Synthesis of Mono- and Sesquiterpenoids; XXIII.[1] Synthesis of (*E*)-*endo*-Bergamoten-12-oic Acids (α-form, β-form), Moth Oviposition Stimulants Isolated from Wild Tomato Leaves[2]

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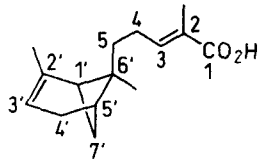
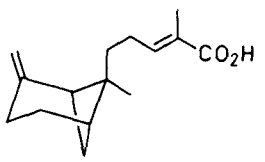
(*E*)-*endo*-Bergamoten-12-oic acids (α-form: **1**, β-form: **2**), moth oviposition stimulants isolated from wild tomato leaves, were synthesized starting from the lactone **7**.

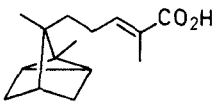
(*E*)-*endo*-Bergamoten-12-oic acids (α-form: **1**, β-form: **2**) are sesquiterpenes isolated from the leaves of wild tomato (*Lycopersicon hirsutum*) by Coates, Juvik, and their coworkers together with (+)-(*E*)-α-santalen-12-oic acid (**3**). They (**1** and **2**) stimulate the oviposition behaviour of female gravid moths (*Heliothis zea*), whose larvae are major agricultural pests of tomatoes, corn, and cotton.[3] The activity of these compounds prompted us to attempt a synthesis of enantiomerically pure **1** and **2**.



(*E*)-*endo*-Bergamoten-12-oic acid (α-form) **1**



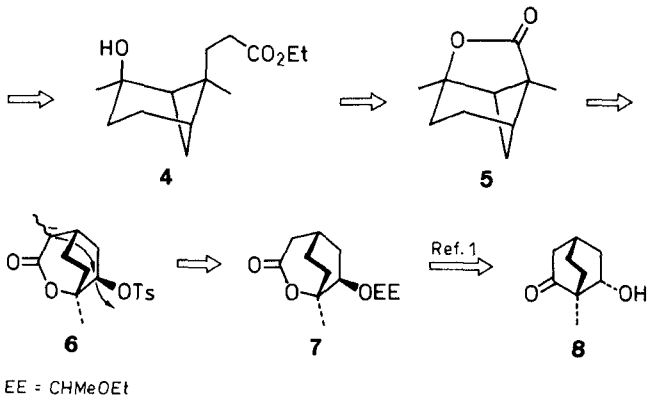
(*E*)-*endo*-Bergamoten-12-oic acid (β-form) **2**



(*E*)-α-Santalen-12-oic acid **3**

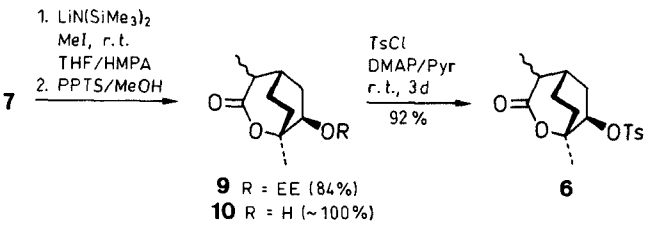
Our retrosynthetic analysis is shown in Scheme 1. We recently reported the synthesis of (+)-pinthunamide.[1] To construct the pinane-type carbon skeleton of the bergamotenoic acids we can use the intramolecular alkylation of the tosyloxylactone **6** as the key reaction as in the synthesis of (+)-pinthunamide.[1] The first stage of our work was the preparation of tosyloxylactone **6** as shown in Scheme 2. The starting material **7**, an intermediate in the synthesis of (+)-pinthunamide,[1] was obtained in enantiomerically pure form in three steps from β-hydroxy ketone **8**, the yeast reduction product.[1,4] The lactone **7** was alkylated with methyl iodide using lithium 1,1,1,3,3,3-hexamethyldisilazide [$LiN(SiMe_3)_2$] as a base to give **9**. After the removal of the 1-ethoxyethyl (EE) protecting group, the resulting alcohol **10** was treated with *p*-toluenesulfonyl chloride (TsCl) in the presence of 4-(dimethylamino)pyridine (DMAP) to give the key intermediate **6** as crystals.[1]

The next step was the crucial key intramolecular alkylation as shown in Scheme 3. We successfully executed this reaction by employing $LiN(SiMe_3)_2$ in tetrahydrofuran/hexamethylphosphoric triamide (HMPA) as the base. In addition to the desired tricyclic lactone **5** (ca. 52% yield) with $\nu = 1770\,cm^{-1}$, an undesired byproduct, a nitrile **11** ($\nu = 2245\,cm^{-1}$) was obtained in accord with our experience in the course of pinthunamide synthesis.[1]

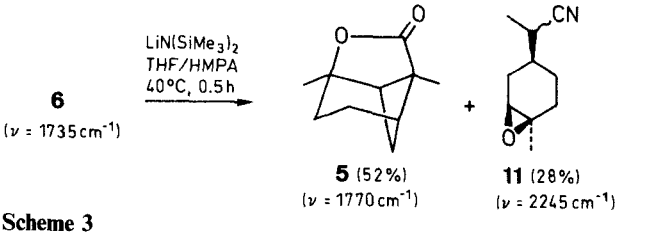


EE = CHMeOEt

Scheme 1

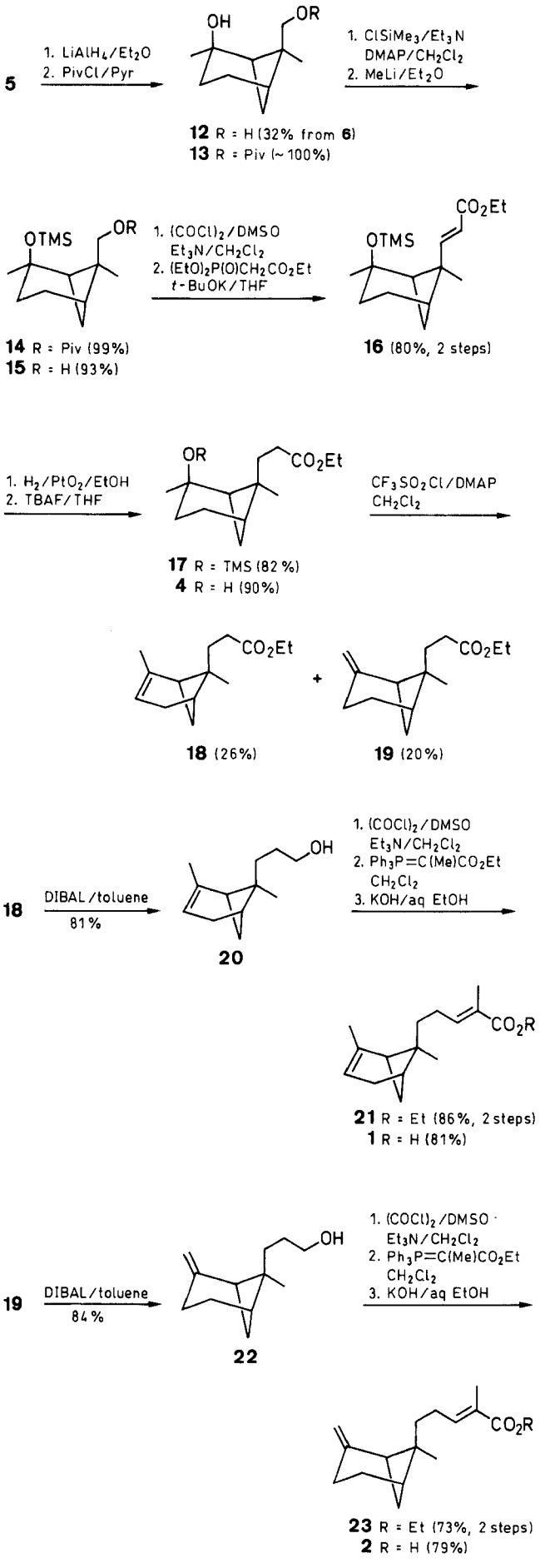


Scheme 2



Scheme 3

The remaining steps of the synthesis were the construction of the side chain and dehydration to afford bergamoten-12-oic acids as shown in Scheme 4. The lactone **5** was reduced with lithium aluminum hydride to give diol **12**, whose enantiomeric purity was determined to be almost 100% ee by the 300 MHz ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA monoesters. The primary hydroxy group of **12** was selectively protected as pivaloyl (Piv) ester. Compound **13** was then converted to the unsaturated ester **16** by the following sequence: (i) protection of the tertiary hydroxy group of **13** as trimethylsilyl ether to give **14**, (ii) removal of the Piv protective group of **14** with methyllithium to afford **15**, and (iii) Swern oxidation[5] of **15** to give crude unstable aldehyde, which was immediately submitted to Horner reaction. The double bond of the resulting ester **16** was hydogenated in the presence of Adams' platinum dioxide catalyst to furnish **17**, whose trimethylsilyl protecting group was removed to give hydroxy ester **4**. For the dehydration we used trifluoromethanesulfonyl chloride in the presence of excess DMAP to avoid acidic rearran-



Scheme 4

gement of the carbon skeleton. The ratio of α-form **18** to β-form **19** was ca. 5:4, and these were separable by chromatography using silica gel impregnated with silver nitrate. These compounds were respectively transformed to afford the target molecules by the following sequence: (i) reduction of the ester **18** (**19**) to the alcohol **20** (**22**), (ii) Swern oxidation of **20** (**22**) to give crude aldehyde, which was immediately submitted to Wittig reaction and finally (iii) hydrolysis of the ester **21** (**23**) to give the desired carboxylic acid **1** (**2**). The melting points, specific rotations and spectroscopic properties (IR, ^{1}H and ^{13}C NMR) of our synthetic **1** and **2** were identical with those of the natural compounds, respectively.[2]

All melting and boiling points are uncorrected. NMR spectra were recorded on a JEOL JNM EX-90 or Bruker AC-300 spectrometer. IR spectra were recorded on a Jasco A-102 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Column chromatography was carried out on columns packed with Merck Kieselgel 60 (Art. Nr. 7734). For all new compounds satisfactory microanalyses (C ± 0.37, H ± 0.17) or HRMS values (± 0.0016 amu) were obtained.

(1*R*,5*S*,7*R*)-1,4-Dimethyl-7-(1-ethoxyethoxy)-2-oxabicyclo[3.2.2]-nonan-3-one (9):

A solution of $LiN(SiMe_3)_2$ in anhydr. THF was prepared by the dropwise addition of BuLi (16.5 mL, 1.65 M in hexane, 27.2 mmol) to a stirred solution of $(SiMe_3)_2NH$ (6.01 mL, 28.5 mmol) in anhydr. THF (100 mL) at −78 °C under Ar. HMPA (8.62 mL, 49.5 mmol) was added to the mixture and to this homogeneous solution was added a solution of **7** (6.00 g, 24.8 mmol) in anhydr. THF (30 mL) at −78 °C. MeI (1.99 mL, 31.9 mmol) was added to the mixture at −78 °C. The mixture was warmed to r.t. and stirred for 16 h, poured into H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The combined Et_2O extracts were washed with H_2O (100 mL), sat. aq $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (700 g). Elution with hexane/EtOAc (5:1) gave **9** and (1:1) **7**; yield: 5.35 g (84%), 0.41 g (6%); $n_D^{20.4}$ 1.4727; $[\alpha]_D^{20.4}$ −57.8° (*c* = 0.690, $CHCl_3$).

IR (film): ν = 1720 cm^{-1} (s, C=O).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.09–1.45 (m, 12H, H-1, 4, $OCHC\underline{H}_3O$ and $OCHC\underline{H}_3$), 1.51–2.38 (m, 7H, H-5, 6, 8, 9), 2.59–2.98 (m, 1H, H-4), 3.28–4.09 (m, 3H, H-7 and $OC\underline{H}_2CH_3$), 4.49–4.98 (m, 1H, $OC\underline{H}CH_3O$).

(1*R*,5*S*,7*R*)-1,4-Dimethyl-7-hydroxy-2-oxabicyclo[3.2.2]nonan-3-one (10):

To a stirred solution of **9** (5.25 g, 20.5 mmol) in MeOH (100 mL) was added pyridinium *p*-toluenesulfonate (PPTs) (0.32 g, 1.27 mmol) at r.t. and the mixture was stirred at r.t. for 12 h. The mixture was concentrated in vacuo in the presence of $NaHCO_3$. The residue was poured into sat. aq $(NH_4)_2SO_4$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL) dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (100 g). Elution with hexane/EtOAc (2:1) gave **10**; yield: 3.77 g (quantitative); $n_D^{21.1}$ 1.5026; $[\alpha]_D^{20.1}$ −18.9° (*c* = 0.620, $CHCl_3$).

IR (film): ν = 3460 (br s, O–H), 1700 cm^{-1} (br s, C=O).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.30 (d, 2.2H, *J* = 7.4 Hz, major 4-CH_3), 1.32 (d, 0.8H, *J* = 7.4 Hz, minor 4-CH_3), 1.38 (s, 3H, 1-CH_3), 1.46–2.46 (m, 7H, H-5,6,8,9), 2.60–2.97 (m, 1H, H-4), 3.81–4.14 (m, 1H, 7-H).

(1*R*,5*S*,7*R*)-1,4-Dimethyl-2-oxa-7-*p*-toluenesulfonyloxybicyclo-[3.2.2]nonan-3-one (6):

To an ice-cooled and stirred solution of **10** (3.53 g, 19.2 mmol) in pyridine (50 mL) and DMAP (0.47 g, 3.85 mmol) was added TsCl (37.5 g, 197 mmol). The mixture was stirred at r.t. for 67 h. To the

ice-cooled mixture, crushed ice and H_2O (100 mL) were added. The mixture was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with H_2O (200 mL), sat. aq $NaHCO_3$ (200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (200 g). Elution with hexane/EtOAc (5:1) gave **6**. This was recrystallized from hexane to give pure **6** (5.87 g). The mother liquor was concentrated in vacuo, and the residue was recrystallized after chromatography on silica gel to give an additional amount of **6** (0.10 g); yield: 5.97 g (92%); mp 98–105 °C; $[\alpha]_D^{20.4}$ −69.3° (c = 0.930, $CHCl_3$).

IR (film): ν = 1735 (s, C=O), 1600 (w, C=C), 1380, 1195, 1185 cm^{-1} (s, OSO_2).

^1H NMR ($CDCl_3$/TMS): δ = 1.16 (s, 3H, CH_3), 1.28 (d, 2.2H, J = 7.4 Hz, major 4-CH_3), 1.32 (d, 0.8H, J = 7.4 Hz, minor 4-CH_3), 1.43–2.37 (m, 7H, H-5, 6, 8, 9), 2.48 (s, 3H, Ar–CH_3), 2.53–2.99 (m, 1H, H-4), 4.51–4.78 (m, 1H, H-7), 7.39 (d, 2H_{arom}, J = 8.6 Hz), 7.81 (d, 2H_{arom}, J = 8.6 Hz).

(1*R*,4*S*,6*R*,7*S*)-1,7-Dimethyl-9-oxatricyclo[4.3.0.0^{4,7}]nonan-8-one (5):

A solution of $LiN(SiMe_3)_2$ in anhydr. THF was prepared by dropwise addition of BuLi (16.0 mL, 1.66 M in hexane, 26.6 mmol) to a stirred solution of $(SiMe_3)_2NH$ (5.70 mL, 26.9 mmol) in anhydr. THF (140 mL) at −78 °C under Ar. HMPA (4.63 mL, 26.7 mmol) was added to the mixture and to this homogeneous solution was added dropwise a solution of **6** (3.00 g, 8.86 mmol) in anhydr. THF (13 mL at −78 °C. The mixture was warmed to 40 °C and stirred for 0.5 h. The mixture was poured into H_2O (200 mL) and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with H_2O (200 mL), sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (250 g). Elution with hexane/EtOAc (10:1) gave crude **5** contaminated with a trace amount of unknown impurities; yield: 770 mg (ca. 52%). This crude **5** was used for the next reaction without further purification. Further elution with hexane/EtOAc (5:1) gave nitrile **11**; yield: 412 mg (28%).

5:

IR (CCl_4): ν = 1770 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.37 (s, 3H, 7-CH_3), 1.46 (s, 3H, 1-CH_3), 1.68 (d, 1H, J = 9.7 Hz, H-5), 1.90 (s, 4H, H-2, 3), 1.98–2.50 (m, 3H, H-4, 5, 6).

10:

IR (film): ν = 2245 cm^{-1} (s, C≡N).

^1H NMR ($CDCl_3$/TMS): δ = 1.28 (d, 3H, J = 8.2 Hz, $CHCH_3$), 1.33 (s, 3H, 1-CH_3), 0.90–2.61 (m, 8H, H-3, 4, 5, 6, and $CHCH_3$), 3.00 (d, 1H, J = 5.0 Hz, H-2).

(1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-hydroxybicyclo[3.1.1]hept-6-yl)-methanol (12):

To an ice-cooled and stirred solution of crude **5** (1.57 g, ca. 9.42 mmol) in anhydr. Et_2O (30 mL) was added $LiAlH_4$ (0.86 g) 22.7 mmol). The mixture was stirred at r.t. for 13 h. To the ice-cooled mixture was added H_2O (0.86 mL), 15% aq NaOH (0.86 mL) and H_2O (2.58 mL) successively. The mixture was stirred at r.t. for several min and filtered through Celite and eluted with hot THF. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (100 g). Elution with hexane/EtOAc (2:1) gave **12**. This was recrystallized from hexane to give pure **12** as needles; yield: 995 mg [32% in 2 steps from **6** (6.18 g)]; mp 85–86 °C; $[\alpha]_D^{22.4}$ −33.9° (c = 0.900, $CHCl_3$).

IR (CCl_4): ν = 3630 (w, monomeric OH), 3360 cm^{-1} (br s, OH).

^1H NMR ($CDCl_3$/TMS): δ = 1.04 (d, 1H, J = 10.0 Hz, H_{endo}-7′), 1.32 (s, 6H, 2′, 6-CH_3), 1.57–2.50 (m, 7H, H-1′, 3′, 4′, 5′, and H_{exo}-7′), 2.70–3.10 (br, 1H, 1-OH), 3.21 (d, 1H, J = 10.8 Hz, one of H-1), 4.03 (d, J = 10.8 Hz, one of H-1).

(1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-hydroxybicyclo[3.1.1]hept-6-yl)-methyl 2,2-Dimethylpropanoate (13):

To an ice-cooled solution of **12** (405 mg, 2.38 mmol) in pyridine (13 mL) was added pivaloyl chloride (PivCl) (585 μL, 4.75 mmol). The mixture was stirred at r.t. for 2 h. To the ice-cooled mixture was added crushed ice and H_2O (50 mL). The mixture was extracted with Et_2O (2 × 100 mL). The extract was washed with H_2O (100 mL), sat. aq $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (18 g). Elution with hexane/EtOAc (6:1) gave **13**; yield: 605 mg (quantitative): $n_D^{21.7}$ 1.4669; $[\alpha]_D^{22.0}$ −6.36° (c = 1.74, $CHCl_3$).

IR (film): ν = 3525 (br s, OH), 1730, 1710 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.02 (d, 1H, J = 7.0 Hz, H_{endo}-7′), 1.19 (s, 9H, t-C_4H_9), 1.28 (s, 6H, H-2′, 6′), 1.47–2.46 (m, 3H, H-1′, 5′, and H_{exo}-7′), 1.87 (s, 4H, H-3′, 4′), 4.09 (d, 1H, J = 11.3 Hz, CHHOCO), 4.37 (d, 1H, J = 11.3 Hz, CHHOCO).

(1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-trimethylsilyloxybicyclo[3.1.1]-hept-6-yl)methyl 2,2-Dimethylpropanoate (14):

To an ice-cooled solution of **13** (591 mg, 22.3 mmol), DMAP (56 mg, 0.46 mmol) and Et_3N (3.32 mL, 23.8 mmol) was added Me_3SiCl (1.51 mL, 11.9 mmol). The mixture was stirred for r.t. for 1.5 h. The mixture was poured into sat. aq $NaHCO_3$ (100 mL), and extracted with Et_2O (2 × 100 mL). The extract was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (25 g). Elution with hexane/EtOAc (15:1) gave **14**; yield: 754 mg (99%); $n_D^{22.2}$ 1.4574; $[\alpha]_D^{22.5}$ −3.60° (c = 1.33, $CHCl_3$).

IR (film): ν = 1730 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.13 (s, 9H, $SiCH_3$), 1.07 (d, 1H, J = 9.4 Hz, H_{endo}-7′), 1.20 (s, 9H, t-C_4H_9), 1.29 (s, 6H, 2′,6′-CH_3), 1.45–2.38 (m, 3H, H-4′,5′, H_{exo}-7′), 1.84 (s, 4H, H-3′,4′), 3.83 (d, 1H, J = 12.2 Hz, CHHOCO), 4.60 (d, 1H, J = 12.2 Hz, CHHOCO).

(1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-trimethylsilyloxybicyclo[3.1.1]-hept-6-yl)methanol (15):

To an ice-cooled and stirred solution of **14** (736 mg, 25.2 mmol) in anhydr. Et_2O (15 mL) was added MeLi (10.2 mL, 1.10 M in hexane, 11.2 mmol) under Ar. The mixture was stirred for an additional 1 h, poured into ice-cooled sat. aq NH_4Cl (50 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (25 g). Elution with hexane/EtOAc (10:1) gave **15**; yield: 506 mg (93%); $n_D^{22.1}$ 1.4748; $[\alpha]_D^{22.6}$ −36.2° (c = 2.22, $CHCl_3$).

IR (film): ν = 3460 cm^{-1} (br s, OH).

^1H NMR ($CDCl_3$/TMS): δ = 0.20 (s, 9H, $SiCH_3$), 1.00 (d, 1H, J = 9.5 Hz, H_{endo}-7′), 1.33 (s, 3H, 6′-CH_3), 1.36 (s, 3H, 2′-CH_3), 1.52–2.42 (m, 7H, H-1′,3′,4′,5′, and H_{exo}-7′), 2.67 (dd, 1H, J = 3.0, 10.7 Hz, OH), 3.06 (dd, 1H, J = 10.7, 10.7 Hz, one of H-1), 3.98 (dd, 1H, J = 3.0, 10.7 Hz, one of H-1).

Ethyl (1′*R*,2′*R*,5′*S*,6′*S*)-(*E*)-3-(2,6-Dimethyl-2-trimethylsilyloxy-bicyclo[3.1.1]hept-6-yl)prop-2-enoate (16):

A solution of the Swern reagent was prepared by the dropwise addition of DMSO (600 μL, 8.45 mmol) to a stirred solution of $(COCl)_2$ (350 μL, 4.02 mmol) in anhydr. CH_2Cl_2 (10 mL) at −78 °C under Ar. To the stirred Swern reagent was added dropwise a solution of **15** (488 mg, 2.01 mmol) in anhydr. CH_2Cl_2 (4 mL) at −78 °C. After stirring for 1.5 h, Et_3N (2.24 mL, 16.1 mmol) was added to the mixture and the mixture was stirred at −78 °C for additional 10 min. The mixture was warmed gradually to r.t. during 1 h, poured into H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting crude aldehyde (ν = 1710 cm^{-1}) was immediately used for the next reaction without purification.

To an ice-cooled solution of triethyl phosphonoacetate (2.35 g, 10.5 mmol) in anhydr. THF (50 mL) was added t-BuOK (1.13 g, 9.25 mmol) under Ar. The mixture was stirred at r.t. for 1 h, and cooled to −78 °C. To this solution was added a solution of crude aldehyde in anhydr. THF (6 mL) at −78 °C and the mixture was warmed to 50 °C and stirred for 21 h. The mixture was poured into

H_2O (150 mL) and extracted with Et_2O (2 × 150 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (35 g). Elution with hexane/EtOAc (15:1) gave **16**; yield: 499 mg (80% in 2 steps from **15**); $n_D^{21.5}$ 1.4809; $[\alpha]_D^{21.5}$ + 50.9° (*c* = 1.48, $CHCl_3$).

IR (film): *v* = 1720 (s, C=O), 1640 cm^{-1} (m, C=C).

^1H NMR ($CDCl_3$/TMS): *δ* = 0.11 [s, 9H, $Si(CH_3)_3$], 1.05 (d, 1H, *J* = 9.5 Hz, H_{endo}-7′), 1.31 (s, 3H, 6′-CH_3), 1.31 (t, 3H, *J* = 9.0 Hz, OCH_2CH_3), 1.35 (s, 3H, 2′-CH_3), 1.72–2.47 (m, 7H, H-1′,3′,4′,5′, and H_{exo}-7′), 4.18 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 5.61 (d, 1H, *J* = 16.9 Hz, H-3), 7.60 (d, 1H, *J* = 16.9 Hz, H-2).

Ethyl (1′*R*,2′*R*,5′*S*,6′*S*)-3-(2,6-Dimethyl-2-trimethylsilyloxybicyclo-[3.1.1]hept-6-yl)propanoate (17):

To a solution of **16** (484 mg, 1.56 mmol) in EtOH (5 mL) was added PtO_2 (100 mg, 0.440 mmol) and this suspension was stirred at r.t. for 1 h under H_2. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (30 g). Elution with hexane/EtOAc (15:1) gave **17** and (10:1) **4**; yield: 398 mg (82%), 21 mg (6%); $n_D^{22.0}$ 1.4670; $[\alpha]_D^{22.0}$ − 3.20° (*c* = 1.08, $CHCl_3$).

IR (film): *v* = 1740 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): *δ* = 0.11 [s, 9H, $Si(CH_3)_3$], 1.02 (d, 1H, *J* = 9.9 Hz, H_{endo}-7′), 1.19 (s, 3H, 6′-CH_3), 1.28 (t, 3H, *J* = 6.3 Hz, OCH_2CH_3), 1.29 (s, 3H, 2′-CH_3), 1.43–2.61 (m, 11H, H-1′,3′,4′,5′, and H_{exo}-7′ and H-2,3), 4.13 (q, 2H, *J* = 6.3 Hz, OCH_2CH_3).

Ethyl (1′*R*,2′*R*,5′*S*,6′*S*)-3-(2,6-Dimethyl-2-hydroxybicyclo[3.1.1]-hept-6-yl)propanoate (4):

To an ice-cooled solution of **17** (387 mg, 1.24 mmol) in anhydr. THF (8 mL) was added TBAF (4 mL, 1 M in THF, 4 mmol). The mixture was stirred at r.t. for 2 h. It was then poured into H_2O (50 mL) saturated with $(NH_4)_2SO_4$ and extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine (100 mL) dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (30 g). Elution with hexane/EtOAc (3:1) gave **4**; yield: 268 mg (90%); $n_D^{22.0}$ 1.4799; $[\alpha]_D^{22.0}$ + 9.75° (*c* = 0.885, $CHCl_3$).

IR (film): *v* = 3510 (br s, OH), 1735, 1720 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): *δ* = 1.05 (d, 1H, *J* = 10.2 Hz, H_{endo}-7′), 1.19 (s, 3H, 6′-CH_3), 1.26 (s, 3H, 2′-CH_3), 1.33 (t, 3H, *J* = 11.7 Hz, OCH_2CH_3), 1.53–2.64 (m, 11H, H-1′,3′,4′,5′, and H_{exo}-7′ and H-2,3), 4.12 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3).

Ethyl (1′*S*,5′*S*,6′*S*)-3-(2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)-propanoate (18) and Ethyl (1′*S*,5′*S*,6′*S*)-3-(6-Methyl-2-methylene-bicyclo[3.1.1]hept-6-yl)propanoate (19):

To an ice-cooled and stirred solution of **4** (256 mg, 1.07 mmol) and DMAP (1.56 g, 12.8 mmol) in anhydr. CH_2Cl_2 (40 mL) was added dropwise CF_3SO_2Cl (568 µL, 5.33 mmol). The mixture was stirred at r.t. for 7 h. The mixture was poured into H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (20 g). Elution with hexane/EtOAc (15:1) gave a crude mixture of **18** and **19**. This was chromatographed on silica gel coated with $AgNO_3$ (15 g). Elution with hexane/EtOAc (15:1) gave **18** and **19**; yield: 63.3 mg (26%), 49.0 mg (20%).

18; $n_D^{21.2}$ 1.4747; $[\alpha]_D^{21.2}$ − 29.5° (*c* = 1.09, $CHCl_3$).

IR (film): *v* = 1740 (s, C=O), 1655 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): *δ* = 1.10 (d, 1H, *J* = 8.6 Hz, H_{endo}-7′), 1.24 (s, 3H, H-6′), 1.24 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.38–2.48 (m, 9H, H-1′,4′,5′, and H_{exo}-7′), 1.70 (d, 3H, *J* = 1.6 Hz, 2′-CH_3), 4.11 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 5.24 (br s, 1H, H-3′).

19; $n_D^{19.4}$ 1.4821; $[\alpha]_D^{19.4}$ − 9.63° (*c* = 1.26, $CHCl_3$).

IR (film): *v* = 3080 (w, C=CH), 1735 (s, C=O), 1640 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): *δ* = 1.21 (s, 3H, 6′-CH_3), 1.25 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.45 (d, 1H, *J* = 9.5 Hz, H_{endo}-7′), 1.72–2.62 (m, 11H, H-1′,3′,4′,5′, and H_{exo}-7′ and H-2,3), 4.11 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.59, 4.67 (each br s, 2H, C=CH_2).

(1′*S*,5′*S*,6′*S*)-3-(2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)propan-1-ol (20):

To a stirred solution of **18** (63.3 mg, ca. 0.280 mmol) in anhydr. toluene (3 mL) was added dropwise diisobutylaluminum hydride (DIBAL) (820 µL, 1.02 M in toluene, 0.840 mmol). The mixture was stirred at 4°C for 13 h. To the ice-cooled mixture was added H_2O (33 µL), 15% aq NaOH (33 µL) and H_2O (33 µL) successively. The mixture was stirred at r.t. for several min and filtered through Celite. The Celite layer was eluted with hot THF. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (10 g). Elution with hexane/EtOAc (4:1) gave **20**; yield: 41.5 mg (81%); $n_D^{21.1}$ 1.4927; $[\alpha]_D^{21.1}$ − 41.2° (*c* = 1.15, $CHCl_3$).

IR (film): *v* = 3350 (br s, OH), 3040 (w, C=CH), 1655 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): *δ* = 0.70–1.77 (m, 4H, H-1,2), 1.19 (d, 1H, *J* = 8.6 Hz, H_{endo}-7′), 1.27 (s, 3H, 6′-CH_3), 1.71 (s, 3H, 2′-CH_3), 1.81–2.46 (m, 5H, H-1′,4′,5′, and H_{exo}-7′), 3.46–3.72 (m, 2H, H-3), 5.22 (br s, 1H, H-3′).

Ethyl (1′*S*,5′*S*,6′*S*)-(*E*)-5-(2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)-2-methylpent-2-enoate (21):

A solution of the Swern reagent was prepared by the dropwise addition of DMSO (220 µL, 3.11 mmol) to a stirred solution of $(COCl)_2$ (135 µL, 1.55 mmol) in anhydr. CH_2Cl_2 (5 mL) at − 78°C under Ar. To the stirred Swern reagent was added dropwise a solution of **20** (137.2 mg, 0.761 mmol) in anhydr. CH_2Cl_2 (3 mL) at − 78°C. After stirring for 0.5 h, Et_3N (508 µL, 5.02 mmol) was added to the mixture and the stirring was continued at − 78°C for additional 0.5 h. The mixture was warmed gradually to r.t. during 1 h, poured into H_2O (50 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting crude aldehyde (*v* = 1730 cm^{-1}) was immediately used for the next reaction without purification.

To a stirred solution of the crude aldehyde in anhydr. CH_2Cl_2 (5 mL) was added (carbethoxyethylidene)triphenylphosphorane (780 mg, 2.15 mmol) at r.t. The mixture was stirred at r.t. for 16 h. After concentration, hexane was added and the mixture was filtered through Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (10 g). Elution with hexane/EtOAc (15:1) gave **21**; yield: 171.1 mg (86%); $n_D^{21.3}$ 1.4931 $[\alpha]_D^{20.1}$ − 26.6° (*c* = 0.715, $CHCl_3$).

IR (film): *v* = 1710 (s, C=O), 1650 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): *δ* = 0.80–2.50 (m, 9H, H-1′,4′,5′, and H_{exo}-7′ and H-4,5), 1.08 (d, 1H, *J* = 13.3 Hz, H_{endo}-7′), 1.29 (s, 3H, 6′-CH_3), 1.29 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.71 (s, 3H, 2′-CH_3), 1.83 (s, 3H, 2-CH_3), 4.19 (q, 2H, *J* = 7.3 Hz, OCH_2CH_3), 5.23 (br s, 1H, H-3′), 6.73 (t, 1H, *J* = 8.1 Hz, H-3).

(1′*S*,5′*S*,6′*S*)-(*E*)-5-(2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)-2-methylpent-2-enoic Acid [(*E*)-*endo*-α-Bergamoten-12-oic Acid] (1):

To a stirred solution of **21** (145.8 mg, 0.556 mmol) in EtOH (11 mL) was added 2 N KOH (4.5 mL, 9.0 mmol) at r.t. The mixture was stirred for 44 h at r.t. EtOH was removed in vacuo and the residual aqueous solution was acidified to pH 1 with 2 N HCl. The mixture was extracted with Et_2O (3 × 50 mL). The extract was washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized twice from pentane at − 16°C to give **1** as needles (49.6 mg). The mother liquor was concentrated in vacuo and the residue was recrystallized from pentane at − 78°C after chromatography on silica gel to give additional **1** (56.0 mg); yield: 105.6 mg (81%); mp 59–60°C; $[\alpha]_D^{19.2}$ − 32.8° (*c* = 1.05, $CHCl_3$).

IR (CCl_4): *v* = 1687 (s, C=O), 1642 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): *δ* = 1.18 (d, 1H, *J* = 8.5 Hz, H_{endo}-7′), 1.14–1.38 (m, 2H, H-5), 1.29 (s, 3H), H-6′), 1.51 (dt, 1H, *J* = 5.4, 12.2 Hz, H-5′), 1.70 (d, 3H, *J* = 1.4 Hz, H-2′), 1.82 (s, 3H, 2-CH_3), 1.66–2.29 (m, 5H, 4-H, H-1′,4′), 2.36 (dt, 1H, *J* = 5.4, 8.5 Hz, H_{exo}-7′), 5.22 (br s, 1H, H-3′), 6.86 (t, 1H, *J* = 7.8 Hz, H-3).

^{13}C NMR ($CDCl_3$): δ = 11.8 (C), 22.85 (C), 22.94 (C), 24.3 (C), 31.0 (C), 31.5 (C), 32.4 (C), 40.2 (C), 40.4 (C), 46.1 (C), 116.8 (C), 126.4 (C), 143.5 (C), 146.0 (C), 173.3 (C-1).

(1′*S*,5′*S*,6′*S*)-3-(6-Methyl-2-methylenebicyclo[3.1.1]hept-6-yl)-propan-1-ol (22):

To a stirred solution of **19** (49.0 mg, ca. 0.220 mmol) in anhydr. toluene (3 mL) was added dropwise DIBAL (640 µL, 1.02 M in toluene, 0.650 mmol). To the ice-cooled mixture was added H_2O (26 µL) 15% aq NaOH (26 µL) and H_2O (77 µL) successively. The mixture was stirred at r.t. several min and filtered through Celite. The Celite layer was eluted with hot THF. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (10 g). Elution with hexane/EtOAc (4:1) gave **22**; yield: 33.4 mg (84%); $n_D^{19.8}$ 1.5026; $[\alpha]_D^{19.8}$ − 4.46° (*c* = 0.840, $CHCl_3$); this was used for the next reaction without further purification.

IR (film): ν = 3340 (br s, OH), 3080 (w, C=CH), 1640 cm^{-1} (w, C=C).

^{1}H NMR ($CDCl_3$/TMS): δ = 0.82–2.85 (m, 11 H, H-1′,3′,4′,5′, and H_{exo}-7′ and H-2,3), 1.24 (s, 3 H, H-6′), 1.44 (d, 1 H, *J* = 9.9 Hz, H_{endo}-7′), 3.36–3.74 (m, 2 H, H-1), 4.59, 4.68 (each br s, 2 H, C=CH_2).

Ethyl (1′*R*,5′*S*,6′*S*)-(*E*)-2-Methyl-5-(6-methyl-2-methylenebicyclo-[3.1.1]hept-6-yl)pent-2-enoate (23):

A solution of the Swern reagent was prepared by the dropwise addition of DMSO (131 µL, 1.86 mmol) to a stirred solution of $(COCl)_2$ (77 µL, 0.88 mmol) in anhydr. CH_2Cl_2 (3 mL) at − 78 °C under Ar. To the stirred Swern reagent was added dropwise a solution of **22** (79.4 mg, 0.440 mmol) in anhydr. CH_2Cl_2 (3 mL) at − 78 °C. After stirring for 0.5 h, Et_3N (368 µL, 2.64 mmol) was added to the mixture and the stirring was continued at − 78 °C for additional 0.5 h. The mixture was warmed gradually to r.t. during 1 h, poured into H_2O (50 mL) and extracted with Et_2O (2 × 50 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting crude aldehyde (ν = 1725 cm^{-1}) was immediately used for the next reaction without purification.

To a stirred solution of the crude aldehyde in anhydr. CH_2Cl_2 (4 mL) was added (carbethoxyethylidene)triphenylphosophorane (529 mg, 1.46 mmol) at r.t. and stirred for 16 h. After concentration, hexane was added and the mixture was filtered through Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (20 g). Elution with hexane/EtOAc (10:1) gave **23**; yield: 84.5 mg (73%); $n_D^{20.3}$ 1.5001; $[\alpha]_D^{20.7}$ + 22.9° (*c* = 0.640, $CHCl_3$).

IR (film): ν = 3075 (w, C=CH), 1710 (s, C=O), 1650 cm^{-1} (w, C=C).

^{1}H NMR ($CDCl_3$/TMS): δ = 0.80–2.75 (m, 11 H, H-1′,3′,4′,5′, and H_{exo}-7′, H-4,5), 1.26 (s, 3 H, H-6′), 1.29 (t, 3 H, *J* = 7.3 Hz, OCH_2CH_3), 1.53 (d, 1 H, H_{endo}-7′), 1.81 (s, 3 H, 2-CH_3), 4.19 (q, 2 H, *J* = 7.3 Hz, OCH_2CH_3), 4.60, 4.69 (each br s, 2 H, C=CH_2), 6.72 (t, 1 H, *J* = 7.3 Hz, H-3).

(1′*S*,5′*S*,6′*S*)-(*E*)-2-Methyl-5-(6-methyl-2-methylenebicyclo[3.1.1]-hept-6-yl)pent-2-enoic Acid [(*E*)-*endo*-β-Bergamoten-12-oic Acid] (2):

To a stirred solution of **23** (73.7 mg, ca. 0.281 mmol) in EtOH (6 mL) was added 2 N KOH (2.2 mL, 4.4 mmol) at r.t. The mixture was stirred for 44 h at r.t. EtOH was removed in vacuo and the residual aqueous layer was acidified to pH 1 with 2 N HCl. The mixture was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo The residue was recrystallized twice from pentane at − 16 °C after chromatography on silica gel to give **2** (24.1 mg). The mother liquor was concentrated in vacuo and the residue was chromatographed to give additional **2** (27.7 mg); yield: 51.8 mg (79%); mp 64.5–67.0 °C; $[\alpha]_D^{21.1}$ + 29.5° (*c* = 0.640, $CHCl_3$).

IR (CCl_4): ν = 1687 (s, C=O), 1642 cm^{-1} (w, C=C).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.11–1.35 (m, 2 H, H-5), 1.26 (s, 3 H, H-6′), 1.44 (d, 1 H, *J* = 10.2 Hz, H_{endo}-7′), 1.67–1.89 (m, 2 H, H-4′), 1.81 (s, 3 H, H-2′), 1.94–2.15 (m, 3 H, H-5, 5′), 2.21–2.37 (m, 1 H, H-1′), 2.32 (dt, 1 H, *J* = 5.6, 9.9 Hz, H_{exo}-7′), 2.55 (t, 2 H, *J* = 5.4 Hz, H′-3), 4.60, 4.67 (2 s, 1 H each, C=CH_2), 6.86 (t, 1 H, *J* = 7.9 Hz, H-3).

^{13}C NMR ($CDCl_3$): δ = 11.8 (2-CH_3), 22.4 (6′-CH_3), 23.0 (C-4, 4′), 23.6 (C-3′), 26.6 (C-7′), 33.6 (C-5), 40.2 (C-5′), 42.7 (C-6′), 50.9 (C-1′), 106.9 (C=CH_2), 126.4 (C-2), 145.9 (C-3), 151.3 (C-2′), 173.3 (C-1).

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