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Enantioselective total synthesis and assignment of the absolute configuration of (+)-laurokamurene B

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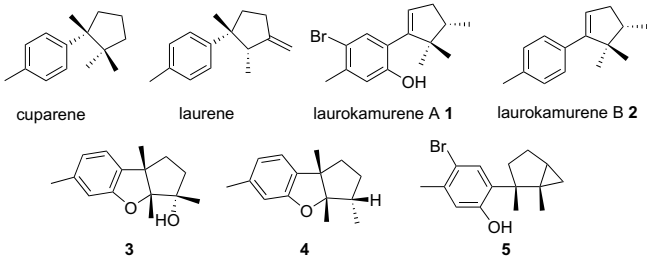
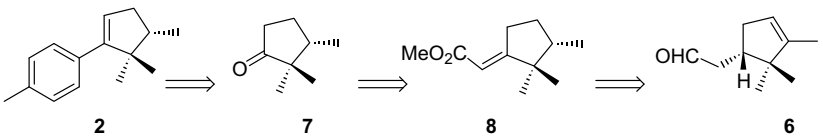
Abstract—The first enantioselective total synthesis of the rearranged aromatic sesquiterpene (+)-laurokamurene B, isolated from the Chinese red algae *Laurencia okamurai* Yamada, has been accomplished starting from (*S*)-campholenaldehyde, establishing the absolute configuration of laurokamurenes.

1. Introduction

Over the last four decades, a significant number of cuparene and laurene sesquiterpenoids have been isolated from the genus *Laurencia*, which are characteristic of the genus.[1] Recently, Mao and Guo in the course of their investigations on the isolation of biologically active compounds from Chinese marine organisms reported the isolation of two new aromatic sesquiterpenes laurokamurenes A and B **1** and **2**, containing a new rearranged laurane skeleton, along with known laurene sesquiterpenes **3**–**5**.[2] The structures of laurokamurenes A and B **1** and **2** were established on the basis of 1 and 2D NMR spectra, however, their absolute configuration was not assigned. A large number of brominated and non-brominated sesquiterpenes, which can be classified into more than 20 sesquiterpenoid skeletons, are known from the red algae of the genus *Laurencia*. However, in most cases, three methyls in the aliphatic portion were located at either positions 1,2,3 (laurene type) or 1,2,2 (cuparene type).[3] Laurokamurenes **1** and **2** were the first members of a new class of sesquiterpenes with three methyls in the aliphatic ring arranged in a 2,2,3 fashion.



The presence of a new sesquiterpene carbon framework prompted us to investigate the synthesis of laurokamurene B **2**. Recently,[4] we have accomplished the first total synthesis of laurokamurene B **2** employing a combination of an Ireland–Claisen rearrangement and RCM reactions establishing the structure of the marine natural product. Herein, we report the first enantioselective synthesis of (+)-laurokamurene B **2** establishing the absolute configuration of laurokamurenes. It was contemplated that the three methyl groups present on the vicinal carbons of campholenaldehyde **6** could be exploited for the enantioselective generation of laurokamurenes via 2,2,3-trimethylcyclopentanone **7** and the α,β-unsaturated ester **8** (Scheme 1).



Scheme 1.

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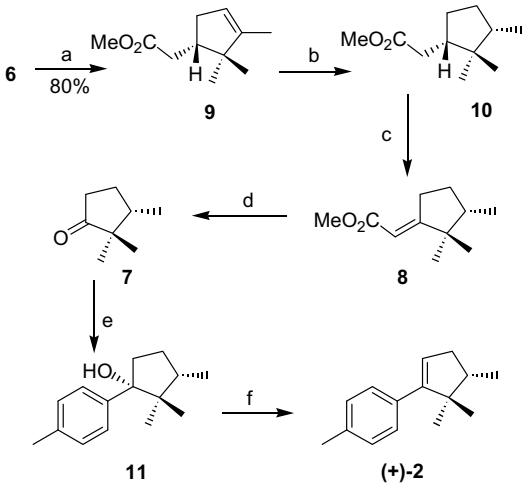
2. Results and discussion

The synthetic sequence is depicted in Scheme 2. The requisite stereogenic centre of the laurokamurenes has been created by stereoselective hydrogenation. Thus, oxidation of campholenaldehyde **6** with Jones' reagent followed by esterification of the resultant campholenic acid,[5] generated methyl campholenate **9**. Hydrogenation of campholenate **9** in hexane with 10% palladium over carbon as the catalyst furnished dihydrocampholenate **10** in a stereoselective manner (>95% by NMR) in near quantitative yield. The stereochemistry of the secondary methyl group was assigned on the basis of hydrogenation from the less hindered face. As the NOESY spectrum of ester **10** was inconclusive, the stereochemistry of ester **10** was confirmed by single crystal X-ray diffraction analysis of a crystalline derivative.[6] A selenation–deselenation strategy was employed for the conversion of ester **10** into the α,β-unsaturated ester **8**. Thus, treatment of ester **10** with lithium diisopropylamide in THF followed by treatment of the resultant enolate with phenylselenyl chloride furnished the α-phenylselenylated ester, which on oxidation with 30% hydrogen peroxide in methylene chloride and pyridine furnished the conjugated ester **8** in 79% yield. Ozonolysis of the unsaturated ester **8** in methylene chloride and methanol, followed by reductive workup with dimethyl sulfide generated cyclopentanone **7**,[7] which via a sonochemically accelerated Barbier reaction with lithium and 4-bromotoluene furnished laurokamurenol **11**. Finally, dehydration of the tertiary alcohol **11** with 4-toluenesulfonic acid (PTSA) in methylene chloride furnished (+)-laurokamurene B **2** in 85% yield. Synthetic (+)-laurokamurene B **2** exhibited spectral data (IR and NMR) and specific rotation identical to that reported for the natural product,[2] establishing the absolute configuration of the laurokamurenes.



Scheme 2. Reagents, conditions and yields: (a) (i) Jones reagent, acetone; (ii) CH_2N_2, Et_2O, 92%; (b) 10% Pd/C, H_2, hexane, 97%; (c) (i) LDA, THF; PhSeCl; (ii) H_2O_2, py, CH_2Cl_2, 79%; (d) (i) O_3/O_2, CH_2Cl_2–MeOH; (ii) Me_2S; (e) Li, *p*-MeC_6H_4Br, THF,))), 60% (for 2 steps); (f) PTSA, CH_2Cl_2, 85%.

3. Conclusion

In conclusion, we have accomplished the first enantioselective total synthesis of the sesquiterpene laurokamurene (+)-**2**, starting from (*S*)-campholenaldehyde **6**, and established the absolute configuration of the laurokamurenes containing a new sesquiterpene carbon framework.

4. Experimental

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^1H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) NMR spectra were recorded on JEOL JNM λ-300 and Brucker Avance 400 spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Ozonolysis experiments were carried out using Fischer 502 ozone generator. Hydrogenation reactions were carried out at one atmospheric pressure using a balloon filled with hydrogen.

4.1. Methyl 2-[(1*S*,3*S*)-2,2,3-trimethylcyclopent-1-yl]acetate 10

To a solution of methyl campholenate **9** (1.423 g, 7.82 mmol) in hexane (7 mL) was added activated 10% Pd–C (150 mg) and the reaction mixture was stirred at 1 atm pressure of hydrogen atmosphere (balloon), created by evacuative displacement of air, for 6 h. The reaction mixture was filtered through a short silica gel column to remove the catalyst. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:9) as eluent furnished dihydrocampholenate **10** (1.392 g, 97%) as an oil. $[\alpha]_D^{23} = -9.0$ (*c* 3.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2956, 2927, 2871, 1741, 1466, 1437, 1388, 1367, 1321, 1261, 1194, 1161, 1101, 1018, 802; ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (3H, s, OCH_3), 2.37 (1H, dd, *J* 14.4 and 3.0 Hz) and 2.05 (1H, dd, *J* 14.4 and 10.5 Hz) [H-2], 1.95–1.85 (2H, m), 1.85–1.70 (1H, m), 1.60–1.50 (1H, m), 1.30–1.15 (2H, m), 0.88 (3H, s) and 0.53 (3H, s) [2 × *tert*-CH_3], 0.85 (3H, d, *J* 6.9 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3 + CCl_4$): δ 174.2 (C, OC=O), 51.4 (CH_3, OCH_3), 47.1 (CH, C-1′), 44.8 (CH, C-3′), 42.3 (C, C-2′), 35.4 (CH_2), 30.0 (CH_2), 28.2 (CH_2), 25.4 (CH_3), 14.5 (CH_3), 14.0 (CH_3); HRMS *m*/*z*: (M+H) calcd for $C_{11}H_{21}O_2$, 185.1541; found, 185.1546.

4.2. Methyl 2-[(3*S*)-2,2,3-trimethylcyclopent-1-ylidene]-acetate 8

To a cold (−70 °C), magnetically stirred solution of diisopropylamine (0.62 mL, 4.4 mmol) in anhydrous THF (0.5 mL) was added a solution of ^{n}BuLi (2.4 M in hexane,

1.6 mL, 3.85 mmol) over a period of 5 min and stirred for 20 min at the same temperature. To LDA thus formed was added dropwise a solution of ester **10** (200 mg, 1.1 mmol) in anhydrous THF (2 mL) over a period of 5 min and stirred for 1 h. A solution of PhSeCl (253 mg, 1.32 mmol) in anhydrous THF (1 mL) was added to the reaction mixture and stirred for 1.5 h at the same temperature and then for 10 h at rt. Saturated aq NH_4Cl (10 mL) was added to the reaction mixture and extracted with ether (2×7 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure. The residue was taken in CH_2Cl_2 (2 mL) and 30% aq H_2O_2 (5 mL) and pyridine (0.3 mL) were added, and stirred at ice temperature for 3 h. The reaction mixture was then diluted with water (5 mL) and extracted with CH_2Cl_2 (2×5 mL). The combined organic extract was washed with brine (5 mL) and dried over 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 α,β-unsaturated ester **8** (156 mg, 79%) as an oil. $[\alpha]_D^{24} = -7.5$ (*c* 4.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2956, 2872, 1724, 1652, 1456, 1435, 1388, 1376, 1360, 1234, 1194, 1170, 1026, 896, 862; ^1H NMR (400 MHz, $CDCl_3 + CCl_4$): δ 5.71 (1H, s, H-2), 3.66 (3H, s, OCH_3), 2.52–2.40 (2H, m), 1.80–1.68 (3H, m), 1.30 (3H, s) and 1.07 (3H, s) [$2 \times$ *tert*-CH_3], 0.93 (3H, d, *J* 6.6 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3 + CCl_4$): δ 175.0 (C, OC=O), 165.7 (C, C-1′), 112.2 (CH, C-2), 50.7 (CH_3, OCH_3), 47.3 (CH, C-3′), 44.8 (C, C-2′), 36.0 (CH_2), 30.4 (CH_2), 24.2 (CH_3), 18.8 (CH_3), 13.6 (CH_3); HRMS *m/z*: (M+H) calcd for $C_{11}H_{19}O_2$, 183.1385; found, 183.1385.

4.3. (1*R*,3*S*)-1-(4-Methylphenyl)-2,2,3-trimethylcyclopentan-1-ol 11

Dry ozone in oxygen was passed through a cold (−70 °C) solution of ester **8** (143 mg, 0.79 mmol) and a catalytic amount of $NaHCO_3$ (15 mg) in 1:4 MeOH–CH_2Cl_2 (10 mL) until it turned blue. Excess ozone was purged with oxygen. Me_2S (0.66 mL, 7.9 mmol) was added to the reaction mixture and stirred for 8 h at rt. Water (7 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (2×5 mL). The combined organic extract was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent furnished ketone **7**, which was used without further purification.[7] To a suspension of Li (35 mg, 5.0 mmol) in anhydrous THF (1 mL) in a round bottom flask, placed in an ultrasonic cleaning bath, was added a solution of ketone **7** obtained above, and 4-bromotoluene (0.62 mL, 5.0 mmol) in anhydrous THF (3 mL) and the reaction mixture was sonochemically irradiated for 1 h. The reaction mixture was decanted from excess lithium, and quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ether (2×5 mL). The ether layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:3) as eluent furnished the tertiary alcohol **11** (103 mg, 60% for two steps) as an oil. $[\alpha]_D^{23} = +10.7$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3487, 3025, 2961, 2873, 1512, 1456, 1385, 1368, 1110, 1009, 815; ^1H NMR (400 MHz, $CDCl_3 + CCl_4$): δ 7.28 (2H, d, *J* 8.1 Hz) and 7.08 (2H, d, *J* 8.1 Hz) [Ar-H], 2.33 (3H, s, Ar-CH_3), 2.44–2.26 (1H, m), 2.05–1.70 (3H, m), 1.60–1.50 (2H, m), 0.93 (3H, d, *J* 5.4 Hz, *sec*-CH_3), 0.92 (3H, s) and 0.50 (3H, s) [$2 \times$ *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3 + CCl_4$): δ 143.0 (C), 136.0 (C), 128.1 (2C, CH), 126.6 (2C, CH), 86.0 (C, C-1), 46.6 (C, C-2), 41.2 (CH, C-3), 38.0 (CH_2, C-5), 29.9 (CH_2, C-4), 25.8 (CH_3), 21.0 (CH_3), 17.5 (CH_3), 16.6 (CH_3); HRMS *m/z*: (M+Na) calcd for $C_{15}H_{22}ONa$, 241.1568; found, 241.1576.

4.4. (3*S*)-1-(4-Methylphenyl)-2,2,3-trimethylcyclopentene 2 (laurokamurene B)

To a magnetically stirred solution of tertiary alcohol **11** (18 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added PTSA (10 mg) and stirred for 1.5 h at room temperature. It was then quenched with saturated aq $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (2×2 mL). The CH_2Cl_2 extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished laurokamurene B **2** (14 mg, 85%) as an oil. $[\alpha]_D^{22} = +14.0$ (*c* 1.2, $CHCl_3$) {lit.[2] $[\alpha]_D^{24} = +10.0$ (*c* 0.09, $CHCl_3$)}; IR (neat): ν_{max}/cm^{-1} 3043, 3025, 2958, 2924, 2869, 2835, 1612, 1564, 1510, 1466, 1455, 1384, 1372, 1361, 805; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (2H, d, *J* 8.1 Hz) and 7.07 (2H, d, *J* 8.1 Hz) [Ar-H], 5.67 (1H, br s, H-5), 2.33 (3H, s, Ar-CH_3), 2.45–2.30 (1H, m), 2.03–1.93 (2H, m), 1.08 (3H, s, *tert*-CH_3), 1.00 (3H, d, *J* 6.6 Hz, *sec*-CH_3), 0.97 (3H, s, *tert*-CH_3).

Acknowledgements

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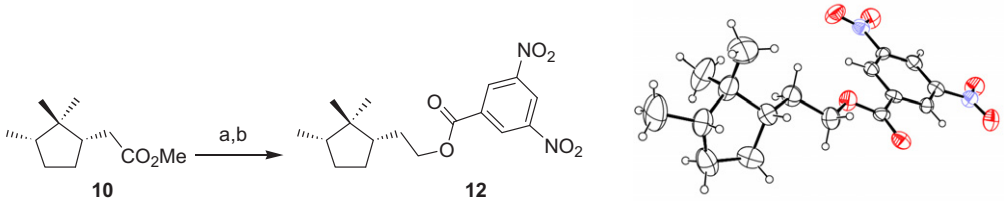
References

1. Martin, J. D.; Darias, J. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. I, pp 151–161.
2. Mao, S.-C.; Guo, Y.-W. *J. Nat. Prod.* **2006**, *69*, 1209–1211.
3. Mao, S.-C.; Guo, Y.-W. *Chin. Tradit. Herb. Drugs* **2004**, *35*, 8–17.
4. Srikrishna, A.; Khan, I. A.; Babu, R. R.; Sajjanshetty, A. *Tetrahedron* **2007**, *63*, 12616–12620.
5. Liu, H.-J.; Chan, W. H. *Can. J. Chem.* **1982**, *60*, 1081–1091.
6. For confirming the structure of ester **10**, it was converted into the crystalline derivative **12**. Thus, the reduction of ester **10** with LAH followed by coupling of the resulting primary alcohol with 3,5-dinitrobenzoic acid using DCC and DMAP furnished dinitrobenzoate **12**, which was recrystallized from methanol at room temperature. Mp 55–57 °C; selected spectra data for ester **12**; $[\alpha]_D^{23} = -10.5$ (*c* 2.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3104, 2956, 2871, 1732, 1630, 1549, 1463, 1345, 1280, 1167, 921, 730; ^1H NMR (400 MHz, $CDCl_3 + CCl_4$): δ 9.21 (1H, t, *J* 2.1 Hz) and 9.14 (2H, d, *J* 2.1 Hz) [Ar-H], 4.50–4.35

(2H, m, OCH_2), 2.10–1.75 (3H, m), 1.70–1.40 (3H, m), 1.35–1.20 (2H, m), 0.87 (3H, d, *J* 6.8 Hz, *sec*-CH_3), 0.93 (3H, s) and 0.58 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3 + CCl_4$): δ 162. 2 (C), 148.7 (2C, C), 134.1 (C), 129.2 (2C, CH), 122.2 (CH), 66.9 (CH_2), 47.6 (CH), 44.9 (CH), 42.6 (C), 30.2 (CH_2), 29.8 (CH_2), 28.2 (CH_2), 25.6 (CH_3), 14.5 (CH_3), 13.9 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{17}H_{22}N_2O_6Na$, 373.1376; found, 373.1381. Crystal data for ester **12**: X-ray data were collected at 273 K on a SMART CCD-BRUKER diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SIR 92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms were refined isotropically. Mol. For. $C_{17}H_{22}N_2O_6$; MW = 350.37; colourless; crystal system: orthorhombic; Space group *P*2(1)2(1)2(1); cell parameters, $a = 8.943(6)$ Å, $b = 10.481(7)$ Å, $c = 40.27(3)$ Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 3774(4)$ Å^3, $Z = 8$, $D_c = 1.233$ g cm^{-3}, $F(000) = 1488$, $\mu = 0.094$ mm^{-1}. Total number of l.s. parameters = 457, $R_1 = 0.1031$ for 3118 $F_0 > 2\sigma(F_0)$ and 0.2118 for all 7022 data. $wR_2 = 0.2595$, GOF = 1.029, restrained GOF = 1.029 for all data. An ORTEP diagram of **12** is depicted below. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 675955).



Reagents and conditions: (a) LAH, Et_2O, rt, 1 h, 95%; (b) DCC, DMAP, 3,5-$(NO_2)_2C_6H_3CO_2H$, CH_2Cl_2, rt, 3 h, 79%.

7. Although attempted purification of ketone **7** was unsuccessful, treatment of the crude mixture with *p*-toluenesulfonylhydrazine followed by purification on a silica gel column furnished the corresponding tosylhydrazone **13**. Selected spectral data for the tosylhydrazone **13**: mp 134–136 °C; $[\alpha]_D^{22} = -2.3$ (*c* 1.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3224, 1333, 1171, 714, 663; ^1H NMR (400 MHz, $CDCl_3 + CCl_4$): δ 7.83 (2H, d, *J* 8.0 Hz), 7.67 (1H, br s), 7.28 (2H, d, *J* 8.0 Hz), 2.43 (3H, s), 2.31 (1H, dd, *J* 18.4 and 8.8 Hz), 2.20–2.00 (1H, m), 1.93–1.80 (1H, m), 1.70–1.58 (1H, m), 1.45–1.28 (1H, m), 1.00 (3H, s), 0.87 (3H, d, *J* 6.8 Hz), 0.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3 + CCl_4$): δ 172.4 (C), 143.3 (C), 135.8 (C), 129.2 (2C, CH), 128.1 (2C, CH), 45.1 (C), 43.4 (CH), 28.9 (CH_2), 26.2 (CH_2), 24.6 (CH_3), 21.6 (CH_3), 20.4 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{15}H_{22}N_2O_2SNa$, 317.1300; found, 317.1290; Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7.53; N, 9.51; S, 10.89. Found: C, 60.91; H, 7.40; N, 9.80; S, 11.14.