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Total synthesis of (+)-massarinolin B and (+)-4-*epi*-massarinolin B, fungal metabolites from *Massarina tunicata*

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Abstract—The Cr(II)- and Ni(II)-mediated coupling of several tricyclic chiral aldehydes with (*E*)-β-iodomethacrylates (Nozaki–Hiyama–Kishi reaction) was successfully applied to the preparation of some valuable key intermediates of our synthetic strategy to the fungal metabolites (+)-massarinolin B, (+)-4-*epi*-massarinolin B and (+)-massarinolin C.

1. Introduction

Massarinolins A–C (**1**–**3**) are novel bioactive sesquiterpenoids isolated from the freshwater aquatic fungus *Massarina tunicata* Shearer & Fallah (A-25-1; Lophiostomataceae) by Gloer and Shearer in 1999 (Fig. 1).[1] Massarinolins A and B are presumably cyclization products of massarinolin C and all of them appear to be sesquiterpenoids biosynthesized from a farnesyl-type precursor. Compounds **1** and **2** were active against *Bacillus subtillis* (ATCC 6051), and possess unusual tricyclic and bicyclic ring systems, exhibiting similar functionalization within the lateral chain derived from (*E*)-4-hydroxy-2-methyl-2-pentenoic acid.

Although, the absolute configuration at C-4 of **2** and **3** has been determined by NMR studies on (*R*)-phenylbutyric acid (PBA) derivatives carried out by the discoverers,[1] it has not been possible yet to correlate the stereochemistry of the tricyclic portion of **2** and **3** with that of the side chain, so the absolute stereochemistry of the ring systems in massarinolins B and C still need to be ascertained. Since the absolute stereochemistry of the bicyclo[3.1.1]heptane subunit common to **2** and **3** has not yet been reported, the total synthesis of these two sesquiterpenoids remains a challenge.

On the basis of our retrosynthetic analysis, access to the lateral chain functionalities of these sesquiterpenoids was

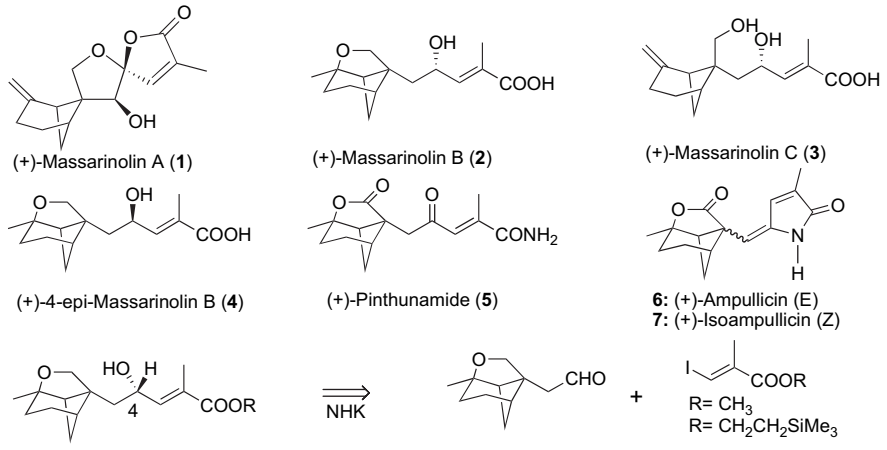

Figure 1. Bioactive sesquiterpenoids from *Massarina tunnicata* and *Ampulliferina Sp 27*. Retrosynthetic analysis of (+)-massarinolin B.

Keywords: Sesquiterpenes; β-Iodomethacrylates; (+)-Massarinolin B; *R*-(−)-carvone.
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envisioned to take place by Cr(II)- and Ni(II)-mediated coupling of the corresponding chiral aldehyde with (*E*)-β-iodomethacrylates (Nozaki–Hiyama–Kishi NHK reaction).[2]

We wish to report the results obtained for the coupling reaction of chiral aldehydes **12** and **15** with different (*E*)-β-iodomethacrylates and the application of these transformations to the synthesis of (+)-massarinolin B (**2**), (+)-massarinolin C (**3**) and (+)-4-*epi*-massarinolin B (**4**). The formal synthesis of (+)-pinthunamide (**5**)[3] will also be described as an application of the same coupling process to the chiral aldehyde **9**.

2. Results and discussion

On the basis of our retrosynthetic analysis, access to the lateral chain functionalities of sesquiterpenoids **3**–**5** was envisioned to take place by Cr(II)- and Ni(II)-mediated coupling of the corresponding chiral aldehyde with (*E*)-β-iodomethacrylates (Nozaki–Hiyama–Kishi NHK reaction).

The preparation of the chiral aldehydes **9**, **12** and **15** was easily achieved by multistep sequences starting from lactone **8** (Scheme 1), which was first described by Mori[4] and we have previously reported from *R*-(−)-carvone with occasion of the synthesis of (+)-ampullicin (**6**) and (+)-isoampullicin (**7**).[5]

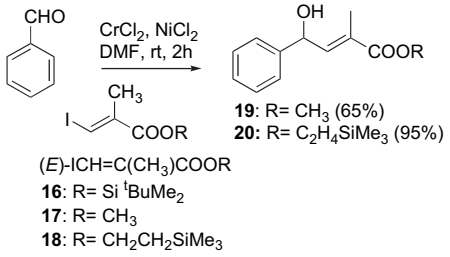
Ozonolysis of **8** followed by treatment with dimethyl sulfide afforded the aldehyde **9** in nearly quantitative yields.

The LAH reduction of **8** followed by tosylation of the primary alcohol **10** allowed us to isolate the tricyclic ether **11**, which was further ozonolyzed to yield aldehyde **12** with 80% overall yield.

On the other hand the diol **10** was sequentially protected by treatment with acetic anhydride followed by trimethylsilyl chloride in triethyl amine and DMAP to afford the unsaturated ester **14**, which was further ozonolyzed to yield aldehyde **15** with 76% yield (three steps).

The preparation of functionalized allylic alcohols has been successfully achieved by Cr(II)- and Ni(II)-mediated coupling of olefinic halides or triflates to aldehydes.[6] The insertion of chromium(II) chloride to β-iodomethacrylates in DMF furnishes the functionalized chromium(III) organometallics, which react with aldehydes to afford γ-hydroxy-α,β-unsaturated esters. This process appears to involve the activation of the carbon–iodine bond via Ni(0) or Ni(I), transmetallation of Ni to Cr and carbon–carbon bond formation via the organochromium reagent. The exceptional chemo- and stereoselectivity displayed by the d[3] organometallic reagent precludes any protection of the ester group or the double bond.

We first studied the coupling reaction of (*E*)-β-iodomethacrylates **16**–**18** with an achiral aldehyde. The Cr(II)- and Ni(II)-mediated coupling of β-iodomethacrylates **17**[7] and **18**[8] with benzaldehyde took place at room temperature in DMF with moderate to excellent yields (See Scheme 2). However, under these conditions the coupling with **16** failed.

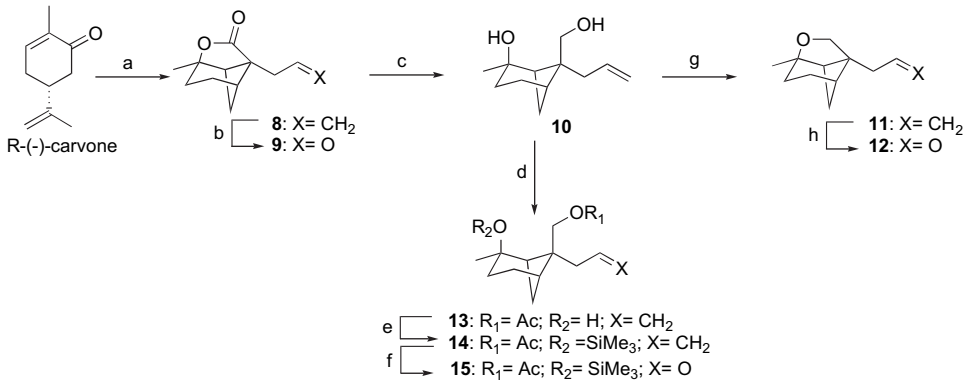


Scheme 2. Coupling reactions of (*E*)-β-iodomethacrylates with benzaldehyde.

Isolation of the methyl and trimethylsilylethyl esters **19** and **20** by flash chromatography[9] on silica gel took place with 65 and 95% yields, respectively. Yields were lower in both THF (15–45%) and CH_3CN (5–15%).

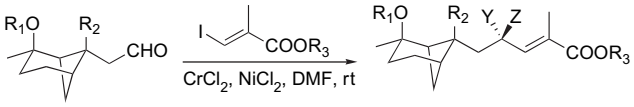
The Cr(II)- and Ni(II)-mediated coupling of aldehydes **9**, **12** and **15** with (*E*)-β-iodomethacrylates **17** and **18** took place with moderate yields but with poor diastereoselectivity (Table 1). However, the isolation and structural elucidation of the reaction products was possible in all cases.

The Cr(II)- and Ni(II)-mediated coupling of aldehyde **9** with β-iodomethacrylate **18** in DMF at room temperature afforded a mixture of diastereomers (**21**:**22**=1:1) with 56% yield.[10] Isolation of both isomers by flash chromatography was followed by Dess–Martin oxidation of each diastereomer to afford the enone **23** with 75 and 80 yields, respectively.

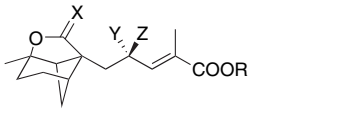


Scheme 1. Reagents and conditions: (a) Ref. 5; (b) O_3, −78 °C, Me_2S, 97%; (c) LAH, ether, rt, 91% (X=CH_2); (d) Ac_2O, Py, 95%; (e) Me_3SiCl, Et_3N, DMAP, CH_2Cl_2, 84%; (f) O_3, −78 °C, Me_2S, 95%; (g) TsCl, Py, DMAP, CH_2Cl_2, rt, 90%; (h) O_3, −78 °C, Me_2S, 98%.

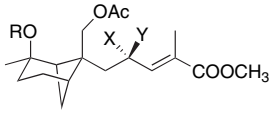
Table 1. Coupling reaction of aldehydes **9**, **12** and **15** with (*E*)-β-iodomethacrylates **17** and **18**[a]



Aldehyde	Methacrylate	dr[b]	Yield (%)[c]
9: R_1,R_2=CO	**18**: R_3=$CH_2CH_2SiMe_3$	**21**:**22**=1:1	56
12: R_1,R_2=CH_2	**17**: R_3=CH_3	**24**:**25**=3:2	65
12: R_1,R_2=CH_2	**18**: R_3=$CH_2CH_2SiMe_3$	**27**:**28**=1.2:1	95
15: R_1=$SiMe_3$; R_2=CH_2OAc	**17**: R_3=CH_3	**29**:**30**=1.2:1	87



21: X= O; Y= OH, Z= H; R= $CH_2CH_2Si(CH_3)_3$
22: X= O ; Y= H, Z= OH; R= $CH_2CH_2Si(CH_3)_3$
24: X= H_2; R= CH_3; Y= OH, Z= H
25: X= H_2; R= CH_3; Y= H, Z= OH
27: X= H_2; R= $CH_2CH_2SiMe_3$; Y= OH; Z= H
28: X= H_2; R= $CH_2CH_2SiMe_3$; Y= H; Z= OH



29: R= $SiMe_3$; X= OH; Y= H
30: R= $SiMe_3$; X= H; Y= OH

23: X= O; Y, Z= O; R= $CH_2CH_2Si(CH_3)_3$
26: X= H_2; Y, Z= O; R= CH_3

31[d]: R= $SiMe_3$; X= OSi^tBuPh_2; Y= H
32[d]: R= H; X= OSi^tBuPh_2; Y= H

[a] All reactions were run in DMF at room temperature with $CrCl_2$/haloester/aldehyde=4:2:1 ratio.
[b] Determined by GLPC (3% silicone OV-17, 1.5 m).
[c] Isolated yields.

Transformation of the enone **23** into (+)-pinthunamide (**5**) has been described previously.[4]

The Cr(II)- and Ni(II)-mediated coupling of aldehyde **12** with each of the β-iodomethacrylates **17** and **18** afforded mixtures of diastereomers [(**24**:**25**=3:2) and (**27**:**28**=1.2:1)] with 65 and 95% isolated yields, respectively. Reaction was fast in DMF, the usual solvent of choice. Furthermore, the reactions were slower in THF and CH_3CN and both solvents afforded similar stereoselectivities but with lower reaction yields: THF, 47% (**24**+**25**) and 40% (**27**+**28**); CH_3CN, 48% (**24**+**25**) and 45% (**27**+**28**).

Isolation of isomers was possible by flash chromatography on silica gel.[11] The spectroscopic data obtained for **24** were identical to those previously described for the methyl ester of (+)-massarinolin B.[1] Fluoride-promoted deprotection of **27** yielded the target molecule **2** with quantitative yields. Analogously, deprotection of the silyl derivative **28** afforded 4-*epi*-(+)-massarinolin B (**4**) quantitatively.[12]

Since the absolute stereochemistry of the starting material **8** is known,[13] it is possible now to correlate the stereochemistry of the bicyclo[3.1.1]heptane portion of **2** with that of the side chain, therefore, the absolute stereochemistry of **2** and **4** has been unambiguously established.

For preparative purposes, we attempted to enhance the diastereomeric ratio in favour of **24** by a two-step oxidation–reduction sequence via enone **26**. Among the reagents screened, neither L-Selectride nor zinc borohydride gave acceptable results with respect to either chemo- or stereoselectivity.[14]

The coupling reaction of aldehyde **15** with β-iodomethacrylate **17** gave a mixture of diastereoisomers (**29**:**30**=1.2:1) with 87% yield. Separation of both diastereomers was possible by flash chromatography and the structural elucidation was based on full spectroscopic analysis and comparison with the spectroscopic evidence obtained for **24** and **25**. Hydroxyester **29** is an advanced intermediate in the synthesis of (+)-massarinolin C (**3**).[15]

3. Conclusion

The Cr(II)- and Ni(II)-mediated coupling of chiral aldehydes **9**, **12** and **15** with (*E*)-β-iodomethacrylates yielded the corresponding γ-hydroxy-α,β-unsaturated esters with moderate yields but with poor stereoselectivity. Starting from the allylic lactone **8**, application of these transformations to the synthesis of (+)-massarinolin B (**2**), (+)-4-*epi*-massarinolin B (**4**), (+)-pinthunamide (**5**) and the preparation of an advanced intermediate (**29**) in the synthesis of (+)-massarinolin C (**3**) have been described.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H 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 (^1H) or solvent (^{13}C), except where noted 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 the maximum *m*/*z* range of 600. Optical rotations were determined on a digital Perkin–Elmer 241 polarimeter in a 1 dm cell. Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over CaH_2, distd under reduced pressure and degassed before use. Acetonitrile is

fractionally distd after refluxing over CaH_2. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques.[9] R_f values refer to TLC carried out on 0.25 mm silica gel plates, with the same eluant as that indicated for the column chromatography unless otherwise noted. Yields reported are for chromatographically pure isolated products unless mentioned otherwise. Anhydrous $CrCl_2$ and $NiCl_2$ were purchased from Aldrich and Strem Chemicals and were used without purification.

4.2. Preparation of intermediates 10, 11, 13 and 14

4.2.1. (1*R*,2*R*,5*S*,6*S*)-2-Hydroxy-2-methyl-6-(2-propenyl)-bicyclo[3.1.1]hept-6-yl-methanol 10. To an ice-cooled and stirred solution of crude **8** (2 g, 10.41 mmol) in anhydrous ether (45 mL) $LiAlH_4$ (0.394 g, 10.41 mmol) was added. The mixture was stirred at room temperature for 15 h. To the ice-cooled mixture were added H_2O (0.4 mL), 15% NaOH (0.4 mL) and H_2O (1.2 mL) successively. The mixture was stirred at room temperature for 1 h and filtered through Celite and eluted with ether. The filtrate was concentrated in vacuo and the residue was flash chromatographed on silica gel. Elution with hexane/ethyl acetate 6:4 afforded diol **10** (1.83 g, 91%) as a colourless oil. $[\alpha]_D^{20}$ −24.51 (*c* 1.04, $CHCl_3$). R_f 0.33 (hexane/ethyl acetate 1:1). IR (KBr): ν 3365, 3081, 2973, 2931, 1637, 1471, 1261, 1121, 1029, 912, 803 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (d, 1H, J=10.4 Hz), 1.33 (s, 3H), 1.75–2.10 (m, 5H), 2.16 (m, 1H), 2.25 (m, 1H), 2.4 (dd, 1H, J_1=7.5 Hz, J_2=14.2 Hz), 2.65 (dd, 1H, J_1=7.2 Hz, J_2=14.16 Hz), 3.45 (d, 1H, J=11.6 Hz), 3.9 (d, 1H, J=11.6 Hz), 5.1 (m, 2H), 5.9 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.16 (t), 27.61 (t), 31.33 (q), 32.79 (t), 36.34 (d), 37.94 (t), 45.24 (s), 51.20 (d), 63.11 (t), 76.02 (s), 116.98 (t), 135.59 (d) ppm. MS (EI), *m/z* (%): 196 (M^+, 2), 178 (10), 137 (35), 110 (35), 94 (100), 79 (85), 67 (55). HRMS-EI (M^+) calcd for $C_{12}H_{20}O_2$: 196.1463, found: 196.1457.

4.2.2. (1*R*,4*S*,6*R*,7*S*)-1-Methyl-9-oxa-7-(2-propenyl)-tricyclo[4.3.0.0^{4,7}]nonane 11. To a solution of diol **10** (0.67 g, 3.42 mmol) in CH_2Cl_2 (50 mL) at 0 °C, pyridine (0.82 mL, 10.26 mmol), DMAP (0.084 g, 0.684 mmol) and tosyl chloride (1.3 g, 6.84 mmol) were successively added. The reaction mixture was stirred at room temperature for 48 h. Then, 10% $NaHCO_3$ (10 mL) was added and the reaction mixture was further stirred for 1 h. The crude mixture was extracted with methylene chloride (3×25 mL) and the combined organic layers were successively washed with 1 N HCl (3×10 mL), 10% $NaHCO_3$ (3×10 mL) and brine (3×10 mL). The organic phase was dried with Na_2SO_4 and evaporated to yield a crude (1.5 g), which was fractionated by flash chromatography on silica gel (hexane/ethyl acetate 9:1) to afford **11** (0.55 g, 90%) as a colourless oil. $[\alpha]_D^{20}$ +17.9 (*c* 0.8, $CHCl_3$). R_f 0.68 (hexane/ethyl acetate 1:1). IR (neat): ν 3077, 2926, 2866, 1726, 1642, 1452, 1375, 1032, 912, 849 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.45 (m, 1H), 1.65–1.9 (m, 5H), 2.0–2.2 (m, 2H), 2.3–2.5 (m, 2H), 3.5 (d, 1H, J=8.9 Hz), 3.74 (d, 1H, J=8.9 Hz), 5.05 (m, 2H), 5.7 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.70 (t), 22.96 (t), 25.18 (q), 32.60 (t), 38.05 (t), 39.60 (d), 50.72 (d), 54.96 (s), 70.46 (t), 86.77 (s), 116.62 (t), 134.74 (d) ppm. MS (EI) *m/z* (%): 178 (M^+, 13.1), 67 (25), 79 (44), 95 (28.6), 107 (17), 123 (100), 163 (14.3). HRMS-EI (M^+) calcd for $C_{12}H_{18}O$: 178.1358, found: 178.1348.

4.2.3. (1*R*,2*R*,5*S*,6*S*)-2-Hydroxy-2-methyl-6-(2-propenyl)-bicyclo[3.1.1]hept-6-yl-methyl acetate 13. To a solution of diol **10** (0.205 g, 1.0 mmol) in CH_2Cl_2 were successively added pyridine (0.16 mL, 2.2 mmol) and acetic anhydride (0.2 mL, 2.0 mmol). The reaction mixture was stirred for 12 h. Then, ether (5 mL) was added and the reaction mixture was poured on satd $NaHCO_3$ (5 mL) and stirred for 1 h. The organic phase was successively washed with 2 N HCl (3×10 mL), satd $NaHCO_3$ (3×10 mL) and brine (3×10 mL), dried (Na_2SO_4) and evaporated to yield a crude product (0.260 g), which was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate 8:2, acetate **13** (0.237 g, 95%) was obtained as a colourless oil. $[\alpha]_D^{20}$ −5.05 (*c* 1.01, $CHCl_3$). R_f 0.48 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): ν 3480, 3078, 2922, 1716, 1639, 1456, 1237, 1027, 962 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.09 (d, 1H, J=10.2 Hz), 1.28 (s, 3H), 1.27–2.35 (m, 7H), 2.04 (s, 3H), 2.45 (d, 2H, J=7.52 Hz), 4.21 (dd, 2H, J_1=11.8 Hz, J_2=36.8 Hz), 5.05 (m, 2H), 5.84 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.04 (q), 23.73 (t), 27.44 (t), 31.47 (q), 31.95 (t), 37.47 (t), 37.95 (d), 43.23 (s), 50.75 (d), 65.70 (t), 75.21 (s), 116.97 (t), 134.81 (d), 170.79 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{14}H_{22}O_3Na$: 261.1461, found: 261.1447.

4.2.4. (1*R*,2*R*,5*S*,6*S*)-2-Methyl-2-(trimethylsilyloxy)-6-(2-propenyl)-bicyclo[3.1.1]hept-6-yl-methyl acetate 14. To a solution of **13** (0.20 g, 0.84 mmol) in CH_2Cl_2 (25 mL) at 0 °C were successively added Et_3N (0.24 mL, 1.7 mmol), DMAP (20.4 mg, 0.17 mmol) and Me_3SiCl (0.16 mL, 1.25 mL). The reaction mixture was stirred for 12 h at room temperature, diluted with ether (20 mL) and poured on satd $NaHCO_3$ (20 mL). The mixture was stirred for 1 h and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to yield a crude product (0.27 g), which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate 8:2 afforded the silyl acetate **14** (0.22 g, 84%) as a colourless oil. $[\alpha]_D^{20}$ −10.95 (*c* 1.21, $CHCl_3$). R_f 0.62 (hexane/ethyl acetate 7:3). IR ($CHCl_3$): ν 3075, 2961, 2928, 2873, 1739, 1381, 1250, 1130, 1004, 968, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 9H), 1.5 (d, 1H, J=9.7 Hz), 1.28 (s, 3H), 1.15–2.25 (m, 7H), 2.01 (s, 3H), 2.44 (d, 2H, J=7.35 Hz), 4.09 (dd, 2H, J_1=12.2 Hz, J_2=76.6 Hz), 5.04 (m, 2H), 5.80 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 2.53 (q), 20.87 (q), 23.97 (t), 27.06 (t), 30.57 (q), 33.47 (t), 37.65 (t), 38.33 (d), 43.24 (s), 51.66 (d), 66.02 (t), 78.34 (s), 116.76 (t), 135.28 (d), 170.95 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{17}H_{30}O_3$SiNa: 333.1856, found: 333.1821.

4.3. Ozonolysis of alkenes 8, 11 and 14. Obtention of aldehydes 9, 12 and 15. General procedure

4.3.1. (1*R*,4*S*,6*R*,7*S*)-1-Methyl-9-oxa-8-oxo-tricyclo-[4.3.0.0^{4,7}]non-7-yl-acetaldehyde 9. Ozone was bubbled through a solution of **8** (2.5 g, 13.01 mmol) in 75 mL of

CH_2Cl_2 at −78 °C until a blue-grey colouration developed. Then, excess ozone was eliminated using argon, and then SMe_2 (2.85 mL, 39 mmol) was added. After stirring for 3 h (from –78 °C to room temperature) the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 6:4) to yield a colourless oil **9** (2.4 g, 95%). $[\alpha]_D^{20}$ +49.06 (*c* 1.35, $CHCl_3$). R_f 0.24 (hexane/ethyl acetate 1:1). IR (neat): *ν* 2972, 2899, 2745, 1759, 1723, 1458, 1383, 1252, 1198, 1082, 939, 893 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.49 (s, 3H), 1.72 (d, 1H, *J*=10.7 Hz), 1.92 (s, 4H), 2.19 (m, 1H), 2.45 (m, 1H), 2.64 (t, 1H, *J*=5.4 Hz), 2.83 (dd, 2H, J_1=18.2 Hz, J_2=30.5 Hz), 9.74 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 22.88 (t), 24.78 (q), 29.83 (t), 40.81 (d), 43.36 (t), 47.74 (d), 52.87 (s), 88.71 (s), 177.42 (s), 199.12 (d) ppm. HRMS-EI (M+H^+) calcd for $C_{11}H_{15}O_3$: 195.1016, found: 195.0998.

4.3.2. (1*R*,4*S*,6*R*,7*S*)-1-Methyl-9-oxa-tricyclo[4.3.0.0^{4,7}]-non-7-yl-acetaldehyde 12. Ozonolysis of alkene **11** (1.5 g, 8.43 mmol) afforded aldehyde **12** (1.49 g, 98%) as a colourless oil. $[\alpha]_D^{20}$ +40.54 (*c* 1.07, $CHCl_3$). R_f 0.33 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): *ν* 2928, 2870, 2726, 1721, 1452, 1377, 1024, 853 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.25 (s, 3H), 1.45 (d, 1H, *J*=10.3 Hz), 1.7–2.25 (m, 7H), 2.75 (dd, 2H, J_1=18 Hz, J_2=30 Hz), 3.75 (d, 1H, *J*=9.3 Hz), 4.04 (d, 1H, *J*=9.3 Hz), 9.74 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 22.42 (t), 22.63 (t), 24.92 (q), 32.25 (t), 40.01 (d), 48.36 (t), 51.20 (d), 52.25 (s), 70.58 (t), 86.03 (s), 200.64 (d) ppm. HRMS-EI (M+H^+) calcd for $C_{11}H_{17}O_2$: 181.1223, found: 181.1223.

4.3.3. (1*R*,2*R*,5*S*,6*S*)-2-Methyl-2-(trimethylsilyloxy)-6-(2-oxoethyl)-bicyclo[3.1.1]hept-6-yl-methyl acetate 15. Ozonolysis of alkene **14** (1 g, 3.22 mmol) yielded aldehyde **15** (0.950 g, 95%) as a colourless oil. $[\alpha]_D^{20}$ −22.32 (*c* 1.257, $CHCl_3$). R_f 0.46 (hexane/ethyl acetate 7:3). IR (KBr): *ν* 2959, 2738, 1730, 1452, 1376, 1233, 1000, 956, 835 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 0.1 (s, 9H), 1.3 (s, 3H), 1.35 (d, 1H, *J*=11.0 Hz), 1.9–2.4 (m, 7H), 2.0 (s, 3H), 2.6–2.8 (m, 2H), 4.15 (d, 1H, *J*=12.2 Hz), 4.58 (d, 1H, *J*=12.1 Hz), 9.85 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 2.38 (q), 20.71 (q), 23.47 (t), 27.69 (t), 30.28 (q), 33.04 (t), 37.75 (d), 42.89 (s), 47.93 (t), 52.98 (d), 67.33 (t), 77.90 (s), 170.54 (s), 202.07 (d) ppm. HRMS-EI (M+Na^+) calcd for $C_{16}H_{28}O_4SiNa$: 335.1649, found: 335.1639.

4.4. Coupling reactions between (*E*)-β-halo-acrylates and aldehydes. General procedure

4.4.1. (*E*)-4-Hydroxy-2-methyl-4-phenyl-2-butenoic acid methyl ester 19. A mixture of anhydrous $CrCl_2$ (0.60 g, 4.9 mmol) and a catalytic amount of $NiCl_2$ (3.2 mg, 0.02 mmol) in dry oxygen-free dimethylformamide (DMF, 10 mL) was stirred at 25 °C for 10 min under argon atmosphere. To the reagent at 25 °C, solutions of benzaldehyde (0.129 g, 1.02 mmol) in DMF (5 mL) and methyl-(*E*)-3-iodomethacrylate **17** (0.554 g, 2.45 mmol) in DMF (5 mL) were successively added. After stirring at 25 °C for 4 h at room temperature, the reaction mixture was diluted with ether (20 mL), poured into water (20 mL) and extracted with ether repeatedly. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) afforded 0.16 g (65%) of the desired allylic alcohol **19** as a colourless oil. R_f 0.37 (hexane/ethyl acetate 1:1). IR (neat): *ν* 3445, 3050, 2953, 1715, 1651, 1439, 1128, 1017 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.85 (s, 3H), 2.52 (s, 1H), 3.6 (s, 3H), 5.42 (d, 1H, *J*=8.6 Hz), 6.79 (d, 1H, *J*=8.5 Hz), 7.22–7.29 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 12.93 (q), 51.87 (q), 70.8 (d), 126.2 (d), 128.02 (d), 128.4 (s), 128.75 (d), 142.1 (d), 142.2 (s), 168.3 (s) ppm. MS-EI *m*/*z* (%): 206 (M^+, 1.5), 51 (48), 77 (100), 79 (34), 105 (100), 117 (33), 145 (47), 159 (3), 174 (37.5), 188 (19), 191 (3). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.01; H, 6.96.

4.4.2. (*E*)-4-Hydroxy-2-methyl-4-phenyl-2-butenoic acid 2-(trimethylsilyl)ethyl ester 20. Coupling of benzaldehyde (0.118 g, 1.12 mmol) and (*E*)-haloester **18** (0.70 g, 2.24 mmol) afforded 0.320 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 9:1) afforded 0.27 g (95%) of the desired alcohol **20** as a colourless oil. R_f 0.27 (hexane/ethyl acetate 8:2). IR ($CHCl_3$): *ν* 3455, 3030, 2955, 2899, 1709, 1649, 1452, 1252, 1036, 936, 856 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 0.35 (s, 9H), 1.01 (dd, 2H, *J*=8.5 Hz), 1.94 (s, 3H), 4.2 (dd, 2H, *J*=8.45 Hz), 5.52 (d, 1H, *J*=8.6 Hz), 6.68 (d, 1H, *J*=8.7 Hz), 7.25–7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 1.57 (q), 12.85 (q), 17.3 (t), 62.98 (t), 70.73 (d), 126.12 (d), 127.87 (d), 128.6 (d), 128.61 (s), 141.89 (d), 142.16 (s), 167.97 (s) ppm. MS-EI *m*/*z* (%): 275.14 (M+Na, 17.5), 129.1 (100), 169.1 (7.4), 175.1 (10.1), 202.02 (3.7), 247.11 (9.2), 265.13 (5.5). Anal. Calcd for $C_{16}H_{24}O_3Si$: C, 65.71; H, 8.27. Found: C, 65.83; H, 8.37.

4.4.3. Hydroxyesters 21 and 22. Coupling of aldehyde **9** (0.110 g, 0.57 mmol) and (*E*)-haloester **18** (0.354 g, 1.14 mmol) afforded 0.25 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 9:1) afforded **21** (0.06 g, 28%) and **22** (0.06 g, 28%).

4.4.3.1. 2-(Trimethylsilyl)ethyl (1′*R*,4*S*,4′*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-8′-oxo-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-2-pentenoate 21. Colourless oil. $[\alpha]_D^{20}$ −0.79 (*c* 1.305, $CHCl_3$). R_f 0.40 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): *ν* 3475, 3057, 2954, 2871, 1761, 1708, 1653, 1458, 1250, 1062, 942, 834 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 0.04 (s, 9H), 1.01 (t, 2H, *J*=8.3 Hz), 1.42–2.80 (m, 3H), 1.46 (s, 3H), 1.85 (s, 3H), 1.9 (m, 4H), 2.5 (m, 2H), 2.61 (m, 1H), 4.22 (t, 2H, *J*=8.3 Hz), 4.69 (ddd, 1H, J_1=8.5 Hz, J_2=8.5 Hz, J_3=4.3 Hz), 6.66 (dq, 1H, J_1=8.5 Hz, J_2=1.2 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): *δ* −1.65 (q), 12.62 (q), 17.26 (t), 22.74 (t), 22.75 (t), 24.74 (q), 29.66 (t), 36.46 (t), 42.06 (d), 47.18 (d), 54.33 (s), 62.87 (t), 65.97 (d), 88.40 (s), 128.70 (s), 142.09 (d), 167.76 (s), 179.15 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{20}H_{32}O_5NaSi$: 403.1911, found: 403.1914.

4.4.3.2. 2-(Trimethylsilyl)ethyl (1′*R*,4*R*,4′*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-8′-oxo-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-2-pentenoate 22. Colourless oil. $[\alpha]_D^{20}$ +24.89 (*c* 0.953, $CHCl_3$). R_f 0.46 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): *ν* 3456, 3056, 2954, 2855, 1759, 1709, 1650, 1458, 1250, 1044, 986, 839 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): *δ* 0.04 (s, 9H), 1.02 (t, 2H, *J*=8.3 Hz),

1.48 (s, 3H), 1.74 (m, 1H), 1.85–2.10 (m, 6H), 1.88 (s, 3H), 1.98 (s, 4H), 1.9–2.35 (m, 3H), 2.25 (m, 1H), 2.57 (m, 1H), 2.7 (m, 1H), 4.22 (t, 2H, J=8.6 Hz), 4.71 (ddd, 1H, J_1=8.1 Hz, J_2=8.1 Hz, J_3=6.8 Hz), 6.71 (dq, 1H, J_1=8.1 Hz, J_2=1.2 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 1.63 (q), 12.62 (q), 17.27 (t), 22.78 (t), 22.99 (t), 24.74 (q), 29.66 (t), 36.25 (t), 40.57 (d), 49.13 (d), 55.33 (s), 62.80 (t), 66.24 (d), 89.28 (s), 128.14 (s), 142.91 (d), 167.90 (s), 179.56 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{20}H_{32}O_5SiNa$: 403.1911, found: 403.1900.

4.4.4. Hydroxyesters 24 and 25. Coupling of aldehyde **12** (0.124 g, 0.70 mmol) and (*E*)-haloester **17** (0.312 g, 1.38 mmol) afforded 0.228 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 8:2) afforded **24** (0.075 g, 39%) and **25** (0.050 g, 26%).

4.4.4.1. Methyl (1′*R*,4′*S*,4*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-2-pentenoate 24. Colourless oil. $[\alpha]_D^{20}$ +8.6 (*c* 1.1, $CHCl_3$). R_f 0.23 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): ν 3408, 2925, 2855, 1720, 1451, 1122 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 1.23 (s, 3H), 1.50 (m, 1H), 1.62 (m, 1H), 1.78 (m, 1H), 1.84 (m, 1H), 1.85 (d, 3H, J=1.44 Hz), 1.88 (m, 1H), 1.89 (m, 1H), 1.98 (dd, 1H, J_1=14.1 Hz, J_2=4.0 Hz), 2.13 (m, 1H), 2.14 (m, 1H), 2.30 (m, 1H), 3.60 (d, 1H, J=9.45 Hz), 3.74 (s, 3H), 3.89 (d, 1H, J=9.45 Hz), 4.46 (ddd, 1H, J_1=8.9 Hz, J_2=8.9 Hz, J_3=3.8 Hz), 6.67 (dq, 1H, J_1=8.9 Hz, J_2=1.4 Hz) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.78 (q), 23.53 (t), 23.75 (t), 25.35 (q), 33.41 (t), 40.24 (d), 41.72 (t), 52.45 (q), 53.55 (d), 55.53 (s), 66.94 (d), 72.76 (t), 87.62 (s), 127.95 (s), 145.59 (d), 169.95 (s) ppm. MS-EI *m*/*z* (%): 262 (M$^+$−H_2O, 5), 247 (3), 225 (21), 207(46), 203 (10), 187 (8), 175 (21), 151 (37), 147(56), 133(29), 109 (26), 97 (100), 79 (78), 67 (65), 55 (80). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.68.

4.4.4.2. Methyl (1′*R*,4′*S*,4*R*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-2-pentenoate 25. Colourless oil. $[\alpha]_D^{20}$ −0.78 (*c* 1.03, $CHCl_3$). R_f 0.28 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): ν 3407, 2925, 2849, 1717, 1655, 1437, 1265, 1141 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 1.23 (s, 3H), 1.50 (m, 1H), 1.61 (m, 1H), 1.78 (m, 1H), 1.84 (m, 1H), 1.85 (d, 3H, J=1.49 Hz), 1.88 (m, 1H), 1.89 (m, 1H), 2.09–2.25 (m, 3H), 2.4 (m, 1H), 3.54 (d, 1H, J=9.01 Hz), 3.78 (s, 3H), 3.79 (d, 1H, J=9.0 Hz), 4.5 (ddd, 1H, J_1=8.8 Hz, J_2=8.8 Hz, J_3=6.4 Hz), 6.65 (dq, 1H, J_1=8.8 Hz, J_2=1.45 Hz) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.89 (q), 23.38 (t), 23.60 (t), 25.39 (q), 33.37 (t), 41.35 (d), 41.83 (t), 52.5 (q), 53.43 (d), 55.19 (s), 67.50 (d), 71.93 (t), 88.20 (s), 128.47 (s), 145.23 (d), 169.88 (s) ppm. MS-EI *m*/*z* (%): 262 (M$^+$−H_2O, 3), 236 (2), 225 (16), 207 (54), 187 (10), 175 (17), 151 (37), 147 (60), 133 (32), 109 (27), 97 (100), 79 (90), 67 (67), 55 (84). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.65; H, 8.70.

4.4.5. Hydroxyesters 27 and 28. Coupling of aldehyde **12** (0.110 g, 0.61 mmol) and (*E*)-haloester **18** (0.38 g, 1.2 mmol) afforded 0.37 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 8:2) afforded **27** (0.12 g, 54%) and **28** (0.092 g, 41%).

4.4.5.1. (1′*R*,4′*S*,4*S*,6′*R*,7′*S*)-(*E*)-4-Hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-2-pentenoic acid 2-(trimethylsilyl)ethyl ester 27. Colourless oil. $[\alpha]_D^{20}$ +28.25 (*c* 0.89, $CHCl_3$). R_f 0.37 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): ν 3398, 2926, 1710, 1650, 1452, 1250, 1034, 935, 838 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 9H), 1.04 (dd, 2H, J_1=8.6 Hz, J_2=1.8 Hz), 1.27 (s, 3H), 1.47 (d, 1H, J=10.2 Hz), 1.65–2.00 (m, 6H), 1.87 (d, 3H, J=1.5 Hz), 2.1 (m, 1H), 2.15 (t, 1H, J=5.6 Hz), 2.27 (m, 1H), 3.62 (d, 1H, J=9.45 Hz), 3.90 (d, 1H, J=9.45 Hz), 4.25 (m, 2H), 4.53 (ddd, 1H, J_1=8.4 Hz, J_2=8.4 Hz, J_3=4.4 Hz), 6.69 (dq, 1H, J_1=8.4 Hz, J_2=1.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.52 (q), 12.70 (q), 17.27 (t), 22.65 (t), 22.83 (t), 25.13 (q), 32.44 (t), 39.00 (d), 40.61 (t), 52.12 (d), 54.25 (s), 63.10 (t), 66.67 (d), 71.58 (t), 85.85 (s), 128.04 (s), 142.95 (d), 167.99 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{20}H_{34}O_4SiNa$: 389.2118, found: 389.2127.

4.4.5.2. (1′*R*,4′*S*,4*R*,6′*R*,7′*S*)-(*E*)-4-Hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-2-pentenoic acid 2-(trimethylsilyl)ethyl ester 28. Colourless oil. $[\alpha]_D^{20}$ −5.08 (*c* 0.47, $CHCl_3$). R_f 0.42 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): ν 3403, 2925, 2867, 1711, 16490, 1453, 1250, 1038, 936, 839 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 1.02 (dd, 2H, J_1=8.5 Hz, J_2=1.8 Hz), 1.25 (s, 3H), 1.47 (d, 1H, J=10.1 Hz), 1.2–1.9 (m, 6H), 1.84 (d, 3H, J=1.44 Hz), 2.09 (m, 1H), 2.15 (m, 1H), 2.27 (m, 1H), 3.55 (d, 1H, J=9.04 Hz), 3.81 (d, 1H, J=9.04 Hz), 4.22 (m, 2H), 4.52 (ddd, 1H, J_1=7.6 Hz, J_2=7.6 Hz, J_3=7.2 Hz), 6.63 (dq, 1H, J_1=7.6 Hz, J_2=1.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.52 (q), 12.76 (q), 17.29 (t), 22.67 (t), 22.73 (t), 25.16 (q), 32.38 (t), 40.16 (d), 40.74 (t), 52.08 (d), 53.92 (s), 63.12 (t), 67.45 (d), 70.81 (t), 86.44 (s), 128.52 (s), 142.57 (d), 167.86 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{20}H_{34}O_4SiNa$: 389.2118, found: 389.2108.

4.4.6. Hydroxyesters 29 and 30. Coupling of aldehyde **15** (0.18 g, 0.6 mmol) and (*E*)-haloester **17** (0.26 g, 1.15 mmol) afforded 0.230 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 9:1) afforded **29** (0.11 g, 46%) and **30** (0.1 g, 42%).

4.4.6.1. Methyl (1′*R*,2′*R*,4*S*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxymethyl-2′-trimethylsilyloxy-2′-methyl-bicyclo[3.1.1]-hept-6′-yl)-4-hydroxy-2-methyl-2-pentenoate 29. Colourless oil. $[\alpha]_D^{20}$ −40.81 (*c* 1.01, $CHCl_3$). R_f 0.19 (hexane/ethyl acetate 7:3). IR ($CHCl_3$): ν 3469, 2957, 2955, 2873, 1717, 1651, 1437, 1251, 1043, 1003, 840 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 9H), 1.26 (s, 3H), 1.05–2.3 (m, 10H), 1.87 (d, 3H, J=1.3 Hz), 2.03 (s, 3H), 3.75 (s, 3H), 4.3 (d, 1H, J=12 Hz), 4.5 (d, 1H, J=12 Hz), 4.65 (ddd, 1H, J_1=8.4 Hz, J_2=8.4 Hz, J_3=4.4 Hz), 6.70 (dq, 1H, J_1=8.4 Hz, J_2=1.3 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 2.48 (q), 12.75 (q), 21.12 (q), 23.68 (t), 26.99 (t), 30.64 (q), 32.97 (t), 39.11 (d), 39.77 (t), 42.45 (s), 51.88 (q), 52.10 (d), 66.40 (d), 66.96 (t), 78.13 (s), 126.97 (s), 144.06 (d), 168.44 (s), 171.36 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{21}H_{36}O_6SiNa$: 435.2173, found: 435.2169.

4.4.6.2. Methyl (1′*R*,2′*R*,4*R*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxymethyl-2′-trimethylsilyloxy-2′-methyl-bicyclo[3.1.1]hept-6′-yl)-4-hydroxy-2-methyl-2-pentenoate 30. Colourless oil. $[\alpha]_D^{20}$ −4.26 (*c* 0.59, $CHCl_3$). R_f 0.32 (hexane/ethyl

acetate 7:3). IR ($CHCl_3$): ν 3501, 2955, 2932, 2873, 1716, 1651, 1437, 1251, 1044, 1003, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 9H), 1.26 (s, 3H), 1.85 (d, 3H, J=1.2 Hz), 1.8–1.9 (m, 4H), 1.99 (s, 3H), 2.0–2.2 (m, 4H), 2.21 (m, 1H), 2.4 (m, 1H), 3.74 (s, 3H), 4.03 (d, 1H, J=12.5 Hz), 4.62 (d, 1H, J=12.4 Hz), 4.67 (ddd, 1H, J_1=8.8 Hz, J_2=8.8 Hz, J_3=3.6 Hz), 6.7 (dq, 1H, J_1=8.8 Hz, J_2=1.2 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 2.49 (q), 12.61 (q), 20.92 (q), 23.85 (t), 26.81 (t), 30.48 (q), 32.92 (t), 38.70 (d), 40.02 (t), 42.27 (s), 51.88 (q), 53.25 (d), 66.56 (t), 66.60 (d), 78.28 (s), 126.93 (s), 144.22 (d), 168.39 (s), 170.88 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{21}H_{36}O_6SiNa$: 435.2173, found: 435.2167.

4.5. Periodinane oxidations. General procedure

4.5.1. 2-(Trimethylsilyl)ethyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-2-methyl-5-(1′-methyl-9′-oxa-8′-oxo-tricyclo[4.3.0.0^{4,7}]-non-7′-yl)-4-oxo-2-pentenoate 23. To a solution of hydroxyester **21** (0.15 g, 0.40 mmol) in CH_2Cl_2 (5 mL) Dess–Martin periodinane (0.25 g, 0.6 mmol) was added. The reaction mixture was stirred for 5 h at room temperature. Then, 10% $NaCO_3H$ (5 mL) and 10% $Na_2S_2O_3$ (2.5 mL) were successively added. The reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give a crude product (0.16 g), which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate 8:2 afforded ketoester **23** (0.112 g, 75%) as a colourless oil. $[\alpha]_D^{20}$ +52.045 (*c* 0.99, $CHCl_3$). R_f 0.45 (hexane/ethyl acetate 1:1). IR (KBr): ν 3439, 2960, 2925, 1768, 1709, 1621, 1263, 1091, 1000, 925, 865, 835 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 9H), 1.02 (dd, 2H, J=8.6 Hz), 1.51 (s, 3H), 1.70 (d, 1H, J=10.0 Hz), 1.90 (s, 4H), 2.15 (m, 1H), 2.18 (s, 3H), 2.4 (m, 1H), 2.7 (m, 1H), 2.94 (d, 1H, J=19.1 Hz), 3.14 (d, 1H, J=19.05 Hz), 4.25 (dd, 2H, J=8.6 Hz), 7.04 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ −1.67 (q), 14.31 (q), 17.20 (t), 22.66 (t), 22.84 (t), 24.74 (q), 29.87 (t), 40.44 (d), 43.88 (t), 47.31 (d), 53.57 (s), 63.79 (t), 88.25 (s), 130.99 (d), 141.97 (s), 167.41 (s), 177.47 (s), 198.15 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{20}H_{30}O_5SiNa$: 401.1755, found: 401.1746.

4.5.2. Unsaturated ketoester 23 (from 22). Periodinane oxidation of hydroxyester **22** (0.12 g, 0.31 mmol) afforded **23** (0.096 g, 80%).

4.5.3. Methyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0^{4,7}]non-7′-yl)-4-oxo-2-pentenoate 26. Periodinane oxidation of hydroxyester **24** (0.175 g, 0.62 mmol) afforded **26** (0.155 g, 89%). Mp 110–112 °C (hexane). $[\alpha]_D^{20}$ +41.7 (*c* 0.505, $CHCl_3$). R_f 0.46 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): ν 3054, 2920, 2856, 1732, 1626, 1454, 1264, 1122 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.5 (d, 1H, J=10.1 Hz), 1.6–1.8 (m, 4H), 1.95–2.15 (m, 3H), 2.21 (s, 3H), 2.9 (dd, 1H, J_1=13.3 Hz, J_2=66.7 Hz), 3.39 (d, 1H, J=9.47 Hz), 3.81 (s, 3H), 4.15 (d, 1H, J=9.45 Hz), 7.08 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.14 (q), 22.47 (t), 22.76 (t), 24.98 (q), 32.25 (t), 39.67 (d), 49.59 (t), 51.39 (d), 52.39 (q), 52.99 (s), 70.99 (t), 85.74 (s), 131.96 (d), 140.60 (s), 167.80 (s), 200.15 (s) ppm. HRMS-EI (M+H^+) calcd for $C_{16}H_{23}O_4$: 279.1591, found: 279.1582.

4.5.4. Unsaturated ketoester 26 (from 25). Periodinane oxidation of hydroxyester **25** (0.75 g, 0.26 mmol) afforded **26** (0.6 g, 81%).

4.6. Preparation of (+)-massarinolin B (2) and 4-*epi*-(+)-massarinolin B (4)

4.6.1. (+)-Massarinolin B (2). To an ice-cooled solution of **27** (0.083 g, 0.23 mmol) in anhydrous THF (1.5 mL) a solution of TBAF (0.180 g, 0.69 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 2 h at room temperature, poured into water (25 mL), acidified with aq HCl and extracted with ethyl acetate (3×25 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to afford (+)-massarinolin B (**2**) (0.06 g, 99%). $[\alpha]_D^{20}$ +49.63 (*c* 0.72, MeOH). IR ($CHCl_3$): ν 3385, 2926, 1696, 1241, 1142, 1009 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.23 (s, 3H), 1.51 (m, 1H), 1.61 (m, 1H), 1.77 (m, 1H), 1.83 (m, 1H), 1.84 (d, 3H, J=1.2 Hz), 1.87 (m, 1H), 1.89 (m, 1H), 2.00 (dd, 1H, J_1=10.8 Hz, J_2=4.1 Hz), 2.13 (m, 1H), 2.15 (m, 1H), 2.30 (m, 1H), 3.60 (d, 1H, J=9.4 Hz), 3.90 (d, 1H, J=9.4 Hz), 4.45 (ddd, 1H, J_1=8.9 Hz, J_2=8.6 Hz, J_3=4.0 Hz), 6.67 (dq, 1H, J_1=8.6 Hz, J_2=1.2 Hz) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.77 (q), 23.55 (t), 23.78 (t), 25.35 (q), 33.44 (t), 40.27 (d), 41.78 (t), 53.59 (d), 55.54 (s), 67.08 (d), 72.77 (t), 87.65 (s), 128.37 (s), 145.44 (d), 171.37 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{15}H_{22}O_4Na$: 289.1410, found: 289.1416.

4.6.2. 4-*epi*-(+)-Massarinolin B (4). Fluoride deprotection of **28** (0.081 g, 0.22 mmol) afforded **4** (0.058 g, 99%). $[\alpha]_D^{20}$ +8.71 (*c* 1.51, $CHCl_3$). IR ($CHCl_3$): ν 3392, 2926, 2866, 1707, 1238, 1195, 1020 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.22 (s, 3H), 1.47 (d, 1H, J=10.2 Hz), 1.59 (m, 1H), 1.73–1.89 (m, 4H), 1.83 (d, 3H, J=1.2 Hz), 2.09–2.3 (m, 4H), 2.39 (m, 1H), 3.53 (d, 1H, J=9.0 Hz), 3.79 (d, 1H, J=9.0 Hz), 4.91 (ddd, 1H, J_1=9.2 Hz, J_2=9.2 Hz, J_3=6.8 Hz), 6.63 (dq, 1H, J_1=9.2 Hz, J_2=1.2 Hz) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.86 (q), 23.41 (t), 23.62 (t), 25.41 (q), 33.39 (t), 41.33 (d), 41.91 (t), 53.45 (d), 55.20 (s), 67.60 (d), 71.98 (t), 88.20 (s), 128.92 (s), 145.06 (d), 171.28 (s) ppm. HRMS-EI (M+Na^+) calcd for $C_{15}H_{22}O_4Na$: 289.1410, found: 289.1409.

4.7. Methyl (1′*R*,2′*R*,4*S*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxy methyl-2′-trimethylsilyloxy-2′-methyl-bicyclo[3.1.1]hept-6′-yl)-4-*tert*-butyldiphenylsilyloxy-2-methyl-2-pentenoate 31

To a solution of hydroxyester **29** (65 mg, 0.16 mmol) in CH_2Cl_2 at 0 °C were successively added Et_3N (0.045 mL, 0.32 mmol), DMAP (4.8 mg, 0.039 mmol) and $^tBuPh_2SiCl$ (0.062 mL, 0.24 mmol). The reaction mixture was stirred for 48 h at room temperature, diluted with ether (5 mL) and poured on satd $NaHCO_3$ (5 mL). The mixture was stirred for 30 min and extracted with ether. The combined organic layers were successively washed with water and brine, dried (Na_2SO_4) and evaporated to yield a crude product (0.23 g), which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate 9:1 afforded **31** (60 mg, 59%) as a colourless oil. $[\alpha]_D^{20}$ −20.10 (*c* 1.25, $CHCl_3$). R_f 0.54 (hexane/ethyl acetate 7:3). IR (film): ν 2956, 2858, 1737, 1720, 1473, 1251, 859 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 1.03 (s, 9H), 1.05–2.19

(m, 9H), 1.22 (d, 3H, J=1.2 Hz), 1.89 (s, 3H), 2.26 (dd, 1H, J_1=5.6 Hz, J_2=14.4 Hz), 3.63 (s), 3.93 (d, 1H, J=12.3 Hz), 4.37 (d, 1H, J=12.3 Hz), 4.58 (m, 1H), 6.59 (dq, 1H, J_1=1.4 Hz, J_2=9.4 Hz), 7.32–7.66 (m, 10H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.43 (q), 12.38 (q), 19.19 (s), 20.95 (q), 23.59 (t), 26.93 (q), 30.71 (q), 32.64 (t), 39.13 (d), 40.51 (t), 41.80 (s), 51.61 (q), 52.05 (d), 66.26 (t), 68.24 (d), 78.07 (s), 125.87 (s), 127.33 (d), 127.54 (d), 129.47 (d), 129.62 (d), 133.66 (s), 133.92 (s), 135.85 (d), 143.98 (d), 168.19 (s), 170.96 (s) ppm. HRMS-EI ($M+Na^+$) calcd for $C_{37}H_{54}O_{36}Si_2Na$: 673.3351, found: 673.3370.

4.8. Methyl (1′*R*,2′*R*,4*S*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxy methyl-2′-hydroxy-2′-methyl-bicyclo[3.1.1]-hept-6-yl)-4-*tert*-butyldiphenylsilyloxy-2-methyl-2-pentenoate 32

To a solution of **31** (130 mg, 0.20 mmol) in MeOH (5 mL) PPTS (50.3 mg, 0.2 mmol) was added. The mixture was stirred for 30 min. To the ice-cooled mixture was added satd $NaHCO_3$ (5 mL) and the reaction mixture was further stirred for 30 min. The crude mixture was extracted with ether and the combined organic layers were washed with brine. The organic phase was dried with Na_2SO_4 and evaporated to yield a crude (0.13 g), which was fractionated by flash chromatography on silica gel (hexane/ethyl acetate 8:2) to afford **32** (60 mg, 52%). $[\alpha]_D^{20}$ +9.9 (c 0.78, $CHCl_3$). R_f 0.37 (hexane/ethyl acetate 1:1). IR (film): ν 3350, 2858, 1737, 1720, 1473, 1251, 1050, 859 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.19 (d, 3H, J=12 Hz), 1.25–2.30 (m, 10H), 1.91 (s, 3H), 3.63 (s, 3H), 4.24 (s, 2H), 4.58 (q, 1H, J_1=6.7 Hz, J_2=15.3 Hz), 6.59 (d, 1H, J=9 Hz), 7.30–7.66 (m, 10H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.32 (q), 19.19 (s), 20.80 (q), 23.58 (t), 27.00 (q), 27.54 (t), 29.63 (t), 31.71 (q), 38.88 (d), 40.33 (t), 42.16 (s), 51.55 (q), 51.55 (d), 66.21 (t), 68.44 (d), 75.18 (s), 125.92 (s), 127.34 (d), 127.60 (d), 129.56 (d), 129.69 (d), 133.68 (s), 133.93 (s), 135.92 (d), 144.18 (d), 168.23 (s), 170.73 (s) ppm. HRMS-EI ($M+Na^+$) calcd for $C_{34}H_{46}O_6Si_2Na$: 601.2956, found: 601.2965.

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Supplementary data

Spectroscopic data for compounds described in Schemes 1 and 2 and Table 1. HMQC, HMBC, COSY and ROESY experiments for **27**, **28**, **29**, **30**, **2** and **4**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.011.

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10. Satisfactorial spectroscopic data for compounds described in Table 1 and Schemes 1 and 2 have been obtained. See Section 4.
11. Transformation of the mixture of diastereomers **24** and **25** into the corresponding α-*O*-acetyl-mandelic esters gave no results in terms of a more efficient chromatographic separation. The mixture of **24** and **25** was treated with (*S*)-(+)-*O*-acetylmandelic acid, DCC and DMAP in THF at room temperature for 15 h to yield a mixture of (*S*)-(+)-*O*-acetylmandelic esters with 72% yield. See: Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2327–2330.
12. The spectroscopic data obtained for synthetic (+)-(**2**) were superimposable over those described by Gloer for (+)-massarinolin B. $[\alpha]_D^{20}$ +50 (c 0.72 g/dL, CH_3OH); lit. $[\alpha]_D^{20}$ +54 (c 0.65 g/dL, CH_3OH). Structural assignments of **2** and **4** were based mainly on HMQC, HMBC and ROESY experiments.
13. The absolute stereochemistry of the tricyclic core of synthetic (+)-isoampullicin (**7**) has been correlated with that of R-(−)-carvone through a stereocontrolled multistep synthetic sequence. Furthermore, the X-ray analysis of **7** has been reported (see Ref. 5a).
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15. Hydroxyester **29** was sequentially transformed (two steps) into hydroxyester **32** with excellent yields (65% isolated yield). Unfortunately, the stereochemical integrity at C-4 did not survive even under mild dehydration conditions (treatment of **32** with trifluoromethylsulfonic anhydride and dimethyl aminopyridine in methylene chloride at room temperature took 5 days for completion) and afforded only untreatable mixtures of diastereomers belonging to the α and β series of the dehydrated products.