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Enantiospecific first total synthesis and confirmation of the relative and absolute stereostructure of isocalamusenone

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ABSTRACT

The enantiospecific total synthesis of two epimers of the sesquiterpene isocalamusenone has been accomplished starting from the readily available monoterpene (*R*)-limonene, which of the natural product established the stereostructure and the absolute configuration.

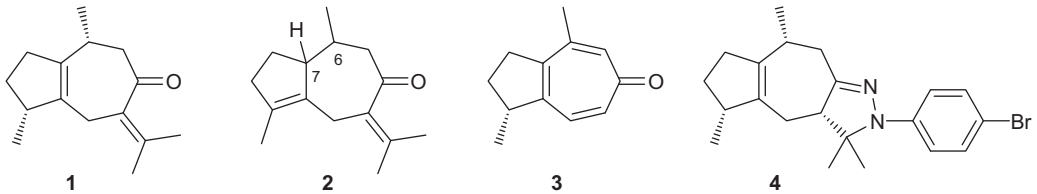
1. Introduction

Of the various bicyclo[5.3.0]decane containing sesquiterpenes, guaianes constitute as a large group and are present in plants and liverwort, as well as marine sources.[1] Sweet flag oil (*Acorus calamus*) is a rich source of oxygenated sesquiterpenes of great structural variety and a large number of sesquiterpenes have been isolated from the plant *Acorus calamus* L that grows in Japan. In 1979, Rohr et al. reported[2] the isolation of two sesquiterpene ketones **1** and **2**, in addition to tropone **3** from the high boiling fractions of sweet flag oil in 3.5% and 0.2% yield, respectively. The major component of the essential oil was named as calamusenone **1** and the minor as isocalamusenone **2**. The structure of calamusenone **1** was deduced on the basis of spectroscopic data (UV, IR, mass, ^{1}H and ^{13}C NMR) and confirmed by a single crystal X-ray diffraction analysis of the *p*-bromophenylpyrazoline derivative **4**. Calamusenone **1** was found to exhibit antinociceptive and antimicrobial activities.[3] The structure of isocalamusenone **2** was assigned on the basis of spectroscopic data (UV, IR, MS, ^{1}H and ^{13}C NMR) in combination with double resonance experiments and europium reagent induced NMR shift analysis. However, the stereochemistry of the secondary methyl group in isocalamusenone **2** was inconclusive.

So far there are no reports in the literature on the synthesis of isocalamusenone **2** and as a result the stereochemistry of the secondary methyl group is yet to be established. In continuation of our interest in the synthesis of natural products[4] starting from the readily available monoterpene (*R*)-limonene **5**, and in order to establish the relative stereostructure as well as the absolute configuration of the natural product, the enantiospecific first total synthesis of both the C-6 epimers of isocalamusenone **2a** and **2b** has been investigated.

2. Results and discussion

Since there are no reports in the literature on either the synthesis or the relative (stereochemistry at C-6 was not assigned) as well as the absolute configuration of isocalamusenone **2**, we decided to develop a synthesis of isocalamusenones **2a** and **2b** with a defined stereochemistry at the C-6 position in order to establish the relative as well as the absolute stereostructure of the natural product. It was thought (Scheme 1) that the synthesis of isomeric isocalamusenones **2a** and **2b** could be achieved starting from the C-6 epimeric hydroxy ketones **6a** and **6b**, whose synthesis from (*R*)-limonene **5** had been recently accomplished in our laboratory, enroute to the aciphyllenes,[4f] employing a type II carbonyl ene reaction[5] of aldehyde **7** as the key step.



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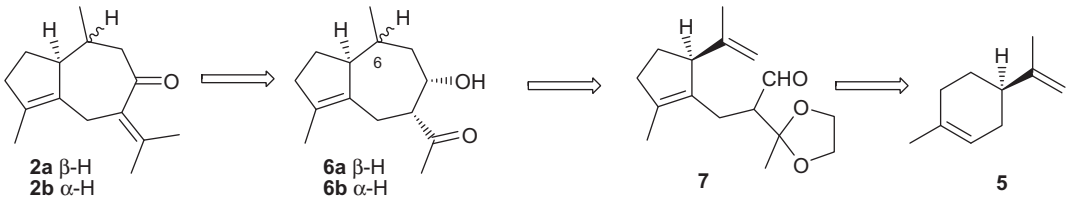
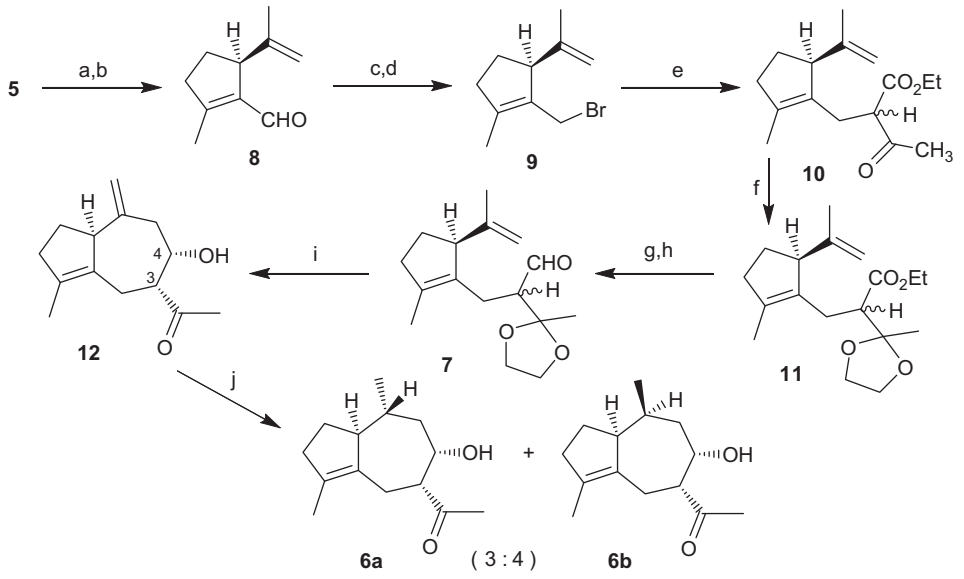
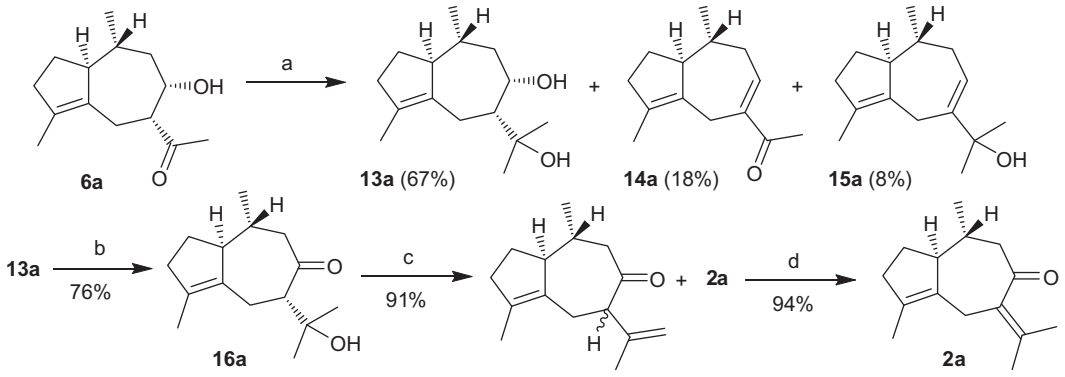


Scheme 1.



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.

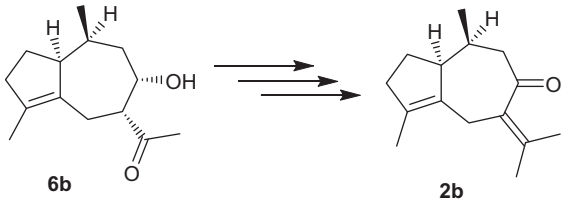


Scheme 3. Reagents and conditions: (a) MeMgCl, THF, rt, 4 h; (b) PCC, NaOAc, CH_2Cl_2, rt, 2 h; (c) MsCl, NEt_3, CH_2Cl_2, rt, 4 h; (d) DBU, CH_2Cl_2, rt, 7 h.

The synthetic sequence is depicted in Schemes 2 and 3. To begin with, the synthesis of the hydroxy ketones **6a** and **6b** was carried out by employing the methodology developed in our laboratory.[4f] Thus, a two step conversion of (*R*)-limonene **5** generated aldehyde **8**. Reduction of the aldehyde **8** followed by its conversion to bromide **9** and its coupling with ethyl acetoacetate generated ketoester **10**. Protection of the ketone as the corresponding ketal **11**, followed by a two step conversion of the ester transformed keto ester **10** into aldehyde **7**. A boron trifluoride diethyl etherate mediated type II carbonyl ene reaction of aldehyde **7** gave the key precursor hydroxy ketone **12** in a stereoselective manner. Stereoselective hydrogenation of the exomethylene group in **12** using Wilkinson catalyst generated a mixture of the hydroxy ketones **6a** and **6b**. The stereochemistry of the secondary methyl group as well as the other stereogenic centers in **6a** and **6b** was confirmed by the single crystal X-ray diffraction analysis[4f] of the minor isomer **6a**.

First the conversion of hydroxy ketone **6a** into enone **2a** was carried out, which required oxidation of the secondary alcohol, the introduction of the fifteenth carbon atom, and the generation of the second olefin (Scheme 3). To avoid the regiochemical problems, the fifteenth carbon atom was introduced by a Grignard reaction. Thus, the reaction of the hydroxy ketone **6a** with an excess of methylmagnesium chloride in anhydrous THF furnished diol **13a** in 67% yield, along with the by-products enone **14a** (18%) and the ter-

tiary alcohol **15a** (8%), whose structures were deduced from their spectroscopic data. Oxidation of the secondary alcohol in diol **13a** using pyridinium chlorochromate (PCC) and sodium acetate in methylene chloride gave hydroxy ketone **16a** in 76% yield. Dehydration of the β-hydroxy ketone **16a** with an excess of methanesulfonyl chloride and triethylamine in methylene chloride furnished a mixture of olefinic ketones, which upon isomerisation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at room temperature gave enone **2a** in 94% yield, whose structure was established from its spectroscopic data. Comparison of the ^{1}H and ^{13}C NMR spectroscopic data and the specific rotation of **2a** with those reported for natural isocalamusenone differed, suggesting that it is epi-isocalamusenone and the natural product might have an opposite stereochemistry at one of the two stereocentres.



The same set of reactions was carried out on the epimeric hydroxy ketone **6b**. Accordingly, the reaction of the hydroxy ketone **6b** with an excess of methylmagnesium chloride in anhydrous THF furnished diol **13b** in 62% yield, as well as enone **14b** (16%) and the tertiary alcohol **15b** (9%). Oxidation of diol **13b** in methylene chloride with PCC and sodium acetate at room temperature furnished the hydroxy ketone **16b** in 76% yield. Dehydration of the β-hydroxy ketone **16b** with an excess of methanesulfonyl chloride and triethylamine in methylene chloride, followed by isomerisation with DBU furnished isocalamusenone **2b** in 95% yield. The synthetic sample **2b** exhibited ^{1}H and ^{13}C spectral data identical to those of the natural isocalamusenone, confirming its relative configuration. However, the sign of the specific rotation of the synthetic isocalamusenone **2b**, $[\alpha]_D^{24} = +176.2$ (*c* 0.5, $CHCl_3$), was found to be opposite to that of natural isocalamusenone, {lit.[2] $[\alpha]_D^{22} = -178$ (*c* 1.02, $CHCl_3$)}, thus establishing the absolute configuration of natural isocalamusenone.

3. Conclusion

The first enantioselective total synthesis of *ent*-isocalamusenone **2b** and *epi*-isocalamusenone **2a** has been accomplished. The present sequence establishes the configuration of natural isocalamusenone as (6*S*,7*S*)-3-isopropylidine-6,10-dimethylbicyclo[5.3.0]-dec-1(10)-en-4-one **2b**.

4. Experimental

4.1. General

IR spectra were recorded on 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, using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent. 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 the spots was accomplished by exposure to iodine vapor. Acme's silica gel (100–200 mesh) was used for column chromatography.

4.2. (3*R*,4*S*,6*R*,7*S*)-6,10-Dimethyl-3-(2-hydroxyprop-2-yl)bicyclo-[5.3.0]dec-1(10)-en-4-ol 13a

To a cold (0 °C), magnetically stirred solution of the hydroxy ketone[4f] **6a** (60 mg, 0.27 mmol) in anhydrous THF (1 mL) was added, drop wise, methylmagnesium chloride (3.0 M in THF, 0.36 mL, 1.08 mmol) and stirred for 4 h at rt. The reaction was quenched with aq NH_4Cl (5 mL) and extracted with ether (3 × 5 mL). The combined organic layer was washed with brine (8 mL) and dried (Na_2SO_4). 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 1-[(6*R*,7*S*)-6,10-dimethylbicyclo[5.3.0]deca-1(10),3-dien-3-yl]ethanone **14a** (10 mg, 18%) as a colorless oil.[4f] $[\alpha]_D^{27} = +17.5$ (*c* 2.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3048, 2952, 2928, 2871, 2841, 1667 (C=O), 1638, 1456, 1376, 1342, 1299, 1260, 1234, 1165, 956, 896; ^{1}H NMR (400 MHz): δ 6.95 (1H, t, *J* 7.3 Hz, H-4′), 3.82 and 2.49 (2H, 2 × d, *J* 14.6 Hz, H-2′), 2.45–2.30 (2H, m), 2.28 (3H, s, CH_3C=O), 2.28–2.00 (5H, m), 1.65 (3H, s, olefinic-CH_3), 1.45–1.20 (2H, m), 1.00 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz): δ 197.3 (C, C=O), 143.6 (C), 143.0 (CH, C-4′), 132.4 (C), 132.0 (C), 58.7 (CH, C-7′), 38.4 (CH, C-6′), 36.0 (CH_2), 35.5 (CH_2), 29.1 (CH_2), 24.9 (CH_3, CH_3C=O), 23.6 (CH_2), 22.4 (CH_3), 14.0 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412. Found: 227.1405.

Further elution of the column with CH_2Cl_2–hexane (1:9) gave the tertiary alcohol 2-[(6*R*,7*S*)-6,10-dimethylbicyclo[5.3.0]deca-1(10),3-dien-3-yl]propan-2-ol **15a** (5 mg, 8%) as a colorless oil. $[\alpha]_D^{27} = -67.5$ (*c* 4.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3378 (OH), 3052, 2969, 2951, 2926, 2870, 2837, 1457, 1374, 1335, 1165, 1138, 948, 890, 854; ^{1}H NMR: δ 5.79 (1H, t, *J* 7.2 Hz, H-4′), 3.16 and 2.66 (2H, 2 × d, *J* 14.6 Hz, H-2′), 2.30–1.95 (6H, m), 1.66 (3H, s, olefinic-CH_3), 1.60–1.20 (2H, m), 1.33 (3H, s) and 1.31 (3H, s) [2 × *tert*-CH_3], 1.30–1.25 (1H, m), 0.92 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR: δ 147.2 (C, C-3′), 133.6 (C), 130.4 (C), 122.2 (CH, C-4′), 73.2 (C, C-2), 58.8 (CH, C-7′), 39.7 (CH, C-6′), 36.1 (CH_2), 34.4 (CH_2), 29.3 (CH_2), 28.7 (CH_3) and 28.6 (CH_3) [C-1 and 3], 26.9 (CH_2), 22.2 (CH_3), 14.3 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{23}$ (M−OH): 203.1800. Found: 203.1795.

Further elution of the column with ethyl acetate–hexane (1:9) yielded the diol **13a** (43 mg, 67%) as a colorless oil. $[\alpha]_D^{27} = +62.8$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3268 (OH), 2952, 2920, 2873, 1461, 1439, 1410, 1372, 1308, 1216, 1147, 1020, 945, 918, 823; ^{1}H NMR: δ 4.45–4.30 (1H, m, H-4), 3.30 (1H, br s, H-7), 2.68 (1H, br s), 2.52 (1H, d, *J* 14.5 Hz), 2.30–1.95 (5H, m), 1.89 (1H, dd, *J* 13.7 and 7.4 Hz), 1.80–1.60 (1H, m), 1.65 (3H, s, olefinic-CH_3), 1.38 (3H, s) and 1.31 (3H, s) [2 × *tert*-CH_3], 1.40–1.15 (3H, m), 0.92 (3H, d, *J* 6.7 Hz, *sec*-CH_3); ^{13}C NMR: δ 139.2 (C), 130.1 (C), 73.7 (C, C-2′), 71.5 (CH, C-4), 58.7 (CH, C-7), 49.7 (CH, C-3), 43.8 (CH_2), 36.6 (CH_2), 34.8 (CH, C-6), 29.9 (CH_2), 29.0 (CH_3) and 28.7 (CH_3) [C-1′ and 3′], 22.3 (CH_3), 21.0 (CH_2), 13.9 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{26}O_2Na$ (M+Na): 261.1830. Found: 261.1824.

4.3. (3*S*,6*R*,7*S*)-6,10-Dimethyl-3-(2-hydroxyprop-2-yl)bicyclo[5.3.0]dec-1(10)-en-4-one 16a

To a suspension of PCC (215 mg, 1 mmol) and NaOAc (123 mg, 1.5 mmol) in dry CH_2Cl_2 (0.5 mL) was added a solution of diol

13a (42 mg, 0.18 mmol) in CH_2Cl_2 (0.5 mL) and stirred vigorously for 2 h at rt. The reaction mixture was then 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 ethyl acetate–hexane (1:19) as eluent furnished the hydroxy ketone **16a** (32 mg, 76%) as a colorless oil. $[\alpha]_D^{26} = -81.1$ (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3453 (OH), 2962, 2931, 2871, 2845, 1689 (C=O), 1461, 1439, 1376, 1328, 1268, 1164, 1138, 943; ^1H NMR: δ 3.13 (1H, br s, H-7), 2.77 (1H, t, *J* 12.0 Hz, H-3), 2.69 (1H, dd, *J* 13.7 and 3.9 Hz), 2.40–2.00 (7H, m), 1.63 (3H, s, olefinic-CH_3), 1.60–1.40 (2H, m), 1.28 (3H, s) and 1.22 (3H, s) [H-1′ and 3′], 1.04 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR: δ 216.8 (C, C=O), 135.0 (C, C-1), 134.9 (C, C-10), 72.0 (C, C-2′), 61.1 (CH, C-3), 57.5 (CH, C-7), 50.8 (CH_2, C-5), 38.5 (CH, C-6), 36.5 (CH_2, C-2), 28.7 (CH_3) and 26.4 (CH_3) [C-1′ and 3′], 28.2 (CH_2), 25.2 (CH_2), 22.2 (CH_3), 13.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{24}O_2Na$ (M+Na): 259.1674. Found: 259.1670.

4.4. (6*R*,7*S*)-3-Isopropylidine-6,10-dimethylbicyclo[5.3.0]dec-1(10)-en-4-one 2a

To a cold (0 °C), magnetically stirred solution of the hydroxy ketone **16a** (24 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (2 mL) were added Et_3N (0.14 mL, 1 mmol) and MsCl (0.08 mL, 1 mmol) and stirred for 4 h at rt. 3 M HCl (8 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layer was washed with brine (8 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 a 2:1:1 mixture of three isomeric olefinic ketones (20 mg, 91%) as a colorless oil. IR (neat): ν_{max}/cm^{-1} 2956, 2929, 2872, 1703 (C=O), 1682, 1642, 1457, 1440, 1376, 1332, 1270, 1122, 1028, 893 (C=CH_2); ^1H NMR: δ 4.91 (s) and 4.84 (s) [C=CH_2], 3.42 (d, *J* 15.2 Hz), 3.00–2.50 (m), 2.45–1.95 (m), 1.95 (s), 1.86 (s), 1.76 (s), 1.65 (s), 1.61 (s), 1.70–1.20 (m), 1.04 and 1.00 (d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR (peaks due to major isomer): 212.0 (C, C=O), 143.2 (C, *C*=CH_2), 135.5 (C), 134.8 (C), 111.9 (CH_2, *C*=CH_2), 59.2 (CH, C-3), 57.9 (CH, C-7), 47.6 (CH_2), 39.8 (CH), 36.7 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 22.5 (CH_3), 22.1 (CH_3), 13.8 (CH_3).

To a magnetically stirred solution of the mixture of the olefins obtained above (18 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added DBU (5 mg, 0.03 mmol) and stirred for 7 h at rt. Next, 3 M HCl was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 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 CH_2Cl_2–hexane (1:9) as eluent furnished the enone, (−)-*epi*-isocalamusenone **2a** (17 mg, 94%) as a colorless oil. $[\alpha]_D^{28} = -6.7$ (*c* 0.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2954, 2923, 2871, 1680 (C=O), 1619, 1456, 1439, 1374, 1295, 1271, 1218, 1181, 1128, 1022; ^1H NMR ($CDCl_3$): δ 3.44 and 2.70 (2H, 2 × d, *J* 15.1 Hz, H-2), 2.74 (1H, dd, *J* 13.4 and 11.1 Hz) and 2.29 (1H, dd, *J* 13.4 and 1.6 Hz) [H-5], 2.30–2.15 (3H, m), 2.04 (1H, ddd, *J* 12.8, 8.4 and 4.8 Hz), 1.95 (3H, s) and 1.86 (3H, s) [C=C(CH_3)$_2$], 1.63 (3H, s, C_{10}–CH_3), 1.60–1.30 (2H, m), 1.00 (3H, d, *J* 6.7 Hz, *sec*-CH_3); ^{13}C NMR ($CDCl_3$): δ 206.5 (C, C=O), 140.4 (C), 135.1 (C), 133.6 (C), 133.5 (C), 57.9 (CH, C-7), 51.3 (CH_2, C-2), 38.2 (CH, C-6), 36.5 (CH_2, C-5), 28.7 (CH_2), 28.4 (CH_2), 22.8 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 14.1 (CH_3, C_6–CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568. Found: 241.1569.

4.5. (3*R*,4*S*,6*S*,7*S*)-6,10-Dimethyl-3-(2-hydroxyprop-2-yl)bicyclo-[5.3.0]dec-1(10)-en-4-ol 13b

To a cold (0 °C), magnetically stirred solution of hydroxy ketone[4f] **6b** (56 mg, 0.25 mmol) in anhydrous THF (1 mL) was added dropwise methylmagnesium chloride (0.33 mL, 1.0 mmol, 3.0 M in THF) and stirred for 3 h at rt. The reaction was quenched with aq NH_4Cl (5 mL) and extracted with ether (3 × 5 mL). The combined organic layer was washed with brine (8 mL) and dried (Na_2SO_4). 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 1-[(6*S*,7*S*)-6,10-dimethylbicyclo[5.3.0]deca-1(10),3-dien-3-yl]ethanone **14b** (8 mg, 16%) as a colorless oil.[4f] $[\alpha]_D^{26} = +297$ (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2955, 2928, 2877, 2841, 1666 (C=O), 1635, 1440, 1379, 1349, 1258, 1232, 1174, 1019; ^1H NMR (400 MHz): δ 6.77 (1H, br s, H-4′), 3.75 and 2.45 (2H, 2 × d, *J* 16.0 Hz, H-2′), 2.86 (1H, br s, H-7′), 2.40–2.10 (6H, m), 2.28 (3H, s, CH_3C=O), 1.90–1.80 (1H, m), 1.59 (3H, s, olefinic-CH_3), 1.60–1.40 (2H, m), 0.82 (3H, d, *J* 6.9 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz): δ 198.2 (C, C=O), 142.7 (CH, C-4′), 142.2 (C), 133.4 (C), 132.8 (C), 54.5 (CH, C-7′), 36.9 (CH_2), 33.7 (CH, C-6′), 32.8 (CH_2), 25.3 (CH_3, *C*H_3C=O), 24.9 (CH_2), 24.3 (CH_2), 16.5 (CH_3), 13.8 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412. Found: 227.1422.

Further elution of the column with CH_2Cl_2–hexane (1:9) gave tertiary alcohol 2-[(6*S*,7*S*)-6,10-dimethylbicyclo[5.3.0]deca-1(10),3-dien-3-yl]propan-2-ol **15b** (5 mg, 9%) as a colorless oil. $[\alpha]_D^{28} = +28.6$ (*c* 0.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3394 (OH), 2969, 2951, 2926, 2870, 2837, 1458, 1374, 1135, 947, 890, 853; ^1H NMR: δ 5.61 (1H, t, *J* 7.1 Hz, H-4′), 3.14 and 2.60 (2H, 2 × d, *J* 14.6 Hz, H-2′), 3.01 (1H, br s, H-7′), 2.35–2.05 (5H, m), 2.00–1.65 (2H, m), 1.64 (3H, s, olefinic-CH_3), 1.45–1.25 (3H, m), 1.35 (3H, s) and 1.34 (3H, s) [H-1 and 3], 0.78 (3H, d, *J* 6.3 Hz, *sec*-CH_3); ^{13}C NMR: δ 146.0 (C, C-3′), 134.1 (C, C-1′), 131.7 (C, C-10′), 120.9 (CH, C-4′), 73.6 (C, C-2), 55.0 (CH, C-7′), 37.1 (CH_2), 34.0 (CH, C-6′), 31.9 (CH_2), 29.1 (CH_3) and 28.9 (CH_3) [C-1 and 3], 27.2 (CH_2), 24.9 (CH_2), 16.3 (CH_3), 14.1 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{23}$ (M−OH): 203.1800. Found: 203.1806.

Further elution of the column with ethyl acetate–hexane (1:9) furnished diol **13b** (37 mg, 62%) as a colorless oil. $[\alpha]_D^{20} = +15.8$ (*c* 2.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3438 (OH), 2962, 2894, 2850, 1464, 1379, 1139, 1112, 1054, 1012, 990, 875; ^1H NMR δ 4.71 (1H, d, *J* 8.4 Hz, H-4), 3.18 (1H, br s), 2.65 (1H, d, *J* 15.5 Hz), 2.42 (1H, td, *J* 11.8 and 8.4 Hz), 2.30–1.85 (7H, m), 1.66 (3H, s, olefinic-CH_3), 1.35–1.15 (3H, m), 1.30 (3H, s) and 1.21 (3H, s) [H-1′ and 3′], 0.87 (3H, d, *J* 7.0 Hz, *sec*-CH_3); ^{13}C NMR: δ 132.9 (C, C-1), 131.7 (C, C-10′), 75.5 (CH, C-4), 73.2 (C, C-2′), 47.8 (CH), 40.7 (CH), 37.5 (CH_2), 34.9 (CH_2), 30.8 (CH_2), 29.7 (CH_3) and 28.9 (CH_3) [C-1′ and 3′], 20.2 (CH_2), 13.6 (CH_3), 13.5 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{26}O_2Na$ (M+Na): 261.1830. Found: 261.1831.

4.6. (3*S*,6*S*,7*S*)-6,10-Dimethyl-3-(2-hydroxyprop-2-yl)bicyclo-[5.3.0]dec-1(10)-en-4-one 16b

To a suspension of PCC (215 mg, 1 mmol) and NaOAc (123 mg, 1.5 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of diol **13b** (36 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) and stirred vigorously for 3 h at rt. The reaction mixture was then 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 ethyl acetate–hexane (1:19) as eluent furnished hydroxyketone **16b** (27 mg, 76%) as a colorless oil. $[\alpha]_D^{20} = -79.5$ (*c* 0.9, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3462 (OH), 2965, 2930, 2884, 2848, 1685 (C=O), 1460, 1439, 1381, 1251, 1222, 1166, 1140, 1099; ^1H NMR: δ 3.97 (1H, s), 2.85 (1H, br s), 2.68 (1H, dd, *J* 13.7 and 4.0 Hz, H-3), 2.56 (1H, dd, *J* 12.1 and 2.2 Hz) and 2.43 (1H, dd, *J* 12.1 and 8.0 Hz) [H-5], 2.40–2.10 (3H, m), 2.10–1.80 (2H, m), 1.67 (3H, s, olefinic-CH_3), 1.70–1.50 (2H, m), 1.28 (3H, s) and 1.19 (3H, s) [H-1′ and 3′], 0.82 (3H, d, *J* 7.1 Hz, *sec*-CH_3); ^{13}C NMR: δ 217.8 (C, C=O), 135.6 (C), 133.8 (C), 72.4 (C, C-2′), 62.1 (CH, C-3), 54.2 (CH, C-7), 49.5 (CH_2, C-5), 37.4 (CH_2, C-2), 33.3 (CH, C-6), 28.8

(CH_3), 26.0 (CH_2), 25.8 (CH_3), 25.2 (CH_2), 15.3 (CH_3, C_{10}–CH_3), 13.7 (CH_3, C_6–CH_3).

4.7. (6*S*,7*S*)-3-Isopropylidine-6,10-dimethylbicyclo[5.3.0]dec-1(10)-en-4-one 2b (isocalamusenone)

To a cold (0 °C), magnetically stirred solution of the hydroxy ketone **16b** (27 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) were added Et_3N (0.15 mL, 1.1 mmol) and MsCl (0.09 mL, 1.1 mmol) and stirred for 4 h at rt. Next, 3 M HCl (7 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (8 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 a mixture of three olefins (22 mg, 90%) as a colorless oil. IR (neat): ν_{max}/cm^{-1} 2957, 2929, 2882, 2850, 1699 (C=O), 1457, 1377, 1249, 1137, 1097, 1020, 891; ^{1}H NMR: δ 4.87 (s) and 4.77 (s) [C=CH_2], 3.12 (br d, *J* 16.3 Hz), 3.00–2.00 (m), 2.05–1.25 (m), 1.75 (s), 1.73 (s), 1.72 (s), 1.65 (s), 1.63 (s), 1.58 (s), 1.70–1.20 (m), 0.87, 0.80 and 0.79 (d, *J* 6.8 Hz, *sec*-CH_3).

To a magnetically stirred solution of the mixture of the olefins, obtained above (20 mg, 0.08 mmol), in dry CH_2Cl_2 (0.5 mL) was added DBU (6 mg, 0.03 mmol) and stirred for 7 h at rt. Next, 3 M HCl was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 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 CH_2Cl_2–hexane (1:9) as eluent furnished (+)-isocalamusenone **2b** (19 mg, 95%) as a colorless oil. $[\alpha]_D^{24} = +176.2$ (*c* 1.02, $CHCl_3$)}; IR (neat): ν_{max}/cm^{-1} 2955, 2927, 2876, 2842, 1678 (C=O), 1607, 1454, 1377, 1299, 1258, 1209, 1144, 1024; ^{1}H NMR ($CDCl_3$): δ 3.18 and 2.77 (2H, 2 × d, *J* 16.2 Hz, H-2), 2.85–2.75 (1H, m), 2.50–2.40 (1H, m), 2.32 (1H, dd, *J* 16.7 and 11.1 Hz), 2.25–2.10 (3H, m), 1.85–1.70 (1H, m), 1.74 (3H, s) and 1.73 (3H, s) [C=C(CH_3)$_2$], 1.58 (3H, s, C_{10}–CH_3), 1.45–1.35 (1H, 3), 0.87 (3H, d, *J* 6.8 Hz, *sec*-CH_3); ^{13}C NMR ($CDCl_3$): δ 210.0 (C, C=O), 135.8 (C), 135.7 (C), 134.0 (C), 132.8 (C), 53.7 (CH, C-7), 47.5 (CH_2, C-2), 37.1 (CH_2, C-5), 31.0 (CH, C-6), 27.5 (CH_2), 23.4 (CH_2), 22.0 (CH_3), 20.6 (CH_3), 16.8 (CH_3), 14.1 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568. Found: 241.1564.

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