH_3), 1.70–1.40 (2H, m), 1.45–1.25 (2H, m), 1.28 (6H, s, H-1 and 3), 1.00–0.80 (1H, m), 0.83 (3H, d, *J* 6.8 Hz, *sec*-CH_3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (1H, s, H-2′), 3.15 (1H, br s, H-7′), 2.45 (1H, br dd, *J* 17.0 and 10.1 Hz), 2.40–2.20 (2H, m), 2.19 (1H, ddd, *J* 11.5, 8.7 and 2.9 Hz), 2.05–1.80 (3H, m), 1.75 (3H, s, olefinic-CH_3), 1.65–1.20 (3H, m), 1.36 (6H, s, 2 × *tert*-CH_3), 0.78 (3H, d, *J* 6.8 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8 (C), 138.0 (C), 134.2 (C), 117.7 (CH, C-2′), 74.4 (C, C-2), 50.9 (CH, C-7′), 37.9 (CH_2), 35.8 (CH_2), 34.8 (CH, C-6′), 29.1 (CH_3), 28.9 (CH_3), 26.9 (CH_2), 25.5 (CH_2), 14.6 (CH_3), 14.5 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{23}$ (M−OH): 203.1800, found: 203.1800.

4.3. 1-[(6*R*,7*S*)-6,10-Dimethylbicyclo[5.3.0]deca-1(10),2-dien-3-yl]ethanone 12b

To a magnetically stirred solution of enone[5f] **11b** (20 mg, 0.10 mmol) in ethanol (1 mL) was added $RhCl_3{\cdot}H_2O$ (6 mg) and refluxed for 24 h. Ethanol was removed under reduced pressure and the reaction mixture was filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:19) as eluent first furnished the unreacted starting material **11b** (8 mg). Further elution of the column using CH_2Cl_2–hexane (1:9) gave the conjugated dienone **12b** (11 mg, 92%, based on starting material consumed) as pale blue oil. $[\alpha]_D^{24} = -150.8$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2954, 2924, 2870, 1660 (C=O), 1620, 1435, 1379, 1353, 1256, 1231, 1021; ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.33 (1H, s, H-2′), 2.64 (1H, dd, *J* 18.0 and 9.5 Hz), 2.60–2.15 (4H, m), 2.37 (3H, s, CH_3C=O), 2.09 (1H, ddd, *J* 12.3, 8.1 and 4.2 Hz), 1.88 (3H, s, olefinic-CH_3), 1.77 (1H, ddd, *J* 13.7, 7.5 and 2.8 Hz), 1.65–1.30 (3H, m), 0.97 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 199.7 (C, C=O), 147.6 (C), 139.9 (C), 136.7 (C), 134.9 (CH, C-2′), 53.8 (CH, C-7′), 38.6 (CH, C-6′), 37.4 (CH_2), 35.1 (CH_2), 29.8 (CH_2), 25.7 (CH_3, CH_3C=O), 23.7 (CH_2), 21.5 (CH_3), 15.3 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412, found: 227.1413.

4.4. 2-[(6*R*,7*S*)-6,10-Dimethylbicyclo[5.3.0]deca-1(10),2-dien-3-yl]propan-2-ol 1b

To a cold (0 °C), magnetically stirred solution of the dienone **12b** (11 mg, 0.05 mmol) in dry THF (0.5 mL) was added methylmagnesium chloride (3.0 M in THF, 0.25 mL, 0.75 mmol) and stirred for 3 h at rt. The reaction was then quenched with aq. NH_4Cl (3 mL) and extracted with ether (3 × 3 mL). The combined organic extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished 11-hydroxyguaiadiene **1b** (11 mg, 93%) as colorless oil. $[\alpha]_D^{26} = -55.1$ (*c* 1.1, $CHCl_3$); {lit.[3] $[\alpha]_D^{21} = -55.0$ (*c* 0.25, $CHCl_3$)}; IR (neat): ν_{max}/cm^{-1} 3398 (OH), 2948, 2923, 2868, 2855, 1453, 1373, 1360, 1164, 1137, 1023, 945; ^1H NMR (400 MHz, C_6D_6): δ 6.56 (1H, s, H-2′), 2.55–2.45 (1H, m), 2.42 (1H, dd, *J* 16.7 and 9.4), 2.35–2.10 (2H, m), 2.10–1.95 (2H, m), 1.81 (1H, dddd, *J* 13.9, 9.9, 5.1 and 2.4 Hz), 1.73 (3H, s, olefinic-CH_3), 1.60–1.20 (4H, m), 1.27 (3H, s) and 1.26 (3H, s) [H-1 and 3], 0.96 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^1H NMR (400 MHz, $CDCl_3$): δ 6.37 (1H, s, H-2′), 2.55–2.40 (1H, m), 2.35–2.10 (2H, m), 2.10–1.95 (2H, m), 1.85–1.70 (1H, m), 1.74 (3H, s, olefinic-CH_3), 1.70–1.10 (5H, m), 1.36 (6H, s, H-1 and 3), 0.95 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, C_6D_6): δ 148.1 (C, C-3′), 137.1 (C), 136.9 (C), 118.0 (CH, C-2′), 73.7 (C, C-2), 54.1 (CH, C-7′), 39.3 (CH, C-6′), 36.9 (CH_2), 36.2 (CH_2), 30.2 (CH_2), 29.2 (CH_3) and 29.0 (CH_3) [C-1 and 3], 26.6 (CH_2), 21.7 (CH_3), 14.8 (CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 (C, C-3′), 137.9 (C), 136.4 (C), 117.5 (CH, C-2′), 74.3 (C, C-2), 53.7 (CH-7′), 38.9 (CH, C-6′), 36.7 (CH_2), 35.9 (CH_2), 29.8 (CH_2), 28.9 (CH_3) and 28.8 (CH_3) [C-1 and 3], 26.4 (CH_2), 21.5 (CH_3), 14.8 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{23}$ (M−OH): 203.1800, found: 203.1803.

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