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Ti(III)-promoted cyclizations. Application to the synthesis of (*E*)-*endo*-bergamoten-12-oic acids. Moth oviposition stimulants isolated from *Lycopersicon hirsutum*

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Abstract—The Ti(III)-promoted radical cyclization of epoxyenone **8** is described as the key step to access the diol **10** as a convenient starting material of the target molecules. The synthesis of β-(*E*)-*endo*-bergamoten-12-oic acid **2a** from (+)-8,9-epoxycarvone **8** was successfully achieved by Suzuki–Miyaura coupling of the terminal alkene **20** with β-iodomethacrylate **21c**, followed by deprotection and dehydration processes. Moreover, synthesis of the α-(*E*)-*endo*-1-hydroxy-bergamoten-12-oic acid derivative **34** was achieved by iterative elongation processes of the diol **10** lateral chain.

1. Introduction

The isolation of the α and β forms of (*E*)-*endo*-bergamoten-12-oic acids **1a** and **2a** (Fig. 1) from the leaves of *Lycopersicon hirsutum* by Coates et al. in 1988[1] opened the door to synthetic work, which was successfully achieved by Mori and Matsushima in 1994.[2] These two sesquiterpenoids seem to influence the oviposition behavior of *Heliothis zea* (Boddie) whose larvae are major agricultural pests of tomatoes, corn and cotton.[3] The synthesis of these *H. zea* oviposition stimulants may have potential application in agriculture since these sesquiterpenoids might prove effective when combined with pesticide baits for current pest control.

The starting material chosen by Mori et al. to construct the pinane-type carbon skeleton of bergamotenoic acids was the tricyclic lactone **6**.[4] Starting from **6**, construction of the side chain of both sesquiterpenes required the application of a preparatively demanding 13-step sequence that included the chromatographic separation of an almost equimolecular mixture of alkenes. Additionally, the stereocontrolled synthesis of **6** from *R*-(−)-carvone **7** was reported by our group in 1998 in a parallel synthetic study aimed at the synthesis of (+)-ampullicin **4** and (+)-isoampullicin **5**.[5]

The use of titanocene(III) chloride in cyclization processes on functionalized epoxides has offered a plausible alternative for accessing polycyclic structures since the time that Nugent and RajanBabu first reported the Ti(III)-promoted epoxide opening reactions and subsequent reactivity of the radical intermediates.[6] Based on the experience gained in the reactivity of Ti(III) against epoxy ketones we considered the possibility of preparing the tricyclic core present in the bergamotene series by using this cyclization method, starting from (+)-8,9-epoxycarvone **8**. If our assumption is correct then this may help to open new strategies for the synthesis of biologically active natural products such as those represented in Figure 1 (**1**–**6**).[7]

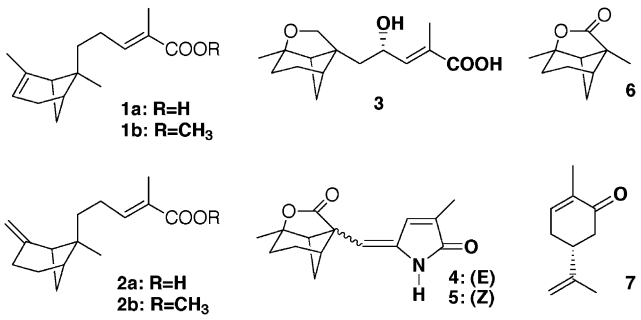

Figure 1.

Keywords: Sesquiterpenoids; β-Halomethacrylates; (*E*)-β-*endo*-Bergamoten-12-oic acids; (*S*)-(+)-Carvone.
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2. Results and discussion

We now wish to describe the synthesis of **6** through a novel route based on the titanium-promoted intramolecular cyclization of (+)-8,9-epoxycarvone **8**, which is easily obtained by epoxidation of (*S*)-(+)-carvone as a mixture of diastereomers.[8]

Addition of the reagent Cp_2TiCl to the epoxide **8** solution (Method A) afforded a mixture of two diastereomeric primary alcohols **9**:**10** in a 3:2 ratio (68% yield) together with a small amount of the β-hydrogen elimination product: (*S*)-(+)-5-[1-(hydroxymethyl)vinyl]-2-methyl-cyclohex-2-enone **11**[9] (10%). No change in the diastereoselectivity was observed by reverse addition (Method B), although a small increase in the elimination product **11** was observed (15%).[10] The reaction, which affords the diols **9** and **10**, is a chemo- and regioselective radical 4-*exo* cyclization process onto a carbonyl based on a seminal work of our group with epoxyenones and Ti(III).[11]

We assume that the outcome of **9** as the major diastereomer in the reaction mixture must be ascribed to the greater stability of one of the two complexes obtained by chelation of titanium within the two diastereomers (see Fig. 2). The equatorial orientation of the hydroxymethyl group in complex **A** led to the major isomer **9** through a more stable titanium complex than the one developed through the axially oriented hydroxymethyl group in complex **B**, which afforded the minor diastereomer **10**.[12]

Treatment of **10** with PPTS in dichloromethane at room temperature led to the tricyclic tertiary alcohol **12** in a 72% yield. Structural assignment of **12** was based on complete spectroscopic analysis, including bidimensional ^1H–^1H and ^1H–^{13}C correlations. The use of *p*-toluenesulfonic acid under the same reaction conditions led to the decomposition of the product.

Deoxygenation of the tertiary hydroxy function of **12** to **14** was achieved in two different ways: first by conversion into thiocarbonylimidazole **13**, followed by treatment with tri-*n*-butyltin hydride in refluxing toluene (60% overall yield for the two-step sequence), and second by direct reduction of alcohol **12**, by using chlorodiphenylsilane as a hydride source in the presence of a catalytic amount of indium trichloride (80% isolated yield) following the procedure recently reported by Baba et al.[13] Deoxygenation methods based on dissolving-metal reductions (Li, HMPA or ethylene diamine) of other functionalities (acetate, mesylate, tosylate) failed repeatedly due to competitive Grob fragmentation processes, activated when the tertiary alcohol was made to react under strong basic conditions.[14] The ether **14** exhibits the tricyclic core of massarinolin B (**3**), a bioactive sesquiterpenic acid isolated from *Massarina tunicata* by Shearer et al. (A-25-1; Lophiostomataceae).[15]

The tricyclic ether **14** was oxidized under treatment with chromium trioxide in acetic anhydride to afford the tricyclic lactone **6** following procedures reported by Magnus and Erman.[4] Transformation of **6** into the terminal olefin **20** was based on a modification of a procedure reported by Mori and Matsushima,[16] which included selective deprotection of the pyvaloate **17** to the primary alcohol **18** by treatment with diisobutylaluminium hydride in a mixture of toluene and dichloromethane at −78 °C (89% yield), followed by Dess–Martin periodinane oxidation[17] to aldehyde **19** and Wittig olefination with methylenetriphenylphosphorane (40% yield for the last two steps) (Scheme 1).

Elongation of olefin **20** was achieved by means of an efficient Pd-catalyzed Suzuki–Miyaura coupling[18] between **20** and the (*E*)-β-halomethacrylates **21a**–**d**.[19] Optimized reaction conditions for the coupling process between the olefinic product and (*E*)-β-halomethacrylates **21a**–**d** were found using (−)-β-pinene **22** as starting material under different reaction conditions (Table 1).

The best yields of the coupling product **23** were obtained by reaction of (−)-β-pinene with 9-BBN and further treatment with β-bromomethacrylate **21a**, using palladium tetrakistriphenylphosphine as the catalyst, potassium carbonate as the base, and a mixture of dimethylformamide and water (20:1) as the solvent at 50 °C for 48 h (Table 1, entry 9).

By applying the optimized conditions to the coupling of the olefin **20** with (*E*)-β-iodomethacrylate **21c** we were able to isolate the coupling product **24a** with 87% isolated yield (Table 1, entry 11).

Deprotection of the silyl groups by treatment of **24a** with tetra-*n*-butylammonium fluoride and further treatment with an ethereal solution of diazomethane led to the isolation of the methyl ester **24c** in quantitative yields.

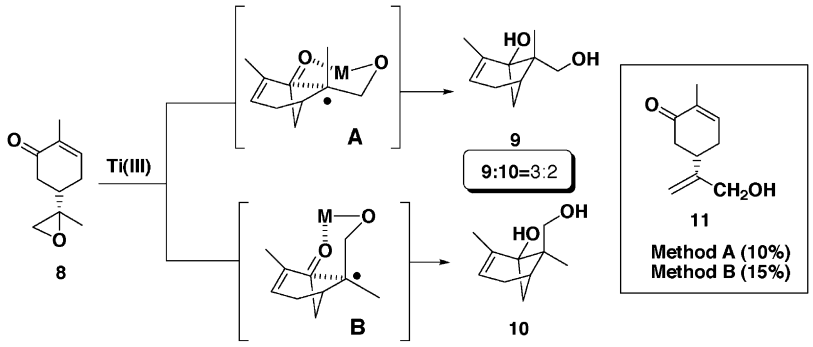
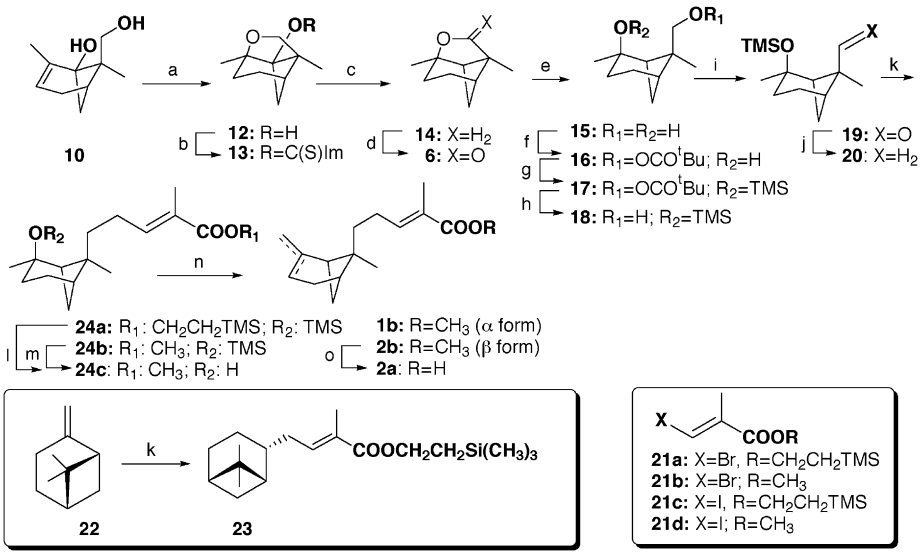
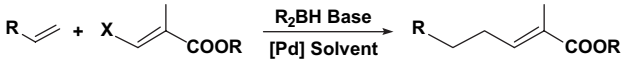


Figure 2.



Scheme 1. (a) PPTS, THF, reflux, 4 h (72%); (b) thiocarbonyldiimidazole, CH_2Cl_2, rt, 24 h (75%); (c) (from **13**) nBu$_3$SnH, AIBN, toluene, reflux, 5 h (80%); (from **12**) $InCl_3$, Ph_2SiHCl, $ClCH_2CH_2Cl$, 80 °C, 3 h (80%); (d) see Ref. 4; (e–g): see Ref. 2; (h) DIBAL-H, CH_2Cl_2–toluene (1:1), 0 °C, 20 min (90%); (i) Dess–Martin, CH_2Cl_2, 0 °C (73%); (j) $(Ph_3P)_3P{=}CH_2$, DME, rt, 15 h (56%); (k) **20**, 9-BBN, THF, rt, 15 h, **21**, DMF–H_2O (20:1), $Pd(PPh_3)_4$, 50 °C, 48 h (see Table 1); (l) (i) nBu$_4$NF, THF, rt; (ii) CH_2N_2, ether (70% two steps); (m) nBu$_4$NF, THF, rt, 48 h (75%); (n) Tf_2O, DMAP, CH_2Cl_2, rt, four days (83%); (o) 2 N KOH, MeOH, rt, 24 h (75%).

Table 1. Pd-catalyzed Suzuki–Miyaura couplings[a]

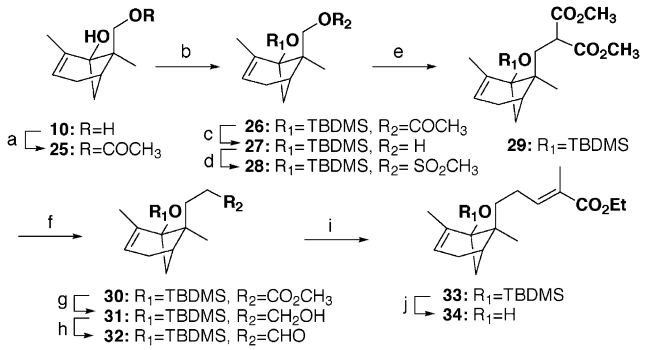


Entry	Alkene	R_2BH	Catalyst	HMA[c]	Base	Solvent	Product yield (%)[d]
1	**22**	$(RO)_2BH$[b]	$PdCl_2$(dppf)	**21a**	K_3PO_4	DMF	**23** (10)
2	**22**	9-BBN	$PdCl_2$(dppf)	**21a**	K_3PO_4	DMF	**23** (15)
3	**22**	$(RO)_2BH$[b]	$PdCl_2(CH_3CN)_2$	**21a**	K_3PO_4	DMF	**23** (15)
4	**22**	9-BBN	$PdCl_2(CH_3CN)_2$	**21a**	K_3PO_4	DMF	**23** (17)
5	**22**	9-BBN	$PdCl_2(CH_3CN)_2$	**21a**	K_2CO_3	DMF	**23** (20)
6	**22**	9-BBN	$PdCl_2(CH_3CN)_2$	**21a**	K_2CO_3	DMF/H_2O[e]	**23** (27)
7	**22**	$(RO)_2BH$[b]	$Pd(Ph_3P)_4$	**21a**	K_2CO_3	DMF/H_2O[e]	**23** (60)
8	**22**	9-BBN	$Pd(Ph_3P)_4$	**21a**	K_3PO_4	DMF/H_2O[e]	**23** (65)
9	**22**	9-BBN	$Pd(Ph_3P)_4$	**21a**	K_2CO_3	DMF/H_2O[e]	**23** (72)
10	**20**	9-BBN	$Pd(Ph_3P)_4$	**21a**	K_2CO_3	DMF/H_2O[e]	**24a** (85)
11	**20**	9-BBN	$Pd(Ph_3P)_4$	**21c**	K_2CO_3	DMF/H_2O[e]	**24a** (87)
12	**20**	9-BBN	$Pd(Ph_3P)_4$	**21b**	K_2CO_3	DMF/H_2O[e]	**24b** (70)
13	**20**	9-BBN	$Pd(Ph_3P)_4$	**21d**	K_2CO_3	DMF/H_2O[e]	**24b** (78)

[a] All reactions were run at 50 °C.
[b] $(RO)_2BH$–catecholborane.
[c] HMA–halomethacrylate.
[d] Isolated yields.
[e] DMF–H_2O (20:1).

Dehydration of **24c** by treatment with trifluoromethylsulfonic anhydride in the presence of excess of DMAP led to a reaction mixture with the β-form **2b** as the major dehydration product (83% isolated yield). Unfortunately, we were not able to isolate the α-form **1b** by chromatography on silica gel impregnated with silver nitrate, although we were able to detect its presence by ^{1}H NMR in the reaction mixture (8% yield). Saponification of the methyl ester **2b** led to the isolation of (+)-**2a** quantitatively.

Additionally, conversion of diol **10** into **27** required a three-step sequence of the protection–deprotection protocol: selective acetylation of the primary alcohol, silylation of the tertiary hydroxy function, and saponification of the acetate with ethanolic potassium hydroxide, to yield the primary alcohol **27** with 92% yield. Previous attempts to elongate the side chain without protection of the tertiary hydroxyl group resulted in a Grob fragmentation to afford the starting carvone. Something similar happened when we attempted a Horner–Wittig reaction with the hydroxyaldehyde obtained by selective oxidation of the diol **10**. Elongation of the lateral chain was first achieved with malonate displacement on the mesylate **28**, followed by decarboxylation to yield the methyl ester **30** with 68% yield (Scheme 2).



Scheme 2. (a) Ac_2O, pyr (100%); (b) TBDMSCl, imidazole, DMF (95%); (c) KOH, EtOH (97%); (d) MsCl, pyr (96%); (e) $NaCH(CO_2CH_3)_2$, toluene (85%); (f) NaCl, H_2O, DMSO (80%); (g) LAH, ether (88%); (h) $(ClCO)_2$, (DMSO), Et_3N, CH_2Cl_2 (98%); (i) NaH, $(EtO)_2POCH(CH_3)COOEt$, toluene (86%); (j) nBu$_4$NF, THF (90%).

Transformation of the methyl ester **30** into α-(*E*)-*endo*-1-hydroxy-bergamoten-12-oic ethyl ester **34** was achieved by LAH reduction to the primary alcohol **31**, followed by Swern oxidation and Wittig olefination of the aldehyde **32** to afford the ethyl ester **33** with 75% overall yield. Finally, deprotection of the silyl ether led us to isolate the ethyl ester **34** analog with 90% yield.

3. Conclusion

The Ti(III)-promoted cyclization of (+)-8,9-epoxycarvone **8** led to an equimolecular mixture of diastereomers, from which the diol **10** was isolated and further used as starting material for the synthesis of β-(*E*)-*endo*-bergamoten-12-oic acid **2a**. The key step in the synthesis proved to be a Suzuki–Miyaura coupling between the terminal alkene **20** and the β-iodomethacrylate **21c**. The synthesis of the α-(*E*)-*endo*-1-hydroxy-bergamoten-12-oic acid derivative **34** starting from **10** was achieved by iterative elongation sequences of the lateral chain.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired by using GC–MS system in EI mode with a maximum *m*/*z* range of 600. Optical rotations were determined on a digital Perkin–Elmer 241 polarimeter in a 1 dm cell. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over CaH_2, distilled under reduced pressure, and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques[20] on Merck silica gel 60 (0.040–0.063 mm). R_f values refer to TLC carried out on 0.25 mm Merck 60 F_{254} silica gel plates, with the same eluant as that indicated for the column chromatography unless otherwise indicated. Yields reported are for chromatographically pure isolated products unless otherwise mentioned.

4.2. Reductive opening of (+)-8,9-epoxycarvone 8: preparation of 9 and 10

Solution a: titanocene dichloride Cp_2TiCl_2 (3.3 g, 13.5 mmol) and powdered Zn (2.6 g, 40.5 mmol) were placed in a two-necked 50 mL round-bottomed flask under an argon atmosphere. Anhydrous freshly distilled and deoxygenated THF (25 mL) was added, and stirring was maintained for 1 h at room temperature (a deep green color appeared after 15 min).

Solution b: (+)-8,9-epoxycarvone **8**[6] (1 g, 6.1 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly distilled and deoxygenated THF (60 mL) was added under an argon atmosphere.

Method A: *solution a* was added dropwise via cannula to *solution b* under an argon atmosphere. The reaction mixture was stirred for 3–5 h at room temperature.

Method B: *solution b* was added dropwise via cannula to *solution a* under an argon atmosphere. The reaction mixture was stirred for 3–5 h at room temperature.

Work up: when the reaction mixture turned from deep green to red, saturated solutions of NaH_2PO_4 (75 mL) and NaCl (75 mL) were added. Stirring was maintained overnight and the reaction mixture was filtered. The filtrate was extracted with ether (3×25 mL), and the combined organic layers were washed with a saturated NaCl solution and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure led to the isolation of the crude reaction product. Fractionation was successfully achieved by flash chromatography on silica gel. Elution with hexane–ethyl acetate (1:1) afforded diols **9** (413 mg, 41%) and **10** (275 mg, 27%) and (*S*)-(+)-5-[1-(hydroxymethyl)vinyl]-2-methyl-cyclohex-2-enone **11**[7] (150 mg, 15%).

4.2.1. (1*R*,5*S*,6*S*)-2,6-Dimethyl-6-hydroxymethylbicyclo[3.1.1]hept-2-en-1-ol 9. $[\alpha]_D^{20}$ +38 (*c* 1.8, $CHCl_3$); R_f 0.15 (hexane–ethyl acetate 4:6); IR ν 3385, 2930, 1653, 1456, 1375, 1339, 1240, 1152, 1107, 995, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 3H), 1.6–2.4 (m, 5H), 1.73 (s, 3H), 3.67 (d, J=11 Hz, 1H), 4.26 (d, J=11 Hz, 1H), 5.2 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 17.0 (CH_3), 30.5 (CH_2), 31.2 (CH), 39.8 (CH_2), 46.7 (C), 69.5 (CH_2), 79.0 (C), 117.3 (CH), 146.1 (C) ppm; EIMS *m*/*z* (%) 168 (M^+, 6), 150 (13), 135 (11), 108 (52), 93 (24), 82 (100), 67 (17). HRMS (EI): calcd for $C_{10}H_{17}O_2$ (M^++H^+) 169.1228, found 169.1233.

4.2.2. (1*R*,5*S*,6*R*)-2,6-Dimethyl-6-hydroxymethylbicyclo[3.1.1]hept-2-en-1-ol 10. $[\alpha]_D^{20}$ −18.4 (*c* 1.2, $CHCl_3$); R_f 0.23 (hexane–ethyl acetate 4:6); IR ν 3338, 2925, 1654, 1597, 1421, 1263, 1164, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.8 (s, 3H), 1.6–2.3 (m, 5H), 3.4 (d, J=10.3 Hz, 1H), 3.75 (d, J=10.3 Hz, 1H), 5.27 (s, 1H)

ppm; ^{13}C NMR ($CDCl_3$) δ 16.7 (CH_3), 17.0 (CH_3), 30.9 (CH_2), 34.2 (CH), 39.4 (CH_2), 46.3 (C), 65.6 (CH_2), 77.6 (C), 117.5 (CH), 145.2 (C) ppm; EIMS *m/z* (%) 168 (M^+, 2.5), 150 (12), 135 (8), 108 (38), 93 (19), 82 (100), 67 (11). HRMS (EI): calcd for $C_{10}H_{17}O_2$ (M^++H^+) 169.1228, found 169.1235.

4.3. Cyclization of diol 10 catalyzed by PPTS: (1*R*,4*S*,6*S*,1*R*)-1,7-dimethyl-6-hydroxy-9-oxa-tricyclo[4.3.0.0.^{4,7}]nonane 12

PPTS (0.38 g, 1.5 mmol) was added to a solution of **9** (0.25 g, 1.5 mmol) in freshly distilled THF (45 mL). The reaction mixture was refluxed for 48 h. The solvent was evaporated at reduced pressure, water (25 mL) was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ (3×25 mL), dried (Na_2SO_4), filtered, and concentrated to give a residue (0.18 g), which was fractionated by flash chromatography over silica gel. Elution with hexane–ethyl acetate (7:3) afforded **12** (0.18 g, 72%); $[\alpha]_D^{20}$ +6 (*c* 0.2, $CHCl_3$); R_f 0.25 (hexane–ethyl acetate 7:3); IR ν 3447, 2926, 1724, 1674, 1462, 1365, 1171, 1035, 917 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.24 (s, 3H), 1.5–2.6 (m, 7H), 3.46 (d, *J*=9 Hz, 1H), 3.81 (d, *J*=9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 20.0 (CH_3), 22.6 (CH_2), 30.4 (CH_2), 34.8 (CH_2), 35.8 (CH), 54.1 (C), 71.6 (CH_2), 81.4 (C), 89.2 (C) ppm; EIMS *m/z* (%), 168 (M^+, 10), 153 (12), 125 (100), 95 (46), 69 (62). HRMS (EI): calcd for $C_{10}H_{17}O_2$ (M^++H^+) 169.1228, found 169.1223.

4.4. (1*R*,4*S*,6*S*,1*R*)-1,7-Dimethyl-6-[1′-(imidazolyl)thiocarbonyloxy]-9-oxa-tricyclo[4.3.0.0.^{4,7}]nonane 13

To a solution of **12** (0.112 g, 0.66 mmol) in freshly distilled dichloromethane (5 mL) thiocarbonyldiimidazole (0.142 g, 0.80 mmol) was added. The reaction mixture was stirred under an argon atmosphere at room temperature for 24 h. Evaporation of the solvent gave a crude product (0.26 g), which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (1:1) afforded **13** (0.139 g, 75%); R_f 0.4 (ethyl acetate); $[\alpha]_D^{20}$ +71.19 (*c* 0.55, $CHCl_3$); IR ν 3133, 2924, 2853, 1678, 1525, 1474, 1462, 1367, 1286, 1235, 1092, 1035, 1021, 895, 886, 823, 761, 667, 645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.68 (t, *J*=5.2 Hz, 1H), 1.08 (dd, J_1=6 Hz, J_2=3 Hz, 1H), 1.34 (s, 3H), 1.49 (s, 3H), 1.61 (m, 2H), 2.10 (m, 3H), 4.22 (d, *J*=10.6 Hz, 1H), 4.66 (d, *J*=10.6 Hz, 1H), 7.07 (s, 1H), 7.42 (s, 1H), 8.15 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.6 (CH_2), 21.3 (CH_3), 23.5 (CH_3), 24.8 (CH), 26.0 (CH_2), 38.8 (CH_2), 46.9 (C), 58.4 (C), 79.4 (CH_2), 91.8 (C), 115.8 (CH), 130.8 (CH), 135.3 (CH), 166.0 (C) ppm; HRMS (EI): calcd for $C_{14}H_{19}O_2N_2S$ (M^++H^+) 279.1162, found 279.1173.

4.5. Preparation of (1*R*,4*S*,6*R*,7*S*)-1,7-dimethyl-9-oxa-tricyclo[4.3.0.0^{4,7}]nonane 14

4.5.1. Compound 14 (from 13). A solution of **13** (0.134 g, 0.53 mmol) and AIBN (20 mg) in toluene (2.5 mL) was heated to reflux and tri-*n*-butyltin hydride (0.12 mL, 1.2 mmol) was added dropwise. The reaction was stirred at the same temperature for 5 h. Then, the solvent was evaporated off and a saturated NaF solution (10 mL) was added and the mixture was stirred overnight at room temperature. The reaction product was extracted with ether (25 mL). The organic layers were dried over Na_2SO_4, and the solvent was evaporated off to afford **14**[4] (0.059 g, 80%); $[\alpha]_D^{20}$ +26.52 (*c* 1.64, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 8:2); IR ν 2965, 2924, 2866, 1452, 1375, 1229, 1173, 1134, 1032, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6H), 1.43 (d, *J*=9.2 Hz, 1H), 1.58–2.03 (m, 7H), 3.36 (d, *J*=8.7 Hz, 1H), 3.81 (d, *J*=8.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 19.7 (CH_3), 22.7 (CH_2), 22.9 (CH_2), 25.3 (CH_3), 32.5 (CH_2), 41.4 (CH), 51.9 (C), 52.3 (CH), 72.6 (CH_2), 86.9 (C) ppm; EIMS *m/z* (%): 152 (M^+, 3.2), 137 (8), 123 (10), 109 (19), 97 (100), 79 (46), 69 (51), 55 (30).

4.5.2. Compound 14 (from 12). To a mixture of $InCl_3$ (11 mg, 0.05 mmol) and **12** (170 mg, 1 mmol) in dry 1,2-dichloroethane (1 mL), chlorodiphenylsilane (0.43 g, 2 mmol) was added under an argon atmosphere. The reaction mixture was stirred at 80 °C for 3 h. The resulting mixture was poured into Et_2O (25 mL) and water (20 mL). The reaction mixture was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. The evaporation of the ether solution gave the crude product, which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (1:1) afforded **14** (0.12 g, 80%), which exhibited the spectroscopic properties described above for **14**.

4.6. (1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-trimethylsilyloxy-bicyclo[3.1.1]-hept-6-yl)-methanol 18

To a solution of **17**[2] (0.74 g, 2.26 mmol) in dichloromethane (8 mL) and toluene (8 mL) at −78 °C, was added dropwise a solution of DIBAL-H (1.5 M in toluene, 23 mL, 33.6 mmol) under inert atmosphere. The reaction mixture was stirred for 30 min and then allowed to settle at −5 °C for 5 h. Ethyl acetate (70 mL) and an aqueous solution of potassium tartrate (5.0 M) were added and the reaction mixture was stirred overnight at room temperature. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **18** (0.49 g, 89.5%); $[\alpha]_D^{20}$ −31.8 (*c* 16.7, $CHCl_3$); R_f 0.4 (hexane–ethyl acetate 98:2); IR ν 3157, 2961, 2922, 2874, 1373, 1252, 1040, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 0.98 (d, *J*=10.9 Hz, 1H), 1.31 (s, 3H), 1.34 (s, 3H), 1.62–2.02 (m, 7H), 2.70 (dd, J_1=3.0 Hz, J_2=10.7 Hz, 1H), 3.15 (dd, J_1=10.7 Hz, J_2=10.7 Hz, 1H), 3.95 (dd, J_1=3.0 Hz, J_2=10.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.5 (CH_3), 22.8 (CH_3), 24.2 (CH_2), 27.7 (CH_2), 30.6 (CH_3), 32.7 (CH_2), 39.3 (CH), 42.0 (C), 53.5 (CH), 66.7 (CH_2), 79.8 (C) ppm; HRMS (EI): calcd for $C_{13}H_{25}O_2NaSi$ (M^++Na^+) 265.1594, found 265.1587.

4.7. (1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-trimethylsilyloxy-bicyclo[3.1.1]-hept-6-yl)-carboxaldehyde 19

To a solution of Dess–Martin periodinane[14] (4.0 g, 9.5 mmol) in dichloromethane (40 mL), at 0 °C under an argon atmosphere, a solution of **18** (1.4 g, 6 mmol) in dichloromethane (20 mL) was added dropwise. The reaction mixture was stirred for 20 min. Then, the reaction mixture

was diluted with ether (50 mL) and aqueous 1.5 M NaOH solution (75 mL) was added. The reaction mixture was stirred for 15 min. The organic layer was washed with 1.5 M NaOH, water, and brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (99.5:5) afforded **19** (0.93 g, 72.5%); $[\alpha]_D^{20}$ −5.13 (*c* 15.8, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 99:1); IR ν 2957, 2930, 1716, 1251, 1132, 1046, 1007, 859, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 9H), 1.13 (d, J=10 Hz, 1H), 1.27 (s, 6H), 1.6–2.6 (m, 7H), 9.66 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.3 (CH_3), 16.5 (CH_3), 23.0 (CH_2), 26.1 (CH_2), 29.2 (CH_3), 33.1 (CH_2), 39.9 (CH), 50.2 (C), 57.9 (CH), 76.6 (C), 203.9 (C) ppm; HRMS (EI): calcd for $C_{13}H_{24}O_2NaSi$ (M^++Na^+) 263.1438, found 263.1426.

4.8. (1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-6-vinylbicyclo-[3.1.1]hept-2-yloxy)-trimethylsilane 20

To a solution of aldehyde **19**[2] (0.88 g, 14.16 mmol) in dry DME (5 mL), a solution of methylenetriphenylphosphorane (4.7 g, 17 mmol) in DME (25 mL) was added dropwise. A white precipitate was formed immediately. The reaction mixture was stirred at room temperature overnight. Then, a saturated $NaHCO_3$ solution (25 mL) was added and the volatiles were removed in vacuo. The reaction product was then extracted with dichloromethane. The combined layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane afforded **20** (0.49 g, 56%); $[\alpha]_D^{20}$ +31.20 (*c* 1.5, $CHCl_3$); R_f 0.5 (hexane); IR ν 3075, 2961, 2919, 2868, 1629, 1451, 1411, 1370, 1343, 1249, 1167, 1128, 1047, 1020, 1001, 903, 858, 838, 753, 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 9H), 0.99 (d, J=10.1 Hz, 1H), 1.29 (s, 3H), 1.31 (s, 3H), 1.5–2.4 (m, 7H), 4.80 (dd, J_1=1.2 Hz, J_2=2.2 Hz, 1H), 4.87 (dd, J_1=2.0 Hz, J_2=10.4 Hz, 1H), 6.48 (dd, J_1=11.2 Hz, J_2=17.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.7 ($3CH_3$), 24.8 (CH_3), 25.8 (CH_2), 29.4 (CH_2), 30.6 (CH_3), 34.1 (CH_2), 41.6 (CH), 43.5 (C), 55.7 (CH), 78.6 (C), 109.6 (CH_2), 145.9 (CH) ppm; HRMS (EI): calcd for $C_{14}H_{26}ONaSi$ (M^++Na^+) 261.1645, found 261.1671.

4.9. (−)-(1*S*,2*R*,5*S*)-5-(6,6-Dimethylbicyclo[3.1.1]hept-2-yl)-2-methyl-pent-2-enoic acid 2-(trimethyl-silanyl)-ethyl ester 23

4.9.1. Suzuki–Miyaura couplings. General procedure.

Solution a: (–)-β-pinene **22** (0.26 g, 1.9 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly distilled and deoxygenated THF (1 mL) was added under an argon atmosphere. Hydroborane (catecholborane, 9-BBN) (2.3 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature.

Solution b: to a solution of β-bromomethacrylate **21a** (0.65 g, 2.25 mmol) in a exhaustively degasified mixture of DMF–H_2O (20 mL, 20:1) the catalyst [$Pd(Ph_3P)_4$, $PdCl_2$(dppf), $PdCl_2(CH_3CN)_2$] (0.08 mmol) and the base (K_3PO_4 or K_2CO_3) (9 mmol) were added.

Solution a was added via syringe to *solution b* and the reaction mixture was stirred at 50 °C for 48 h. Then, the mixture was allowed to reach room temperature, water (50 mL) was added, and the reaction mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **23** (see yields Table 1). $[\alpha]_D^{20}$ −5.11 (*c* 1.27, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 9:1); IR ν 2921, 1711, 1648, 1383, 1250, 1153, 1116, 1066, 938, 838, 748, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.84 (d, J=10 Hz, 1H), 1.04 (s, 3H), 0.9–2.4 (m, 12H), 1.16 (s, 3H), 1.80 (s, 3H), 4.21 (t, J=10 Hz, 2H), 6.72 (t, J=6Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −1.5 ($3CH_3$), 12.5 (CH_3), 17.4 (CH_2), 22.3 (CH_2), 23.2 (CH_3), 27.0 (CH_2), 28.2 (CH_3), 33.8 (CH_2), 36.3 (CH_2), 38.7 (C), 41.1 (CH), 41.4 (CH), 45.8 (CH), 62.4 (CH_2), 127.5 (C), 141.6 (CH), 168.4 (C) ppm; HRMS (EI): calcd for $C_{19}H_{34}O_2NaSi$ (M^++Na^+) 345.2220, found 345.2210.

4.10. (+)-(1′*R*,2′*R*,5′*R*,6′*S*)-(*E*)-5-[2,6-Dimethyl-2-(trimethyl-silanyloxy)bicyclo[3.1.1]hept-6-yl]-2-methyl-pent-2-enoic acid trimethyl-silanylmethyl ester 24a

Solution a: (2,6-dimethyl-6-vinylbicyclo[3.1.1]hept-2-yloxy)-trimethylsilane **20** (0.15 g, 0.63 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly distilled and deoxygenated THF (1 mL) was added under an argon atmosphere. 9-BBN (0.5 M in THF, 1.9 mL, 0.95 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature.

Solution b: to a solution of halomethacrylate **21c** (0.26 g, 0.82 mmol) in a exhaustively degasified mixture of DMF–H_2O (7.5 mL, 20:1), $Pd(Ph_3P)_4$ (40 mg, 0.04 mmol) and powdered K_2CO_3 (0.46 g, 3.34 mmol) were added.

Solution a was added via syringe to *solution b* and the reaction mixture was stirred at 50 °C for 48 h. Then, the mixture was allowed to reach room temperature, water (25 mL) was added, and the reaction mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **24a** (0.39 g, 87%); $[\alpha]_D^{20}$ +6.28 (*c* 1.36, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 9:1); IR ν 2955, 2916, 1711, 1651, 1463, 1365, 1250, 1139, 1054, 1002, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 9H), 0.08 (s, 9H), 1.02 (t, J=8.0 Hz, 2H), 1.21 (s, 3H), 1.26 (s, 3H), 1.82 (s, 3H), 1.4–2.4 (m, 12H), 4.22 (t, J=8.0 Hz, 2H), 6.78 (t, J=7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −1.5 ($3CH_3$), 2.7 ($3CH_3$), 12.3 (CH_3), 17.3 (CH_2), 23.9 (CH_3), 24.1 (CH_2), 27.9 (CH_2), 29.6 (CH_2), 31.3 (CH_3), 33.2 (CH_2), 35.0 (CH_2), 39.8 (CH), 40.7 (C), 54.9 (CH), 62.4 (CH_2), 78.7 (C), 127.0 (C), 143.7 (CH), 168.5 (C) ppm; HRMS (EI): calcd for $C_{23}H_{44}O_3NaSi_2$ (M^++Na^+) 447.2721, found 447.2719.

4.11. (+)-(1′*R*,2′*R*,5′*R*,6′*S*)-(*E*)-5-[2,6-Dimethyl-2-(trimethyl-silanyloxy)bicyclo[3.1.1]hept-6-yl]-2-methyl-pent-2-enoic acid methyl ester 24b

Solution a: (2,6-dimethyl-6-vinylbicyclo[3.1.1]hept-2-yloxy)-trimethylsilane **20** (0.12 g, 0.52 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly

distilled and deoxygenated THF (1 mL) was added under an argon atmosphere. 9-BBN (0.5 M in THF, 1.6 mL, 0.78 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature.

Solution b: to a solution of halomethacrylate **21d** (0.13 g, 0.57 mmol) in a exhaustively degasified mixture of DMF–H_2O (7.5 mL, 20:1), $Pd(Ph_3P)_4$ (40 mg, 0.04 mmol) and powdered K_2CO_3 (0.38 g, 2.76 mmol) were added.

Solution a was added via syringe to *solution b* and the reaction mixture was stirred at 50 °C for 48 h. Then, the mixture was allowed to reach room temperature, water (25 mL) was added, and the reaction mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **24b** (0.14 g, 79.9%); $[\alpha]_D^{20}$ +10.62 (*c* 1.97, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 9:1); IR ν 2955, 2917, 1717, 1645, 1437, 1249, 1128, 1045, 1005, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 9H), 0.98 (d, J=10.0 Hz, 1H), 1.20 (s, 3H), 1.25 (s, 3H), 1.75 (s, 3H), 1.4–2.4 (m, 11H), 3.70 (s, 3H), 6.78 (t, J=7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.7 ($3CH_3$), 12.2 (CH_3), 23.9 (CH_3), 24.1 ($2CH_2$), 27.9 (CH_2), 31.3 (CH_3), 33.2 (CH_2), 35.0 (CH_2), 39.8 (CH), 40.7 (C), 51.5 (CH_3), 54.9 (CH), 78.7 (C), 126.6 (C), 144.1 (CH), 168.8 (C) ppm; HRMS (EI): calcd for $C_{19}H_{34}O_3NaSi$ (M^++Na^+) 361.2169, found 361.2153.

4.12. Preparation of (+)-(1′*R*,2′*R*,5′*R*,6′*S*)-(*E*)-5-[2-hydroxy-2,6-dimethylbicyclo[3.1.1]hept-6-yl]-2-methylpent-2-enoic acid methyl ester 24c

4.12.1. Compound 24c (from 24a). Tetrabutylammonium fluoride (0.2 g, 0.63 mmol) was added to a solution of **24a** (0.16 g, 0.39 mmol) in dry THF (1 mL) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuo and a solution of 5% $NaHCO_3$ was added. The aqueous solution was extracted with ether at basic pH and then acidified with 6 N HCl to pH 4–5. The reaction mixture was then extracted with ether, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with an ethereal diazomethane solution to afford a crude methyl ester (0.110 g). The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) gave **24c** (0.072 g, 70%); $[\alpha]_D^{20}$ +8.0 (*c* 1.5, $CHCl_3$); R_f 0.3 (hexane–ethyl acetate 1:1); IR ν 3507, 2953, 2919, 1712, 1651, 1444, 1282, 1126, 924, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, J=10.0 Hz, 1H), 1.23 (s, 3H), 1.25 (s, 3H), 1.82 (s, 3H), 1.4–2.4 (m, 12H), 3.71 (s, 3H), 6.78 (t, J=7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 23.8 (CH_3), 23.9 (CH_2), 24.2 (CH_2), 28.3 (CH_2), 32.1 (CH_2), 35.1 (CH_2), 40.2 (CH), 40.9 (C), 51.5 (CH_3), 54.0 (CH), 75.9 (C), 126.7 (C), 143.7 (CH), 168.8 (C) ppm; HRMS (EI): calcd for $C_{16}H_{26}O_3NaSi$ (M^++Na^+) 289.1774, found 289.1766.

4.12.2. Compound 24c from 24b. Tetrabutylammonium fluoride (0.29 g, 0.92 mmol) was added to a solution of **24b** (0.28 g, 0.84 mmol) in THF (2 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 48 h at room temperature. Then, the solvent was evaporated off, the residue was dissolved in ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) afforded **24c** (0.16 g, 74.4%).

4.13. (+)-(6′*S*,1′*S*,5′*S*)-2-Methyl-5-(6-methyl-2-methylenebicyclo[3.1.1]hept-6-yl)-pent-2-enoic acid methyl ester: β-(*E*)-*endo*-bergamoten-12-oic acid methyl ester 2b

Trifluoromethanesulfonic anhydride (0.91 g, 3.24 mmol) was added to a solution of **24c** (0.17 g, 0.65 mmol) and dimethylaminopyridine (0.95 g, 7.76 mmol) in dry dichloromethane (30 mL). The reaction mixture was stirred for four days at room temperature. Then, the reaction mixture was poured over a 5% aqueous $NaHCO_3$ solution (50 mL) and extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (9:1) afforded **2b** (0.132 g, 83%); R_f 0.25 (hexane–ethyl acetate 9:1); $[\alpha]_D^{20}$ +20.0 (*c* 2.1, $CHCl_3$); IR ν 2949, 1717, 1443, 1272, 878, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.88 (s, 3H), 0.8–2.8 (m, 12H), 3.73 (s, 3H), 4.62 (m, 1H), 4.82 (m, 1H), 6.77 (t, J=8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3), 18.0 (CH_3), 24.8 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 32.5 (CH_2), 37.0 (CH_2), 42.7 (C), 43.1 (CH), 51.5 (CH_3), 52.3 (C), 103.3 (CH_2), 127.1 (C), 142.8 (CH), 155.6 (C), 168.5 (C) ppm; EIMS *m/z* (%): 248 (M^+, 6), 217 (6), 189 (3), 173 (3), 158 (16), 135 (10), 122 (54), 119 (100), 93 (82), 79 (64), 77 (41), 55 (43). HRMS (EI): calcd for $C_{16}H_{25}O_2$ (M^++H^+) 249.1856, found 249.1862.

4.14. (+)-(6′*S*,1′*S*,5′*S*)-2-Methyl-5-(6-methyl-2-methylenebicyclo[3.1.1]hept-6-yl)-pent-2-enoic acid methyl ester: β-(*E*)-*endo*-bergamoten-12-oic acid 2a

To a stirred solution of **2b** (0.094 g, 0.38 mmol) in MeOH (2 mL), 2 N KOH (2 mL, 4 mmol) was added at room temperature. The mixture was stirred for 24 h at that temperature. MeOH was removed in vacuo and the residual aqueous solution was acidified to pH 3 with 2 N HCl. The aqueous phase was extracted with ether (3×15 mL), the combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (8:2) afforded **2a** (0.067 g, 75%); R_f 0.40 (hexane–ethyl acetate 8:2); $[\alpha]_D^{20}$ +30 (*c* 2.1, $CHCl_3$); IR ν 3072, 2962, 2955, 1687, 1640, 1421, 1384, 1287, 930, 878 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.10–1.36 (m, 2H), 1.45 (d, J=10 Hz, 1H), 1.65–1.90 (m, 2H), 1.84 (s, 3H), 1.95–2.17 (m, 3H), 2.20–2.35 (m, 1H), 2.30 (dt, J_1=5.6 Hz, J_2=10 Hz, 1H), 2.57 (t, J=5.6 Hz, 2H), 4.62 (s, 1H), 4.82 (s, 1H), 6.93 (t, J=8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 11.8 (CH_3), 18.1 (CH_3), 25.1 ($2CH_2$), 28.3 (CH_2), 28.6 (CH_2), 32.4 (CH_2), 37.1 (CH_2), 43.2 (CH), 49.2 (C), 52.4 (CH), 103.4 (CH_2), 126.7 (C), 145.6 (CH), 155.7 (C), 173.6 (C) ppm; HRMS (EI): calcd for $C_{15}H_{22}O_2Na$ (M^++Na^+) 257.1512, found 257.1508.

4.15. (1*RS*,5*SR*,6*RS*)-(1-Hydroxy-2,6-dimethylbicyclo-[3.1.1]hept-2-en-6-yl)-methyl acetate 25

To a solution of diol **10** (594 mg, 3.54 mmol) in pyridine (0.30 mL, 3.89 mmol), acetic anhydride (0.33 mL,

3.54 mmol) was added. The reaction mixture was stirred at 0 °C under an argon atmosphere for 9 h and then diluted with Et_2O, and poured into ice water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with $NaHCO_3$ (5%), brine, and dried with Na_2SO_4. Removal of the solvent afforded acetate **25** (742 mg, 100%), as a colorless oil; R_f 0.60 hexane–ethyl acetate (1:1); IR ν 3480, 2940, 1726, 1452, 1383, 1171, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.51 (d, J=8.1 Hz, 1H), 1.67 (s, 3H), 1.94 (s, 3H), 2.0–2.2 (m, 3H), 2.21 (t, J=7.0 Hz, 1H), 3.80 (d, J=11.0 Hz, 1H), 4.02 (d, J=11.0 Hz, 1H), 5.16 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.3 (CH_3), 16.6 (CH_3), 20.6 (CH_3), 30.6 (CH_2), 34.3 (CH), 38.9 (CH_2), 44.3 (C), 67.3 (CH_2), 76.9 (C), 117.3 (CH), 145.4 (C) 171.4 (C) ppm; HRMS (EI): calcd for $C_{12}H_{18}O_3Na$ (M^++Na^+) 233.1148, found 233.1136.

4.16. (1*RS*,5*SR*,6*RS*)-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]methyl acetate 26

A mixture of the hydroxy ester **25** (581 mg, 2.77 mmol), *tert*-butyldimethylsilyl chloride (1.04 g, 6.91 mmol) and imidazole (573 mg, 8.42 mmol) in dry DMF (14 mL) was stirred for five days under an argon atmosphere at 40 °C, poured into ice water, and extracted with hexane. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was filtered through a small pad of silica gel, and concentrated to yield the silyl ether **26** as a colorless oil (0.82 g, 95%); R_f 0.80 (hexane–ethyl acetate 1:1); IR ν 2955, 2859, 1744, 1470, 1252, 1175, 1063, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.90 (s, 9H), 1.22 (s, 3H), 1.64 (d, J=8.1 Hz, 1H), 1.70 (s, 3H), 2.0–2.2 (m, 3H), 2.01 (s, 3H), 2.48 (t, J=7.2 Hz, 1H), 3.96 (d, J=10.8 Hz, 1H), 4.02 (d, J=10.8 Hz, 1H), 5.24 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −1.9 (CH_3), 17.7 (CH_3), 18.3 (C), 18.8 (CH_3), 20.8 (CH_3), 25.9 ($3CH_3$), 30.8 (CH_2), 34.6 (CH), 39.1 (CH_2), 45.2 (C), 67.1 (CH_2), 78.5 (C), 117.3 (CH), 147.2 (C), 171.4 (C) ppm. HRMS (EI): calcd for $C_{18}H_{33}O_3Si$ (M^++H^+) 325.2193, found 325.2196.

4.17. (1*RS*,5*SR*,6*RS*)-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]methanol 27

To a stirred solution of **26** (545 mg, 1.68 mmol) in EtOH (5.3 mL), 5 M KOH (0.8 mL) was added. The reaction mixture was stirred at room temperature under an argon atmosphere for 80 min and then concentrated to afford a residue, which was dissolved in H_2O and extracted with Et_2O. The combined organic extracts were washed with brine and dried with Na_2SO_4. Removal of the solvent afforded **27** (0.46 g, 97%) as a colorless oil; R_f 0.40 (hexane–ethyl acetate 1:1); IR ν 3403, 2955, 2859, 1462, 1238, 1169, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.15 (s, 3H), 0.87 (s, 9H), 1.25 (s, 3H), 1.60 (d, J=8.2 Hz, 1H), 1.72 (br s, 3H), 2.0–2.2 (m, 3H), 2.48 (t, J=5.2 Hz, 1H), 3.37 (d, J=10.3 Hz, 1H), 3.58 (d, J=10.3 Hz, 1H), 5.25 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −3.0 ($3CH_3$), −2.0 (CH_3), 17.6 (CH_3), 18.2 (C), 18.8 (CH_3), 25.9 ($3CH_3$), 30.6 (CH_2), 34.7 (CH), 39.1 (CH_2), 47.0 (C), 65.7 (CH_2), 79.1 (C), 117.6 (CH), 146.7 (C) ppm; HRMS (EI): calcd for $C_{16}H_{31}O_2Si$ (M^++H^+) 283.2088, found 283.2080.

4.18. (1*RS*,5*SR*,6*RS*)-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]methyl methanesulfonate 28

To a stirred solution of the alcohol **27** (300 mg, 1.06 mmol) in dichloromethane (7 mL) and pyridine (0.17 mL, 2.12 mmol), at 0 °C methanesulfonyl chloride (0.12 mL, 1.6 mmol) was added. After 25 h at 25 °C, the mixture was poured into ice water and stirred for additional 2 h at room temperature. The two-phase system was extracted with ether. The combined ethereal extracts were washed with water and brine, dried (Na_2SO_4) and, concentrated under reduced pressure to give the mesylate **28** (0.37 g, 96%); R_f 0.50 (hexane–diethyl ether 1:1); IR ν 2474, 1464, 1358, 1250, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 1.26 (s, 3H), 1.64 (d, J=8.1 Hz, 1H), 1.70 (q, J=1.5 Hz, 3H), 2.1–2.25 (m, 3H), 2.48 (t, J=6.1 Hz, 1H), 2.94 (s, 3H), 4.06 (d, J=9.2 Hz, 1H), 4.20 (d, J=9.2 Hz, 1H), 5.29 (br s, 1H) ppm.

4.19. (1*SR*,5*SR*,6*SR*)-Dimethyl-2-[1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-methyl malonate 29

To a solution of sodium dimethylmalonate, prepared from sodium (25.5 mg, 1.11 mmol) and dimethylmalonate (201.3 mg, 1.52 mmol) in toluene (1 mL), a solution of the mesyl compound **28** (366 mg, 1.01 mmol) in toluene (3.5 mL) was added. After three days at reflux the mixture was cooled, and then poured into ice water, and extracted with diethyl ether. The combined organic extracts were washed with brine and dried with Na_2SO_4. The solvent was evaporated at reduced pressure to afford a crude product, which was chromatographed on silica gel. Elution with hexane–ether (80:20) gave the diester **29** (0.34 g, 85%); R_f 0.40 (hexane–diethyl ether 1:1); IR ν 2953, 2859, 1740, 1435, 1236, 1165, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.08 (s, 3H), 1.06 (d, J=8.2 Hz, 1H), 1.8–2.2 (m, 5H), 1.70 (q, J=1.5 Hz, 3H), 2.42 (t, J=6.0 Hz, 1H), 3.39 (dd, J_1=3.0 Hz, J_2=5.9 Hz, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 5.25 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −3.0 (CH_3), −2.0 (CH_3), 18.2 (C), 18.8 ($2CH_3$), 25.8 ($3CH_3$), 30.6 (CH_2), 31.8 (CH_2), 36.0 (CH), 39.0 (CH_2), 45.3 (C), 48.3 (CH), 52.1 ($2CH_3$), 79.8 (C), 117.6 (CH), 147.0 (C), 170.4 (C), 170.7 (C) ppm; HRMS (EI): calcd for C_{21} $H_{37}O_5Si$ (M^++H^+) 397.2404, found 397.2397.

4.20. Methyl (1*SR*,5*SR*,6*SR*)-3-[1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-propanoate 30

To a solution of the diester **29** (206 mg, 0.52 mmol) in DMSO (0.6 mL), water (18 mg, 1 mmol) and sodium chloride (61 mg, 1.04 mmol) were added. The suspension was refluxed for 7 h under an argon atmosphere, after which it was diluted with ethyl acetate. The solution was washed with water, and brine, dried (Na_2SO_4), and evaporated to afford the ester **30** (0.14 g, 80%) as a colorless oil; R_f 0.50 (hexane–diethyl ether 7:3); IR ν 2930, 2857, 1742, 1462, 1236, 1167, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.14 (s, 3H), 1.60 (d, J=8.0 Hz, 1H), 1.72 (br s, 3H), 1.8–2.3 (m, 7H), 2.24 (t, J=6.1 Hz, 1H), 3.62 (s, 3H), 5.23 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$)

δ −3.0 (CH_3), −2.0 (CH_3), 18.2 (C), 19.0 (CH_3), 19.1 (CH_3), 25.9 ($3CH_3$), 28.5 (CH_2), 29.5 (CH_2), 30.6 (CH_2), 35.8 (CH), 39.1 (CH_2), 45.3 (C), 51.1 (CH_3), 79.5 (C), 117.5 (CH), 147.0 (C), 174.7 (C) ppm; HRMS (EI): calcd for $C_{19}H_{35}O_3Si$ (M^++H^+) 339.2350, found 339.2338.

4.21. (1*SR*,5*SR*,6*SR*)-3-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]propan-1-ol 31

$LiAlH_4$ (29.64 mg, 0.78 mmol) was added to a solution of the ester **30** (133 mg, 0.39 mmol) in diethyl ether (0.7 mL). The reaction mixture was stirred vigorously at room temperature under an argon atmosphere for 2 h, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was filtered, and the filtrate was then evaporated off under reduced pressure to afford unsaturated alcohol **31** (0.10 g, 88%); R_f 0.40 (hexane–diethyl ether 1:1); IR ν 3356, 2951, 2857, 1462, 1236, 1167, 1063, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.18 (s, 3H), 1.1–2.1 (m, 7H), 1.58 (d, J=8.1 Hz, 1H), 1.72 (br s, 3H), 2.43 (t, J=6.2 Hz, 1H), 3.53 (t, J=6.0 Hz, 2H), 5.19 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −2.0 (CH_3), 18.2 (C), 19.0 (CH_3), 19.4 (CH_3), 25.9 ($3CH_3$), 28.1 (CH_2), 29.3 (CH_2), 30.6 (CH_2), 35.9 (CH), 39.0 (CH_2), 45.6 (C), 63.8 (CH_3), 79.9 (C), 117.3 (CH), 147.3 (C) ppm; HRMS (EI): calcd for $C_{18}H_{35}O_2Si$ (M^++H^+) 311.2400, found 311.2401.

4.22. (1*SR*,5*SR*,6*SR*)-3-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]propanal 32

A solution of DMSO (0.04 mL) in dichloromethane (0.18 mL) was added dropwise to a stirred solution of oxalyl chloride (0.03 mL, 0.35 mmol) in dichloromethane (1.5 mL) under an argon atmosphere at −60 °C. After 5 min, a solution of the alcohol **31** (100 mg, 0.32 mmol) in CH_2Cl_2–DMSO (3:1, 2 mL) was added dropwise. The reaction mixture was stirred for 20 min, triethylamine (0.22 mL, 1.6 mmol) was added at −60 °C, and stirring was continued for 10 min. Then, the mixture was allowed to warm to room temperature and stirred for 4 h, after which water was added. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4), and filtered. The solvent was removed to afford the aldehyde **32** (71 mg, 100%) as a colorless oil; R_f 0.60 (hexane–diethyl ether 1:1); IR ν 2961, 2857, 1726, 1462, 1258, 1236, 1165, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 1.17 (s, 3H), 1.1–2.3 (m, 7H), 1.59 (d, J=8.0 Hz, 1H), 1.72 (s, 3H), 2.44 (t, J=7.4 Hz, 1H), 5.22 (br s, 1H), 9.71 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −1.9 (CH_3), 18.3 (C), 19.1 (CH_3), 19.4 (CH_3), 25.4 (CH_2), 25.9 ($3CH_3$), 30.6 (CH_2), 35.9 (CH), 39.1 (CH_2), 39.8 (CH_2), 45.1 (C), 79.5 (C), 117.7 (CH), 147.0 (C), 203.1 (C) ppm; HRMS (EI): calcd for $C_{18}H_{33}O_2Si$ (M^++H^+) 309.2245, found 309.2240.

4.23. Ethyl (1*SR*,5*SR*,6*SR*)-(*Z*)-5-[1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-2-methylpent-2-enoate 33

A dry three-necked flask equipped with stirrer, condenser, and a dropping funnel was purged with argon and charged with a 65% dispersion oil of sodium hydride in mineral oil (10.2 mg, 0.27 mmol) and dry toluene (0.6 mL). To this stirred mixture at 0 °C triethyl 2-phosphonopropionate (76 mg, 0.32 mmol) was added dropwise, and the mixture was stirred for 30 min at room temperature to ensure a complete reaction. To this nearly clear solution the aldehyde **32** (90 mg, 0.29 mmol) in toluene (0.6 mL) was added dropwise. The mixture was stirred for an additional 3 h and diluted with ether, and water was then added dropwise. The organic layer was separated and the aqueous phase was extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded the unsaturated ester **33** as a colorless oil (98 mg, 86%); R_f 0.50 (hexane–diethyl ether 7:3); IR ν 2930, 2857, 1718, 1620, 1452, 1252, 1167, 1098, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 1.19 (s, 3H), 0.8–2.15 (m, 7H), 1.27 (t, J=7 Hz, 3H), 1.60 (d, J=8.1 Hz, 1H), 1.74 (s, 3H), 1.79 (s, 3H), 2.42 (t, J=6.0 Hz, 1H), 4.15 (q, J=7.0 Hz, 2H), 5.20 (br s, 1H), 6.69 (t, J=7.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −1.9 (CH_3), 11.9 (CH_3), 14.1 (CH_3), 18.2 (C), 19.0 (CH_3), 19.4 (CH_3), 24.2 (CH_2), 25.9 ($3CH_3$), 30.6 (CH_2), 32.1 (CH_2), 36.0 (CH), 39.1 (CH_2), 45.7 (C), 60.1 (CH_2), 79.7 (C), 117.4 (CH), 127.0 (C), 143.0 (CH), 147.2 (C), 168.1 (C) ppm; HRMS (EI): calcd for $C_{23}H_{41}O_3Si$ (M^++H^+) 393.2819, found. 393.2804.

4.24. Ethyl (1*SR*,5*SR*,6*SR*)-(*Z*)-5-[1-hydroxy-2,6-dimethylbicyclo[3.1.1]hept-2en-6-yl]-2-methylpent-2-enoate 34

A solution of the ester **33** (66 mg, 0.16 mmol) and $n$$Bu_4NF$ (159 mg, 0.5 mmol) in THF (1.1 mL) was stirred at room temperature for 19 h. A saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. The solvent was removed to give the alcohol **34** (40 mg, 90%); R_f 0.20 (hexane–diethyl ether 7:3); IR ν 3489, 2932, 1693, 1647, 1449, 1370, 1279, 1235, 1161, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–2.15 (m, 7H), 1.26 (s, 3H), 1.31 (t, J=7.2 Hz, 3H), 1.62 (d, J=8.4 Hz, 1H), 1.81 (s, 3H), 1.83 (s, 3H), 2.25 (t, J=6.8 Hz, 1H), 4.20 (t, J=7.2 Hz, 2H), 5.25 (br s, 1H), 6.71 (t, J=6.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3), 14.2 (CH_3), 17.3 (CH_3), 18.0 (CH_3), 24.3 (CH_2), 30.8 (CH_2), 31.5 (CH_2), 34.9 (CH), 39.9 (CH_2), 45.3 (C), 60.4 (CH_2), 78.3 (C), 117.9 (CH), 127.3 (C), 142.7 (CH), 144.7 (C), 168.3 (C) ppm; HRMS (EI): calcd for $C_{17}H_{27}O_3$ (M^++H^+) 279.1954, found 279.1947.

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Supplementary data

Spectroscopic data for compounds described in Schemes 1 and 2 and Table 1 can be found in the online version.

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