Ring closing metathesis/fragmentation route to geometrically defined medium ring cycloalkenes: total synthesis of (±)-Periplanone C

Aleksandar Ivkovic, Radomir Matovic and Radomir N. Saicic*

Faculty of Chemistry, University of Belgrade, Studentski trg 16, P. O. B. 158, 11000 Belgrade, Serbia and Montenegro, and ICTM – Center for chemistry, Njegoseva 12, 11000 Belgrade

Supporting information

General experimental

All reactions were performed in dried glassware under an inert (Ar) atmosphere. Petroleum-ether refers to the fraction with distillation range 70-90 °C. All chromatographic separations¹ were performed on Silica, 10-18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents.² NMR spectra were recorded on a Varian Gemini 200 instrument, ¹H NMR at 200 MHz, ¹³C NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as internal standard, coupling constants (*J*) are in Hz (In addition to listed spectral data, scanned ¹H- and ¹³C NMR spectra of all compounds are can be found at the end of the supporting information). IR spectra were recorded on a Perkin-Elmer 457 grating FT instrument, and are expressed in cm⁻¹. Mass spectra were obtained on a Finnigan ITDS 700 instrument. Microanalyses were performed at the Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau-Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Methyl 4-isopropyl-4-methoxybenzoate 8 (*o*-lithiation/carboxylation of 3-isopropylanisole 9):³ To a refluxing solution of 3-isopropylanisole **9** (14.8 g; 98 mmol) in cyclohexane (100 mL) a solution of *n*-butyllithium in hexane (66.2 mL of 1.48 M solution; 98 mmol) was added dropwise. The reaction mixture was refluxed for 15 h, then allowed to cool to r. t. and transferred via cannula to a vigorously stirred suspension of dry ice (~100 g) in diethyl ether (350 mL). The resulting mixture was extracted with 3% aqueous NaOH (5 x 25 mL), the water phase was separated, acidified with HCl conc. (with cooling) and extracted with dichloromethane (4 x 20 mL). The organic extract was washed with water (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue (13.8 g) was dissolved in a mixture of toluene (40 mL) and methanol (30 mL), *p*-toluenesulfonic acid (1.5 g) was added and the mixture was refluxed in a Dean-Stark apparatus for 8 h with azeotropic removal of water. The mixture was cooled to r. t., concentrated under reduced pressure, dissolved in dichloromethane (100 mL), washed with water (5 x 10 mL), saturated aqueous NaHCO₃ (3 x 10 mL), water (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Distillation under reduced pressure afforded the title compound **9** (9.15 g; 45%).

Physical data for **9**: Colorless liquid; E₂ 147 °C; Anal. calcd. for C₁₂H₁₆O₃ (208.25): C 69.21, H 7.74; found C 69.05, H 7.82; IR (film): 3055, 2963, 1728, 1609, 1461, 1415, 1294, 1251, 1188, 1148, 1090; ¹H NMR: 7.75 (d, *J*=8.2, 1H); 6.87-6.82 (m, 2H); 3.91 (s, 3H); 3.87 (s, 3H); 3.02-2.82 (hept, *J*=6.9, 1H); 1.26 (d, *J*=7.0, 6H). ¹³C NMR: 166.54; 159.37; 155.42; 131.84; 118.11; 117.22; 110.21; 55.83; 51.73; 34.43; 23.55.

Methyl *cis*-1-allyl-*r*-4-isopropyl-6-oxocyclohex-2-enecarboxylate 7 (reductive alkylation of 8):⁴ To a cold (-68 °C) solution of **8** (916 mg; 4.4 mmol) in liquid ammonia (36 mL), THF (18 mL) and *tert*-butanol, was added potassium metal (400 mg; 10.256 mmol) in small pieces, with stirring. After the addition was complete the reaction mixture was stirred for additional 15 min, then LiBr (840 mg; 9.66 mmol) was added in one portion, when the reaction turned from deep blue to yellow. After 15 min allyl bromide (2.12 g; 17.6 mmol) was added, the reaction mixture was stirred 30 min at that temperature, then cooling bath was removed and the ammonia left to evaporate. The reaction mixture was diluted with saturated aqueous NH₄Cl solution (30 mL) and extracted with dichloromethane (3 x 50 mL). The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue (967 mg) was purified by dry-flash chromatography (eluent: petroleum-ether/acetone=985/15) to obtain the corresponding enol ether (methyl 1-allyl-4-isopropyl-2-methoxycyclohexa-2,5-dienecarboxylate; 714 mg). This compound was dissolved in acetone (5 mL),

cooled to 4 °C, and concentrated HCl (1 mL) was added with stirring. After 1 min the reaction mixture was neutralized by careful addition of NaHCO₃ (990 mg), concentrated under reduced pressure, diluted with water and extracted with dichloromethane (3 × 50 mL). The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the crude product (675 mg) by dry-flash chromatography (eluent: petroleum-ether/diethyl ether=96/4) afforded the title compound **7** (408 mg; 39%), followed by the more polar *trans*-isomer (Methyl *cis*-1-allyl-*r*-4-isopropyl-6-oxocyclohex-2-enecarboxylate; 60 mg; 6%).

Alternatively, the transmetallation with LiBr can be omitted, (the rest of the experimental procedure remains identical), which results in an improved overall yield (56%), but with lower stereoselectivity (*cis:trans*=4:1).

Physical data for **7**: pale-yellow oil; Anal. calcd. for C₁₄H₂₀O₃ (236.31): C 71.16, H 8.53; found C 70.93, H 8.74; IR (film): 2960, 2876, 1740, 1722, 1642, 1435, 1233, 1133; ¹H NMR: 5.94 (dd, *J*₁=10.0, *J*₂=2.2, 1H); 5.24 (dd, *J*₁=10.0, *J*₂=2.2, 1H); 5.72-5.55 (m, 1H); 5.13-5.02 (m, 2H); 3.71 (s, 3H); 2.71 (dd, *J*₁=13.7, *J*₂=7.5, 1H); 2.58 (dd, *J*₁=13.7, *J*₂=6.9, 1H); 2.53-2.35 (m, 3H); 1.81-1.68 (m, 1H); 0.94 (d, *J*=2.0, 3H); 0.91 (d, *J*=2.1, 3H); ¹³C NMR: 206.35 (C); 170.87 (C); 132.83 (CH); 132.68 (CH); 127.96 (CH); 118.80 (CH₂); 59.70 (C); 52.52 (CH₃); 43.84 (CH); 41.03 (CH₂); 38.66 (CH₂); 31.84 (CH); 19.12 (CH₃); 18.58 (CH₃).

Methyl *cis*-1-*trans*-6-diallyl-6-hydroxy-*r*-4-isopropylcyclohex-2-enecarboxylate **10 (allylation of **7**):**⁵ To a solution of **7** (194 mg; 0.822 mmol) and allyl bromide (149 mg; 1.23 mmol) in DMF (0.64 mL), was added Zn powder (80 mg; 1.22 mmol) in one portion with stirring. The reaction mixture was stirred for 20 h, then diluted with saturated aqueous NH₄Cl (10 mL) and extracted with dichloromethane (3 × 50 mL). The organic extract was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the crude residue (225 mg) by dry-flash chromatography (eluent: petroleum-ether/ethyl acetate=97/3) afforded the title compound **10** (204 mg; 89%).

Physical data for **10**: Colorless oil; Anal. calcd. for C₁₇H₂₆O₃ (278.39): C 73.34, H 9.41; found C 73.16, H 9.15; IR (film): 3539, 2957, 1725, 1640, 1438, 1218, 1001; ¹H NMR: 6.01-5.60 (m, 4H); 5.21-5.08 (m, 4H); 3.67 (s, 3H); 2.87 (dd, *J*₁=13.9, *J*₂=5.8, 1H); 2.61 (dd, *J*₁=14.2, *J*₂=6.7, 1H); 2.37 (dd, *J*₁=13.9, *J*₂=8.8, 1H); 2.19-2.05 (m, 2H); 1.98 (s, 1H); 1.84-1.66 (m, 2H); 1.57 (dd, *J*₁=13.7, *J*₂=10.0, 1H); 0.94 (s, 3H); 0.91 (s, 3H); ¹³C NMR: 173.96 (C); 134.85 (CH); 133.58 (CH); 131.53 (CH); 126.82 (CH); 119.14 (CH₂); 118.74 (CH₂); 73.48 (C); 55.35 (C); 51.88 (CH₃); 41.54 (CH₂); 38.46 (CH); 36.91 (CH₂); 32.63 (CH₂); 31.45 (CH); 19.50 (CH₃); 19.45 (CH₃).

***trans*-1-Hydroxy-*cis*-6-methoxycarbonyl-*r*-9-isopropyl-bicyclo[4.4.0]deca-3,7-diene **6** (ring closing metathesis of **10**):** Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium **4** (6 mg; 7.2 μmol) was added to a solution of **10** (204 mg; 0.734 mmol) in dichloromethane (3.7 mL) and the resulting mixture was stirred at room temperature for 15 h. A new portion of **4** (12 mg; 14.4 μmol) was added and the mixture was stirred for additional 8 h, when TLC indicated that the reaction was complete. Lead tetraacetate (14.6 mg; 32.9 μmol) was added and the resulting suspension was stirred for 12 h. The reaction mixture was filtered through a plug of silica (1 g), the plug was washed with dichloromethane (4 × 3 mL) and the organic extract concentrated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum-ether/ethyl acetate=95/5) afforded the title compound **6** (148 mg; 81%).

Physical data for **6**: Colorless oil; Anal. calcd. for C₁₅H₂₂O₃ (250.33): C 71.97, H 8.86; found: C 71.79, H 8.97; IR (film): 3525, 2957, 1732, 1648, 1462, 1440, 1373, 1277, 1176, 1030; ¹H NMR: 5.83-5.77 (m, 1H); 5.75-5.58 (m, 2H); 5.48 (dd, *J*₁=10.0, *J*₂=2.2, 1H); 3.61 (s, 3H); 2.79-2.57 (m, 2H); 2.39-1.97 (m, 5H); 1.79-1.63 (m, 2H); 0.91 (d, *J*=5.5, 3H); 0.87 (d, *J*=5.5, 3H); ¹³C NMR: 132.94 (CH); 127.94 (CH); 125.85 (CH); 125.16 (CH); 70.43 (C); 51.88 (CH₃); 49.80 (C); 38.98 (CH); 37.03 (CH₂); 33.26 (CH₂); 31.48 (CH); 31.45 (CH₂); 19.43 (CH₃); 18.99 (CH₃). The peak of the ester carbonyl was not observed under the recording conditions.

***trans*-1-Hydroxy-*cis*-6-hydroxymethyl-*r*-9-isopropyl-bicyclo[4.4.0]deca-3,7-diene **11** (lithium aluminum hydride reduction of **6**):** To a suspension of lithium aluminum hydride (112 mg; 2.96 mmol) in THF (5.5 mL) was added dropwise a solution of **6** (148 mg; 0.592 mmol) and the reaction mixture was stirred for 15 h at room temperature. The mixture was cooled (4 °C) and ethyl acetate (1 mL) was slowly added, followed by saturated aqueous solution of K₂Na-tartrate (12 mL). The organic layer was separated, the aqueous layer was extracted with diethyl ether (4 × 25 mL), and the combined organic extract was washed with water, brine, dried over anhydrous MgSO₄, filtered and concentrated

under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=85/15) afforded the title compound **11** (125.8 mg; 96%).

Physical data for **11**: White crystals, m.p. 70-76 °C; Anal. calcd. for C₁₄H₂₂O₂ (222.32): C 75.63, H 9.97; found: C 75.17, H 9.49; IR (film): 3401, 3024, 2954, 2920, 1647, 1465, 1438, 1372, 1073, 1002; ¹H NMR: 5.85 (dd, *J*₁=10.2, *J*₂=2.2, 1H); 5.76-5.52 (m, 2H); 5.41 (dd, *J*₁=10.2, *J*₂=2.6, 1H); 3.46 (s, 2H); 2.41-1.57 (m, 10H); 0.94 (d, *J*=3.6, 3H); 0.91 (d, *J*=3.6, 3H); ¹³C NMR: 132.20 (CH); 130.16 (CH); 126.13 (CH); 124.38 (CH); 70.60 (C); 67.52 (CH₂); 43.064 (C); 38.93 (CH); 36.29 (CH₂); 33.40 (CH₂); 31.40 (CH); 29.54 (CH₂); 19.46 (CH₃); 19.13 (CH₃).

(3Z,7Z)-9-isopropyl-6-methylenecyclodeca-3,7-dienone 13 (Grob fragmentation of 11 via the mesylate 12): Methanesulfonyl chloride (49 mg; 0.426 mmol) was added to a cold (-15 °C) solution of **11** (70 mg; 0.355 mmol) and triethylamine (54 mg; 0.532 mmol) in dichloromethane (1.8 mL), with stirring. After 1 min saturated aqueous NaHCO₃ (0.5 mL) was added and the reaction mixture was diluted with diethyl ether (100 mL). The organic extract was thoroughly washed with saturated aqueous NaHCO₃ (4 x 10 mL, 10 min every washing), water, brine, dried over anhydrous MgSO₄, filtered and evaporated under reduced pressure. The crude product **12** (colorless oil, 109 mg) was used in the next step without further purification. To a solution of **12** and 18-crown-6 (332 mg; 1.26 mmol) in benzene (8.8 mL) was added powdered KOH (50.4 mg; 0.9 mmol) with stirring. After 90 min saturated aqueous NH₄Cl (8 mL) was added, the reaction mixture was extracted with dichloromethane (5 x 20 mL), and the organic extract was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the crude residue (100 mg) by dry-flash chromatography (eluent: petroleum-ether/acetone=96/4) afforded the title compound **13** (53.7 mg; 74%).

Physical data for **13**: Colorless liquid; Anal. calcd. for C₁₄H₂₂O₂ (204.31): C 75.63, H 9.97; found: C 75.17, H 9.49; IR (film): 3081, 3023, 2961, 2874, 1709, 1656, 1626, 1598, 1465, 1427, 1391, 1317, 897; ¹H NMR: 5.85 (d, *J*=11.9, 1H); 5.80-5.65 (m, 1H); 5.53-5.44 (m, 1H); 5.23 (dd, *J*₁=*J*₂= 11.6, 1H); 5.10 (s, 1H); 4.98 (s, 1H); 3.85 (dd, *J*₁=15.6, *J*₂=10.7, 1H); 3.34 (dd, *J*₁=16.3, *J*₂=6.3, 1H); 3.20-3.02 (m, 1H); 2.89 (dd, *J*₁=16.3, *J*₂=6.6, 1H); 2.70-2.48 (m, 2H); 2.22 (dd, *J*₁= 13.4, *J*₂= 10.4, 1H); 1.56 (hept, *J*=7.0, 1H); 0.97 (d, *J*=3.2, 3H); 0.93 (d, *J*=3.2, 3H); ¹³C NMR: 210.65 (C); 144.41 (C); 133.75 (CH); 130.94 (CH); 128.91 (CH); 124.59 (CH); 115.66 (CH₂); 50.16 (CH₂); 41.17 (CH); 38.43 (CH₂); 36.49 (CH₂); 33.01 (CH); 20.51 (CH₃); 20.42 (CH₃).

(3Z,7E)-9-isopropyl-6-methylenecyclodeca-3,7-dienone 14 (regioselective E/Z isomerization of 13): In a Pyrex vessel with external water cooling, a solution of **13** (260 mg; 1.272 mmol) and diphenyl disulfide (5.6 mg; 26 μmol) in benzene (2.4 mL) was irradiated with a Xenophot 250 W sunlamp, for 10 min. The solvent was evaporated under reduced pressure and the residue purified by dry-flash chromatography on silver nitrate impregnated silica gel (10% AgNO₃ on SiO₂; eluent: petroleum-ether/ethyl acetate=9/1) to give **13** (eluted first, 150 mg), followed by the title compound **14** (100 mg, 38.5%, 91% based on the recovered **13**) as a colorless liquid. In the repeated experiments the yields varied from 85-100% with the ratio of isomers **14**:**13**=1.2:1-1:1.5.

Physical data for **14**: Colorless liquid; IR (film): 3078, 3023, 2962, 2876, 1709, 1655, 1615, 1448, 1314, 1257, 1118, 1082, 978; ¹H NMR: 5.90 (d, *J*=16.2, 1H); 5.67 (dd, *J*₁=15.9, *J*₂=10.1, 1H); 5.71-5.45 (m, 2H); 4.97 (d, *J*=1.3, 1H); 4.76 (d, *J*=1.4, 1H); 3.53 (dd, *J*₁= 15.9, *J*₂= 10.5, 1H); 3.25-3.14 (m, 1H); 2.80-2.36 (m, 4H); 2.21-2.04 (m, 1H); 1.70-1.53 (m, 1H); 0.93 (d, *J*=4.2, 3H); 0.90 (d, *J*=4.2, 3H); ¹³C NMR: 211.71 (C); 144.70 (C); 134.76 (CH); 131.02 (CH); 129.68 (CH); 123.36 (CH); 112.97 (CH₂); 49.81 (CH₂); 47.61 (CH); 43.66 (CH); 35.94 (CH); 32.20 (CH₂); 20.14 (CH₃); 20.04 (CH₃).

Periplanone C 5 (regioselective methylenation of 14):⁶ To a cold (-20 °C) solution of diisopropyl amine (50 mg; 0.492 mmol) in THF (630 μL) was added the solution of *n*-butyllithium in hexane (294 μL of the 1.67 M solution; 0.491 mmol). The solution was stirred for 15 min at that temperature, then cooled to -78 °C and the solution of compound **14** (91.3 mg; 0.447 mmol) in THF (400 μL) was added. HMPA (319 mg; 1.78 mmol) was added to the solution of the lithium enolate, and the resulting solution was transferred via cannula to a cold (-78 °C) suspension of the Eschenmoser's salt (200 mg; 1.08 mmol) in THF (1 mL; in order to secure the quantitative transfer of the enolate the 1st flask was washed with two 250 μL portions of THF). The reaction mixture was allowed to reach r.t. with stirring, when the yellow suspension turned into solution. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and the product was extracted with ethyl acetate (4 x 25 mL). The organic extract was washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue (430 mg) was dissolved in diethyl ether (3 mL), methyl iodide (1 mL; 2.275 g; 16.28 mmol) was added and the reaction mixture was stirred at r. t. for 2 hours. The solution of NaOAc (1.2 g) in water (7 mL) was added and the reaction mixture was vigorously stirred for 1

hour. The mixture was diluted with *n*-hexane (80 mL) and water (10 mL), the phases were separated and the aqueous phase was extracted with *n*-hexane (2×10 mL). The combined extract was thoroughly washed with water, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. Purification of the crude organic residue (107 mg) by column chromatography (gradient elution with *n*-hexane/diethyl ether=95/5→9/1) afforded Periplanone C **5** (35.3 mg; 36.5%; 53% based on the recovered **14**) followed by the starting compound **14** (28 mg; the yield of **5**, determined by ^1H NMR of the crude reaction mixture, calculated on the basis of the recovered **14**, was 84%). The compound **5** had the IR, ^1H - and ^{13}C NMR spectra identical to those described in the literature.⁷

¹ For the description of the technique of dry-flash chromatography, see: a) Harwood, L. M. *Aldrichimica Acta* **1985**, 18, 25; b) *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific&Technical, 5th edition, London, 1989, p. 220; c) A recent account which includes some improvements of the separation technique: Pedersen, D. S.; Rosenbohm, C. *Synthesis* **2001**, 2431.

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⁷ a) IR and ^1H NMR spectra of the natural compound: Biendl, M.; Hauptmann, H.; Sass, H. *Tetrahedron Lett.* **1989**, 30, 2367; b) ^{13}C NMR spectrum: Nishii, Y.; Watanabe, K.; Yoshida, T.; Okayama, T.; Takahashi, S.; Tanabe, Y. *Tetrahedron* **1997**, 53, 7209.

Scanned NMR spectra for compounds **5**, **6**, **7**, **8**, **10**, **11**, **13** and **14**
(in the numerical order)

Compound **5** (Periplanone C), ^1H NMR

Compound **5** (Periplanone C), ^{13}C NMR

Compound **6**, ^1H NMR

Compound **6**, ^{13}C NMR (APT)

Compound 7, ^1H NMR

Compound 7, ^{13}C NMR (APT)

Compound 7, DEPT

Compound **8**, ^{13}C NMR (APT)

Compound **10**, ^1H NMR

Compound **10**, ^{13}C NMR (APT)

Compound 11, ^1H NMR

Compound 11, ^{13}C NMR (APT)

Compound **13**, ^1H NMR

Compound **13**, ^{13}C NMR (APT)

Compound 14, ^1H NMR

Compound **14**, ^{13}C NMR (APT)