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Total syntheses of (±)-α-acorenol, β-acorenol, α-*epi*-acorenol and β-*epi*-acorenol via an Ireland ester Claisen rearrangement and RCM reaction sequence

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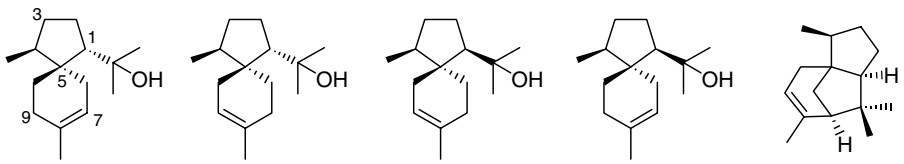
Abstract—Total syntheses of (±)-α- and β-acorenols and (±)-α- and β-*epi*-acorenols, spiro[4.5]decane sesquiterpenes, isolated from the western Australian sandalwood oil, have been accomplished employing a combination of Ireland ester Claisen rearrangement and RCM reactions for an efficient construction of the spiro[4.5]decane present in acoranes.

Australian sandalwood oil obtained from *Santalum spicatum* wood, butts and roots is considered very important in the perfumery industry due to its interesting odour properties. Recently,[1] Braun and co-workers reported the isolation of α-acorenol **1**, β-acorenol **2**, α-*epi*-acorenol **3** and β-*epi*-acorenol **4** from the western Australian sandalwood oil. Although, α-acorenol **1** and β-acorenol **2** have been known since 1970, and were first isolated from the wood of *Juniperus rigida*[2] and subsequently from various essential oils, this isolation of α-*epi*-acorenol **3** and β-*epi*-acorenol **4** is the first from natural sources. The structures of the *epi*-acorenols **3** and **4** were established from their spectral data in comparison with those of α- and β-acorenols **1** and **2**. Acoranes were the first sesquiterpene natural products to be isolated from Nature containing a spiro[4.5]decane carbon framework.[3] α-Acorenol **1** was proved to be the biogenetic precursor of the tricyclic sesquiterpenes cedranoids, for example, α-cedrene **5**. In contrast to other acoranes, so far only three research groups have reported the synthesis of α- and β-acorenols **1** and **2**.[4] Herein, we describe the efficient syntheses of all four acorenols **1**–**4**, starting from cyclohexane-1,4-dione **6** employing a combination of an Ireland ester Claisen rearrangement and ring-closing metathesis (RCM) as key steps for the efficient construction of the spiro[4.5]decane.

As depicted in Scheme 1, it was contemplated that the RCM reaction[5] of diene **7** would generate spiro[4.5]decane system **8**, which would be further elaborated into the acorenols and *epi*-acorenols **1**–**4**. The Ireland ester Claisen rearrangement[6] of pentenoate **9** was considered appropriate for the generation of diene **7** containing the quaternary carbon atom. Ester **9** could be obtained from cyclohexane-1,4-dione **6** via ester **10**.

The synthetic sequence starting from cyclohexane-1,4-dione **6** is depicted in Scheme 2. A controlled Horner–Wadsworth–Emmons reaction of dione **6** with sodium hydride and triethyl phosphonopropionate generated



1 (α-acorenol) **2** (β-acorenol) **3** (α-*epi*-acorenol) **4** (β-*epi*-acorenol) **5** (α-cedrene)

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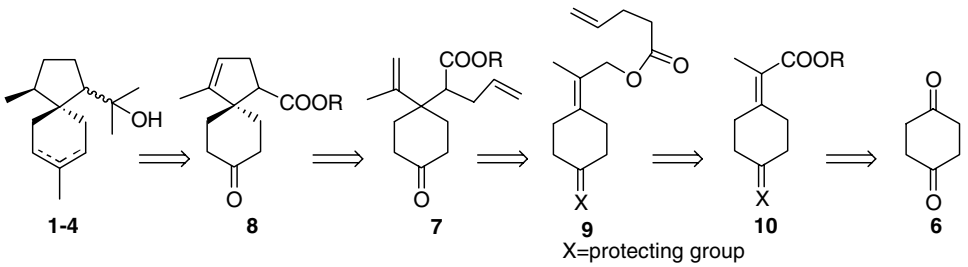
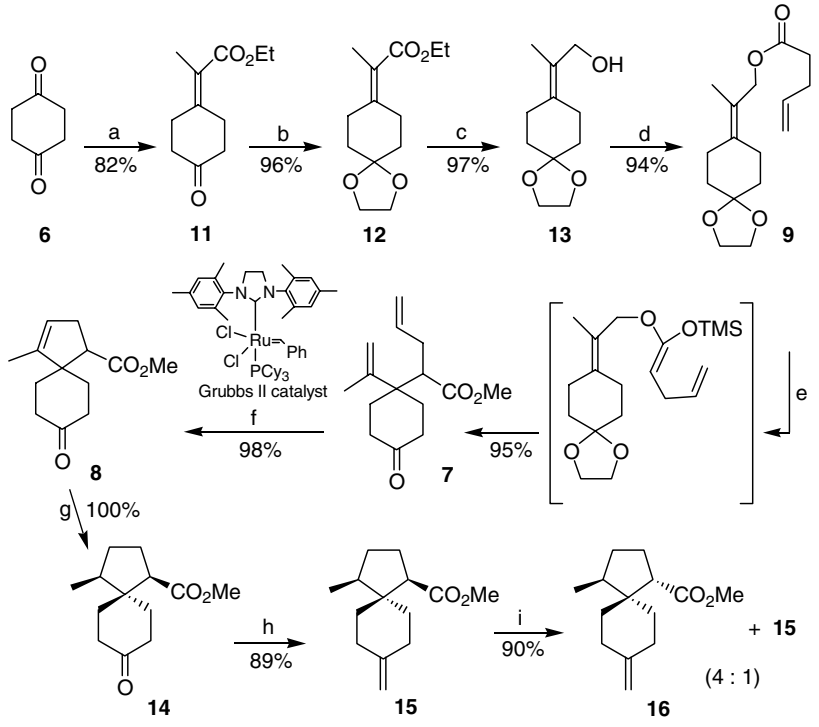
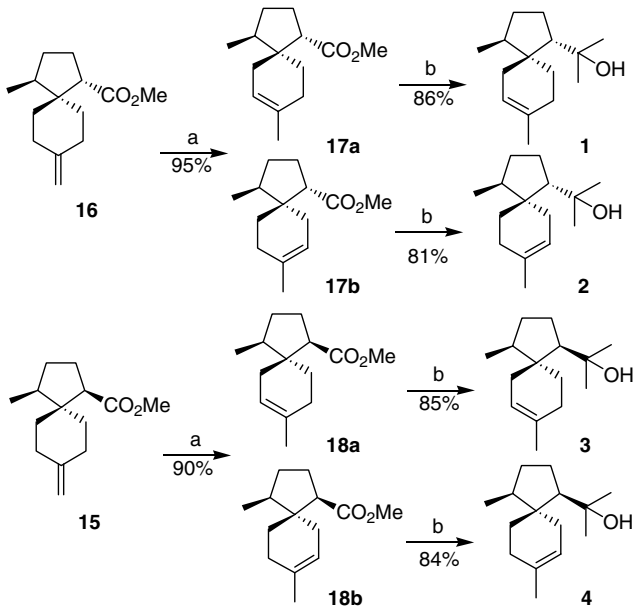


Scheme 1.



Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, 0 °C → rt, 3 h; (b) $(CH_2OH)_2$, PTSA, C_6H_6, reflux (Dean-Stark), 4 h; (c) $LiAlH_4$, Et_2O, −70 → −50 °C, 2 h; (d) DCC, DMAP, $CH_2{=}CH(CH_2)_2CO_2H$, CH_2Cl_2, rt, 5 h; (e) (i) LDA, THF, TMSCl, NEt_3, −70 °C, 30 min; rt, 4 h; reflux, 5 h; (ii) dil. HCl, 40 min; (iii) CH_2N_2, Et_2O, 0 °C, 30 min; (f) Grubbs′ II catalyst (3 mol %), C_6H_6, reflux, 3 h; (g) 10% Pd/C, H_2 (1 atm.), MeOH, rt, 1 h; (h) $Ph_3P^+CH_3Br^-$, $^tAmO^-K^+$, C_6H_6, rt, 1 h; (i) NaOMe, MeOH, reflux, 8 h.

keto ester **11** in 82% yield. Prior to the reduction of the α,β-unsaturated ester in keto ester **11** to an allyl alcohol, the keto group was protected as an ethylene ketal by refluxing with 1,2-ethanediol and a catalytic amount of *p*-toluenesulfonic acid (PTSA) in benzene using a Dean-Stark trap to furnish ketal ester **12** in 96% yield. Regioselective reduction with lithium aluminum hydride (LAH) in ether at low temperature transformed ester **12** into allyl alcohol **13** in 97% yield. Allyl alcohol **13** was then coupled with pent-4-enoic acid using dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-dimethylaminopyridine (DMAP) in methylene chloride to generate the Ireland-Claisen rearrangement precursor ester **9** in 94% yield. Generation of the TMS enol ether of ester **9** with LDA, trimethylsilyl chloride and triethylamine in THF at −70 °C followed by refluxing the reaction mixture for 5 h resulted in the Ireland ester Claisen rearrangement. Hydrolysis of the reaction mixture with dilute hydrochloric acid followed by esterification with ethereal diazomethane furnished keto ester **7** in 95% yield, whose structure was deduced from its spectral data.[7] RCM reaction of diene **7** with 3 mol % of Grubbs' second generation catalyst in refluxing benzene for 3 h cleanly furnished spiro compound **8** in 98% yield, whose structure was deduced from its spectral data.[7] Before introducing the methyl group into the cyclohexane ring, the olefin in the cyclopentene moiety in keto ester **8** was hydrogenated in a highly stereoselective manner in methanol at one atmosphere pressure of hydrogen by employing 10% palladium over charcoal as the catalyst to generate *cis*-ester **14** in quantitative yield. Wittig methylenation of keto ester **14** with methylenetriphenylphosphorane in benzene at room temperature furnished ester **15** in 89% yield. For the generation of a precursor, which was suitable for the synthesis of α- and β-acorenols **1** and **2**, the ester group in **15** was equilibrated in refluxing methanol with sodium methoxide to furnish a 1:4 mixture of *cis*- and *trans*-esters **15** and **16** in 90% yield, which were separated by column chromatography on silica gel.[7]



Scheme 3. Reagents and conditions: (a) PTSA, CH_2Cl_2, rt, 6 h; (**17a:17b** 1:1); (**18a:18b** 4:1); (b) MeMgI, Et_2O, rt, 3 h.

The 1,4-*cis*- and *trans*-esters **15** and **16** were then transformed into *epi*-acorenols **3** and **4** and into acorenols **1** and **2**, respectively, in two steps, as shown in Scheme 3. Thus, isomerisation of the olefin in ester **16** with PTSA in methylene chloride at room temperature furnished a 1:1 mixture of esters **17a** and **17b** in 95% yield, which were separated by column chromatography on silica gel. Grignard reaction of esters **17a** and **17b** with an excess of methylmagnesium iodide furnished α-acorenol **1** and β-acorenol **2**, respectively.[7] In a similar manner, PTSA isomerised the olefin in ester **15** to furnish a 4:1 mixture of esters **18a** and **18b** in 90% yield, which were separated by column chromatography on silica gel. Grignard reaction of esters **18a** and **18b** with an excess of methylmagnesium iodide furnished α-*epi*-acorenol **3** and β-*epi*-acorenol **4**, respectively.[7] The structure of α-acorenol **1** was confirmed by comparison with the ^1H and ^{13}C NMR spectra of the natural sample, and similarly the structures of β-acorenol **2**, α-*epi*-acorenol **3** and β-*epi*-acorenol **4** were confirmed by comparing their ^1H NMR spectral data with those of natural samples.[1]

In conclusion, we have accomplished an efficient total syntheses of spiro sesquiterpenes acorenols **1**–**4**. A combination of an Ireland ester Claisen rearrangement and RCM reactions was employed for the efficient construction of spiro[4.5]decane present in the acorenols. In the present sequence, the key precursor of the acorenols, the spiro[4.5]decanecarboxylate **14**, was obtained in an overall yield of 67%, in seven steps starting from cyclohexane-1,4-dione **6**.

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7. Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data for ester **7**: IR (neat): ν_{max}/cm^{-1} 1732, 1717, 1641, 913; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.54 (1H, ddt, *J* 17.7 Hz, 11.1 Hz, 7.5 Hz), 5.17 (1H, s), 4.92 (1H, d, *J* 17.7 Hz), 4.90 (1H, s), 4.88 (1 H, d, *J* 11.1 Hz), 3.53 (3H, s), 2.49 (1H, dd, *J* 11.7 Hz, 2.7 Hz), 2.40–1.50 (10H, m), 1.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 210.3 (C), 173.7 (C), 143.3 (C), 135.6 (CH), 116.9 (CH_2), 116.6 (CH_2), 52.0 (CH), 51.2 (CH_3), 44.4 (C), 37.7 (CH_2), 37.5 (CH_2), 31.6 (2 C, CH_2), 29.1 (CH_2), 19.1 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1467. Found: 273.1459. For the spiroester **8**: IR (neat): ν_{max}/cm^{-1} 1720; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.25 (1H, br s), 3.58 (3H, s), 3.10 (1H, dd, *J* 8.1 Hz and 5.4 Hz), 2.75–2.10 (6H, m), 2.05–1.67 (4H, m), 1.65 (3H, d, *J* 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 209.7 (C), 174.7 (C), 143.8 (C), 123.3 (CH), 51.9 (C), 51.4 (CH), 51.3 (CH_3), 37.9 (CH_2), 37.8 (CH_2), 34.5 (CH_2), 33.7 (CH_2), 28.8 (CH_2), 12.9 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154. Found: 245.1152. For the *cis*-ester **15:** IR (neat): ν_{max}/cm^{-1} 1733, 1650, 887; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.57 (2H, s), 3.64 (3H, s), 2.53 (1H, dd, *J* 8.4 and 7.2 Hz), 2.30–1.30 (13H, m), 0.96 (3H, d, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 176.3 (C), 148.6 (C), 106.9 (CH_2), 53.7 (CH_3), 51.2 (CH), 48.4 (C), 41.6 (CH), 41.1 (CH_2), 32.4 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 30.4 (CH_2), 27.3 (CH_2), 15.7 (CH_3). For the *trans*-ester **16**: IR (neat): ν_{max}/cm^{-1} 1733, 1651, 886; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.57 (2H, s), 3.65 (3H, s), 2.87 (1H, dd, *J* 8.7 and 5.1 Hz), 2.25–1.70 (8H, m), 1.57–1.15 (5H, m), 0.86 (3H, d, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 176.1 (C) 148.8 (C), 107.0 (CH_2), 51.2 (CH_3), 50.1 (CH),

48.4 (C), 40.0 (CH), 33.4 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 31.1 (CH_2), 25.6 (CH_2), 14.6 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{22}O_2Na$ (M+Na): 245.1517. Found: 245.1523. For α-acorenol **1**: IR (neat): ν_{max}/cm^{-1}: 3479; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.40 (1H, br s), 2.35 (1H, d, *J* 17.4 Hz), 2.10–1.05 (12H, m), 1.66 (3H, s), 1.21 (6H, s), 0.86 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 135.0 (C), 121.4 (CH), 73.7 (C), 54.9 (CH), 45.1 (C), 41.8 (CH), 31.7 (CH_3), 30.7 (CH_2), 30.3 (CH_2), 29.3 (CH_2), 28.2 (CH_3), 28.1 (CH_2), 26.2 (CH_2), 23.5 (CH_3), 15.1 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{26}ONa$ (M+Na): 245.1881. Found: 245.1880. For β-acorenol **2**: IR (neat): ν_{max}/cm^{-1} 3459; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.31 (1H, br s), 2.35 (1H, d, *J* 16.8 Hz), 2.20–1.05 (12H, m), 1.60 (3H, s), 1.31 (3H, s), 1.25 (3H, s), 0.83 (3H, d, *J* 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 133.3 (C), 121.8 (CH), 73.8 (C), 57.6 (CH), 44.5 (C), 41.1 (CH), 33.6 (CH_2), 31.9 (CH_2), 31.2 (CH_3), 30.7 (CH_3), 30.2 (CH_2), 27.8 (CH_2), 26.1 (CH_2), 23.5 (CH_3), 18.2 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{26}ONa$ (M+Na): 245.1881. Found: 245.1877. For α-*epi*-acorenol **3**: IR (neat): ν_{max}/cm^{-1} 3468; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.39 (1H, br s), 2.46 (1H, d, *J* 17.7 Hz), 2.05–1.49 (10H, m), 1.63 (3H, s), 1.50–1.16 (2H, m), 1.24 (3H, s), 1.23 (3H, s), 0.86 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 133.8 (C), 122.1 (CH), 73.4 (C), 60.5 (CH), 44.6 (C), 44.3 (CH), 37.8 (CH_2), 32.0 (CH_3), 31.5 (CH_2), 29.0 (CH_3), 28.9(CH_2), 27.7 (CH_2), 27.1 (CH_2), 23.5 (CH_3), 17.8 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{26}ONa$ (M+Na): 245.1881. Found: 245.1885. For β-*epi*-acorenol **4**: IR (neat): ν_{max}/cm^{-1} 3466; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.28 (1H, br s), 2.20–1.50 (12H, m), 1.62 (3H, s), 1.28 (3H, s), 1.23 (3H, s), 0.93 (3H, d, *J* 7.2 Hz), 0.88–0.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 133.7 (C), 121.3 (CH), 73.4 (C), 61.3 (CH), 44.9 (C), 42.7 (CH), 40.9 (CH_2), 31.5 (CH_3), 30.8 (CH_2), 29.8 (CH_3), 29.2 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 23.5 (CH_3), 16.0 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{26}ONa$ (M+Na): 245.1881. Found: 245.1870.