Synthesis of (+)-Muricatacin and a Formal Synthesis of CMI-977 from L-Malic Acid

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Abstract: A total synthesis of (+)-muricatacin and a formal synthesis of CMI-977 have been achieved using commercially available L-malic acid based on our furan approach to oxacyclic systems, the proven scope of which is thus broadened.

Key words: butenolide, oxygen, natural products, total synthesis, oxidation

The biological activities of the natural products (+)-muricatacin (**1**) and CMI-977 (LDP-977) (**2**) (Figure 1) have stimulated significant interest in their synthesis.[1,2] While (+)-muricatacin (**1**) displays potent cytotoxicity towards several human tumour cell lines, CMI-977 proved to be a promising candidate for chronic asthma.

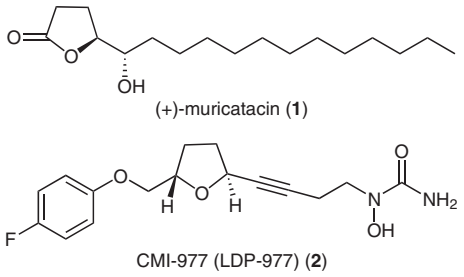
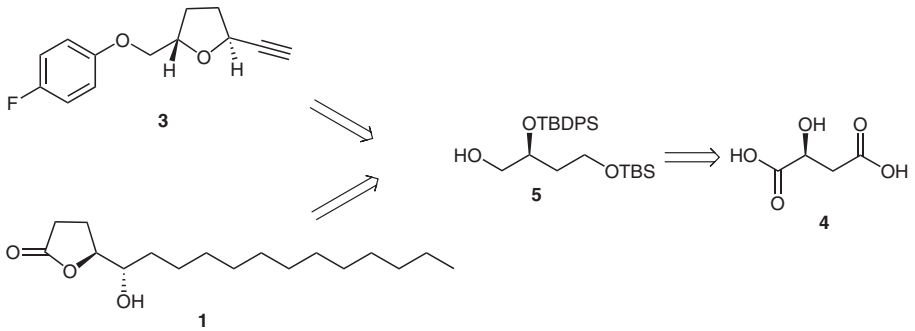


Figure 1 (+)-Muricatacin (**1**) and CMI-977 (LDP-977) (**2**)

Our retrosynthetic strategy for (+)-muricatacin (**1**) and the alkyne precursor **3** of CMI-977 is depicted in Scheme 1.

The relatively inexpensive and readily available chiral reagent L-malic acid (**4**) was easily transformed into alcohol **5** as previously described.[3b] We anticipated that once alcohol **5** had been transformed into chiral furan **16** (Scheme 2), the stage would be set for the synthesis of **1** by what we call our furan approach to oxacyclic systems.[3] Accordingly, alcohol **5** was protected as its pivaloyl ester **6** (90% yield), and selective removal of the TBS protecting group of **6** afforded alcohol **7** (95%), which upon TEMPO oxidation gave aldehyde **8** in 91% yield. Wittig reaction of aldehyde **8** with the phosphonium salt prepared from decyltriphenylphosphonium iodide afforded an 85% yield of alkene **9**, which upon catalytic hydrogenation gave **10** in 99% yield. Deprotection of the primary hydroxyl group of **10** afforded a 91% yield of alcohol **11**, and TEMPO oxidation of **11** gave an 86% yield of aldehyde **12**. Treatment of **12** with the lithium derivative of alkyne **13** gave a mixture of epimeric propynyl alcohols **14**, which were hydrogenated over Lindlar catalyst, providing a mixture of diastereoisomeric *Z*-alkenes **15**, which were used in the next reaction without further purification. Treatment of allylic alcohols **15** with catalytic pyridinium *p*-toluenesulfonate (PPTS) or HCl resulted in cyclisation with loss of two molecules of ethanol, affording the desired furan.[4]

With furan **16** in hand, the stage was set for the crucial oxidation step using singlet oxygen (Scheme 3). Furan **16** was subjected to singlet oxygen oxidation followed by sodium borohydride reduction under Luche's conditions to give an intermediate hydroxy acid, which underwent acid-catalysed in situ lactonisation, affording butenolide **17**[5] in 75% overall yield (3 steps).[1a,6] Catalytic hydrogenation of



Scheme 1 Retrosynthetic analysis of (+)-muricatacin (**1**) and CMI-977 precursor **3**

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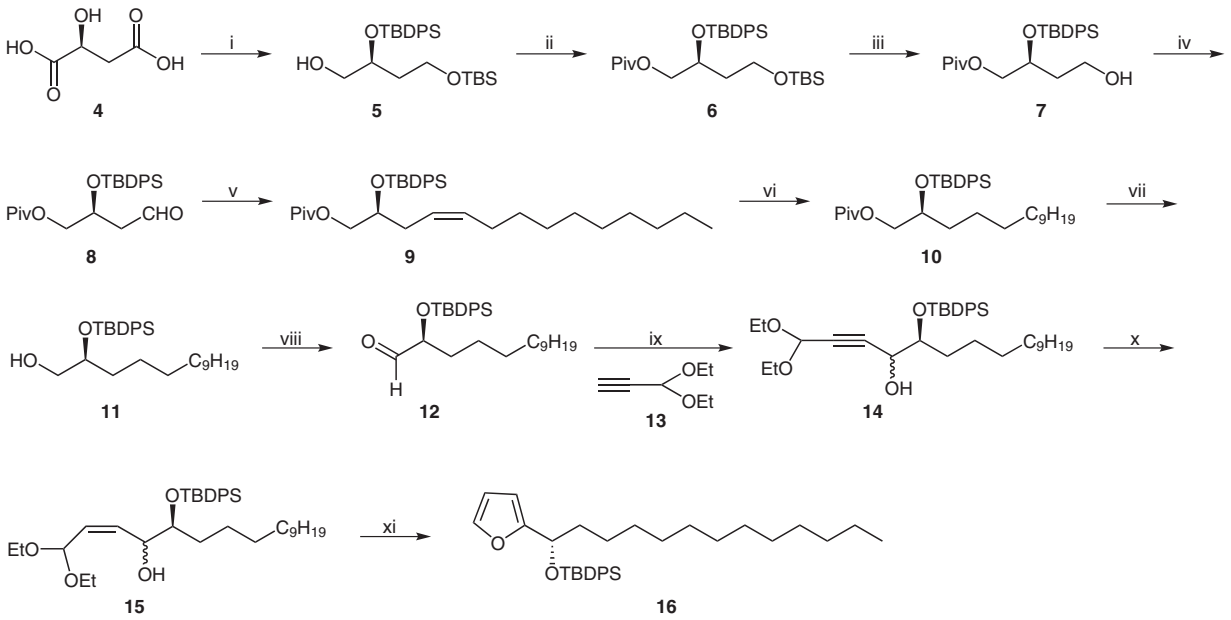


Scheme 2 *Reagents and conditions*: (i) see ref. 3b; (ii) PivCl, DMAP, pyr (99%); (iii) HF–pyr, THF, pyr, 0 °C to r.t. (95%); (iv) TEMPO, BAIB, CH_2Cl_2 (91%); (v) $C_{10}H_{21}IPPh_3$, *n*-BuLi, THF (85%); (vi) H_2, Pd/C, MeOH, r.t. (99%); (vii) DIBAL-H, CH_2Cl_2, –78 °C (91%); (viii) TEMPO, BAIB, CH_2Cl_2 (86%); (ix) **13**, *n*-BuLi, THF, –78 to 0 °C (99%); (x) H_2, Lindlar catalyst, hexane, r.t.; (xi) HCl, or PPTS (73%).

17 gave **18** in 82% yield. Treatment of **18** with TBAF afforded target compound **1** in 90% yield.

The structure of **1** was unambiguously confirmed by X-ray crystallographic analysis of crystals obtained by recrystallisation from hexane (Figure 2).[7]

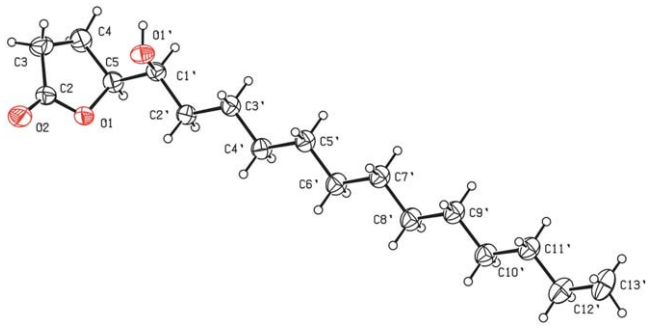
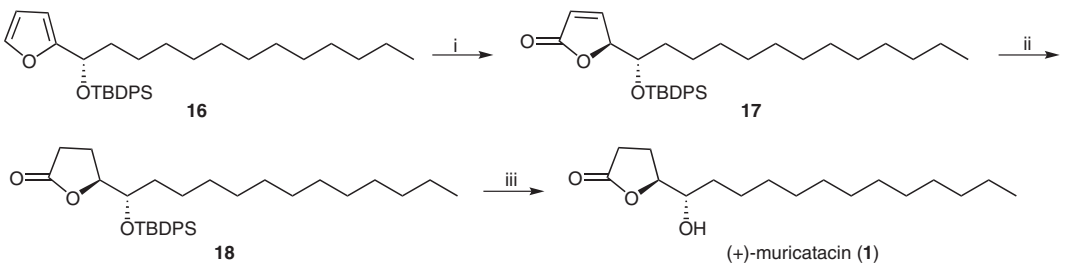


Figure 2 X-ray structure of (+)-muricatacin (**1**)

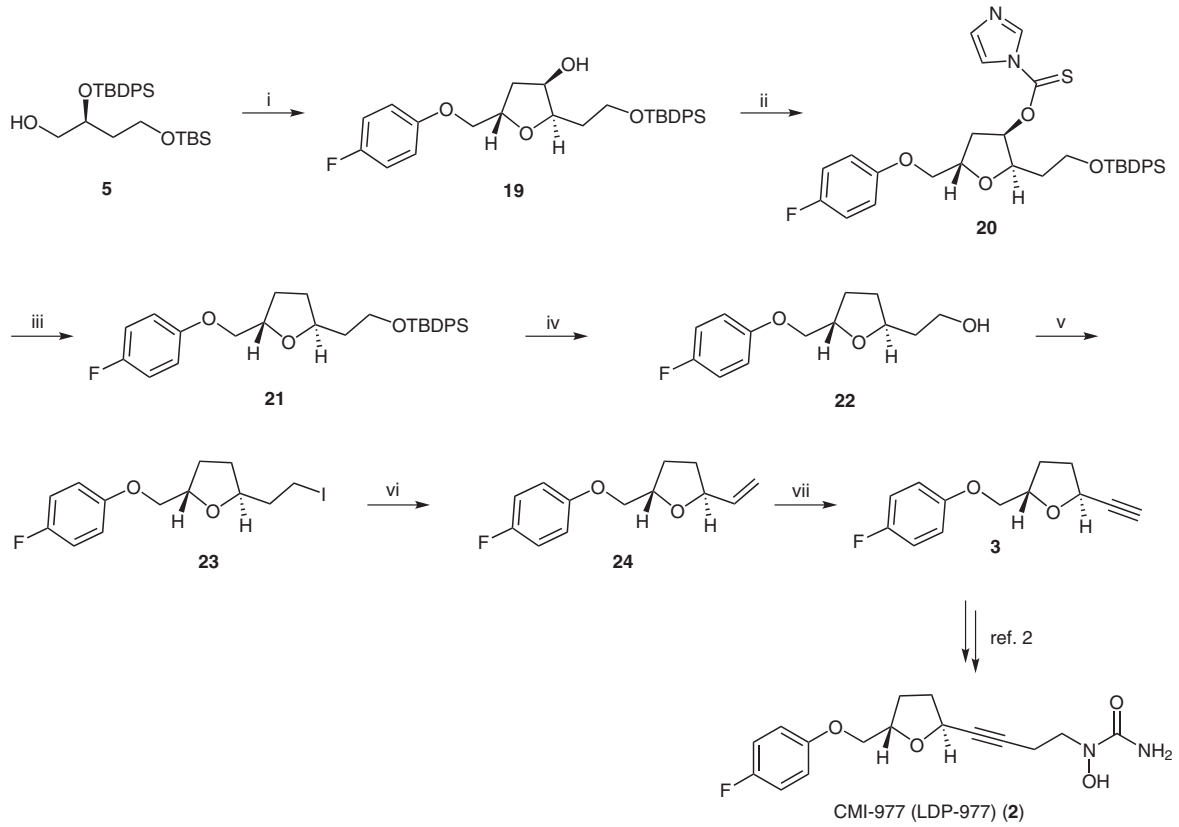
For the synthesis of alkyne **3** the advanced intermediate **19** available from **5**[3b] was used (Scheme 4). Radical deoxygenation[8] of alcohol **19** led to tetrahydrofuran **21** in 74% overall yield. Removal of the silyl protecting group of **21** afforded alcohol **22** (73% yield). Alcohol **22** was uneventfully converted into alkene **24** in 98% overall yield by iodination followed by reaction with *t*-BuOK.[9]

Ozonolysis of alkene **24** gave an aldehyde, which underwent an Ohira–Bestmann homologation[10] to give target alkyne **3** in 69% yield (2 steps). Alkyne **3** is an intermediate in the known synthesis of CMI-977;[2] thus, a formal synthesis of CMI-977 has been achieved.

In summary the synthesis of (+)-muricatacin (**1**) and the alkyne **3** precursor of CMI-977 has been achieved using commercially available L-malic acid. The structure of **1** was unambiguously confirmed by X-ray crystallographic analysis.



Scheme 3 *Reagents and conditions:* (i) (a) O_2, MeOH, rose Bengal, Hünig's base, *hv*; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (c) HCl, MeOH (75%, 3 steps); (ii) H_2, Pd/C, MeOH, r.t. (82%); (iii) TBAF, THF, r.t. (90%).



Scheme 4 Synthesis of CMI-977 precursor **3**. *Reagents and conditions*: (i) see ref. 3b; (ii) $Im_2C{=}S$, THF, 70 °C (83%); (iii) *n*-Bu_3SnH, AIBN, toluene, 120 °C (89%); (iv) TBAF (73%); (v) I_2, Ph_3P, imidazole, THF, 0 °C (99%); (vi) *t*-BuOK, THF (99%); (vii) 1. O_3, Ph_3P, CH_2Cl_2, –78 °C, 2. $(MeO)_2P(=O)C(=N_2)CO_2Me$, K_2CO_3, MeOH, 0 °C (69%, 2 steps).

Solvents were purified and dried by standard procedures. Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm). Melting points were obtained using a Gallenkamp apparatus and are uncorrected. Optical rotations were obtained using a Jasco P-2000 polarimeter. IR spectra of all liquid products were recorded as neat films between NaCl plates on a Jasco FT/IR-6100 Type A spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker ARX-400 spectrometer using TMS as the internal standard; chemical shifts (δ) are quoted in ppm and coupling constants (*J*) in Hz. Mass spectrometry (MS and HRMS) was carried out a Hewlett-Packard 5988A spectrometer.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-(*tert*-butyldimethylsilyloxy)butyl Pivalate (6)

To a solution of **5** (761 mg, 1.66 mmol) in pyridine (37mL) was added a catalytic amount of DMAP and pivaloyl chloride (1.02 mL, 8.3 mmol) at 0 °C and the mixture was stirred at r.t. for 3 h. The reaction was quenched by the addition of H_2O (40 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with 10% aq HCl (3 × 100 mL) and sat. aq $NaHCO_3$ (3 × 100 mL), dried (Na_2SO_4), and evaporated. Purification of the residue by silica gel column chromatography (1% EtOAc–hexane) gave **6**; yield: 894 mg (99%); colourless oil; R_f = 0.69 (10% EtOAc–hexane); $[\alpha]_D^{24}$ –13.9 (*c* 4.60, $CHCl_3$).

IR (neat): 2957, 2931, 2857, 1730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (m, 4 H, CH, *o*-Ph), 7.45 (m, 6 H, CH, *m*,*p*-Ph), 5.23 (m, 1 H, H-4), 4.17 (m, 1 H, H-4), 3.82 (m, 1 H, H-3), 3.71 (m, 2 H, H-1), 1.89 (m, 2 H, H-2), 1.24 (m, 9 H, *t*-C_4H_9, Piv), 1.12 (m, 9 H, *t*-C_4H_9, TBDPS), 0.94 (m, 9 H, *t*-C_4H_9, TBS), 0.11 (m, 6 H, CH_3, TBS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.92 (C=O), 135.66 (CH, *o*-Ph), 133.38 (C, Ph), 129.75 (CH, *m*-Ph), 127.75 (CH, *p*-Ph), 71.70 (CH-3), 65.23 (CH_2-4), 59.41 (CH_2-1), 38.89 (C-*t*-C_4H_9, Piv), 34.05 (CH_2-2), 27.33 (CH_3-*t*-C_4H_9, Piv), 26.81 (CH_3-*t*-C_4H_9, TBDPS), 25.98 (CH_3-*t*-C_4H_9, TBS), 19.31 (C-*t*-C_4H_9, TBDPS), 18.30 (C-*t*-C_4H_9, TBS), –5.35 (CH_3, TBS).

MS (ESI+): *m*/*z* (%) = 565.31 ($[M + Na]^+$, 100), 543.33 ($[M + 1]^+$, 45), 346.14 (3), 291.14 (2).

HRMS (ESI+): *m*/*z* calcd for $C_{31}H_{51}O_4Si_2$: 543.3320; found: 543.3328.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-hydroxybutyl Pivalate (7)

To a solution of **6** (115 mg, 0.212 mmol) in THF (2 mL) was added pyridine (144 μL) and a solution 30% HF in pyridine (71 μL) at 0 °C and the mixture was stirred at r.t. for 6 h. The reaction was quenched by the addition of EtOAc (3 mL) and sat. aq $NaHCO_3$ (3 mL). After stirring for 10 min, the mixture was extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (10% EtOAc–hexane) to afford **7**; yield: 87 mg (95%); colourless oil; R_f = 0.08 (10% EtOAc–hexane); $[\alpha]_D^{23}$ –7.9 (*c* 1.02, $CHCl_3$).

IR (neat): 3760, 3452, 2958, 2932, 2857, 1729, 1589 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (m, 4 H, CH, *o*-Ph), 7.39 (m, 6 H, CH, *m*,*p*-Ph), 4.19 (m, 1 H, H-4), 4.03 (m, 2 H, H-4, H-3), 3.70 (m, 2 H, H-1), 1.82 (m, 2 H, H-2), 1.20 (m, 9 H, *t*-C_4H_9, Piv), 1.17 (m, 9 H, *t*-C_4H_9, TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.36 (C=O), 135.52 (CH, *o*-Ph), 133.71 (C, Ph), 129.64 (CH, *m*-Ph), 127.64 (CH, *p*-Ph), 68.98 (CH-3), 67.67 (CH_2-4), 60.37 (CH_2-1), 38.76 (C-*t*-C_4H_9, Piv), 37.03

(CH_2-2), 27.18 (CH_3-*t*-C_4H_9, Piv), 26.81 (CH_3-*t*-C_4H_9, TBDPS), 19.34 (C-*t*-C_4H_9, TBDPS).

MS (ESI+): *m*/*z* (%) = 451.23 ($[M + Na]^+$, 100), 429.25 ($[M + 1]^+$, 32), 247.04 (11), 221.03 (5), 207.02 (7), 201.04 (40).

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{37}O_4Si$: 429.2455; found: 429.2454.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-oxobutyl Pivalate (8)

To a solution of **7** (297 mg, 0.694 mmol) in CH_2Cl_2 (10 mL) was added bis(acetoxy)iodobenzene (BAIB, 257 mg, 0.798 mmol) and a catalytic amount of TEMPO. The reaction mixture was stirred at r.t. for 5 h. Evaporation gave a residue, which was dissolved in *t*-BuOMe (5 mL), and washed with 10% aq $Na_2S_2O_3$ (3 × 5 mL) and sat. aq $NaHCO_3$ (3 × 5 mL). After drying (Na_2SO_4), and evaporation of solvent under reduced pressure, the residue was purified by chromatography on silica gel (5% EtOAc–hexane) to give **8**; yield: 270 mg (91%); orange oil; R_f = 0.42 (20% EtOAc–hexane); $[\alpha]_D^{19}$ –9.8 (*c* 0.9, $CHCl_3$).

IR (neat): 2946, 2878, 1735, 1716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1 H, H-1), 7.71 (m, 4 H, CH, *o*-Ph), 7.44 (m, 6 H, CH, *m*,*p*-Ph), 4.43 (m, 1 H, H-3), 4.09 (m, 4 H, H-4, H-2), 1.20 (s, 9 H, *t*-C_4H_9, Piv), 1.08 (s, 9 H, *t*-C_4H_9, TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.56 (C=O), 178.15 (C=O, Piv), 135.85 (CH, *o*-Ph), 132.92 (C, Ph), 130.13 (CH, *m*-Ph), 127.79 (CH, *p*-Ph), 67.23 (CH_2-2), 67.02 (CH-3), 48.18 (CH_2-4), 38.83 (C-*t*-C_4H_9, Piv), 27.17 (CH_3-*t*-C_4H_9, Piv), 26.83 (CH_3-*t*-C_4H_9, TBDPS), 19.22 (C-*t*-C_4H_9, TBDPS).

MS (ESI+): *m*/*z* (%) = 449.21 ($[M + Na]^+$, 38), 427.23 ($[M + 1]^+$, 57), 365.17 (8), 279.22 (5), 221.09 (6).

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{35}O_4Si$: 427.2299; found: 427.2305.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)tetradec-4-enyl Pivalate (9)

To a solution of dried phosphonium salt (prepared from decyltriphenylphosphonium iodide) (382 mg, 0.720 mmol) in THF (5.5 mL) cooled to 0 °C was added dropwise *n*-BuLi (2.5 M in hexane, 202 μL, 0.504 mmol) and the solution was stirred for 1 h. To the orange solution was added dropwise compound **8** (240 mg, 0.563 mmol) dissolved in THF (3.6 mL). The mixture was stirred under the same conditions for 15 min, and then sat. aq $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (3 × 5 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (0.5% EtOAc–hexane) to afford **9**; yield: 168 mg (85%); yellow oil; R_f = 0.73 (10% EtOAc–hexane); $[\alpha]_D^{21}$ +11.6 (*c* 1.0, $CHCl_3$).

IR (neat): 2957, 2927, 2856, 1731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (m, 4 H, CH, *o*-Ph), 7.43 (m, 6 H, CH, *m*,*p*-Ph), 5.36 (m, 2 H, H-5, H-4), 4.00 (m, 3 H, H-1, H-2), 2.26 (m, 2 H, H-3), 1.91 (m, 2 H, H-6), 1.30 (m, 14 H, H-7 to H-13), 1.20 (d, *J* = 2.8 Hz, 9 H, *t*-C_4H_9, Piv), 1.08 (s, 9 H, *t*-C_4H_9, TBDPS), 0.91 (t, *J* = 6.8 Hz, 3 H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.43 (C=O), 135.85 (CH, *o*-Ph), 133.89 (C, Ph), 132.80 (CH-5), 129.65 (CH, *m*-Ph), 127.61 (CH, *p*-Ph), 124.04 (CH-4), 71.21 (CH-2), 66.93 (CH_2-1), 38.79 (C-*t*-C_4H_9, Piv), 32.08 (CH_2-3), 31.93–27.30 (7 CH_2), 27.30 (CH_3-*t*-C_4H_9, Piv), 26.91 (CH_3-*t*-C_4H_9, TBDPS), 19.31 (C-*t*-C_4H_9, TBDPS), 14.16 (CH_3).

MS (ESI+): *m*/*z* (%) = 573.37 ($[M + Na]^+$, 59), 551.39 ($[M + 1]^+$, 100), 481.19 (2), 473.34 (9), 403.25 (30).

HRMS (ESI+): *m*/*z* calcd for $C_{35}H_{55}O_3Si$: 551.3915; found: 551.3926.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)tetradecyl Pivalate (10)

Pd/C (10%, 21 mg) was added to a solution of **9** (179 mg, 0.324 mmol) in MeOH (20 mL) at r.t. The reaction mixture was stirred under an atmosphere of H_2 for 4 h after which time it was filtered and concentrated in vacuo to give **10**; yield: 179 mg (99%); colourless oil; R_f = 0.63 (10% EtOAc–hexane); $[\alpha]_D^{22}$ +2.3 (*c* 1.03, $CHCl_3$).

IR (neat): 2956, 2927, 2855, 1731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (m, 4 H, CH, *o*-Ph), 7.43 (m, 6 H, CH, *m*,*p*-Ph), 4.02 (m, 3 H, H-1, H-2), 1.52 (dd, *J* = 5.9, 14.5 Hz, 2 H, H-3), 1.31 (m, 20 H, H-4 to H-13), 1.21 (d, *J* = 4.2 Hz, 9 H, *t*-C_4H_9, Piv), 1.10 (s, 9 H, *t*-C_4H_9, TBDPS), 0.93 (t, *J* = 6.8 Hz, 3 H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.47 (C=O), 135.91 (CH, *o*-Ph), 134.11 (C, Ph), 129.68 (CH, *m*-Ph), 127.59 (CH, *p*-Ph), 71.27 (CH-2), 67.50 (CH_2-1), 38.79 (C-*t*-C_4H_9, Piv), 34.17–29.41 (9 CH_2), 27.21 (CH_3-*t*-C_4H_9, Piv), 26.91 (CH_3-*t*-C_4H_9, TBDPS), 24.65 (CH_2), 22.74 (CH_2), 19.31 (C-*t*-C_4H_9, TBDPS), 14.18 (CH_3).

MS (ESI+): *m*/*z* (%) = 575.38 ($[M + Na]^+$, 71), 554.40 ($[M + 1]^+$, 58), 234.21 (4), 201.04 (35).

HRMS (ESI+): *m*/*z* calcd for $C_{35}H_{57}O_3Si$: 553.4971; found: 553.4086.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)-1-tetradecanol (11)

To a solution of **10** (272 mg, 0.492 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (1 M in hexane, 1.8 mL) at –78 °C and the mixture was stirred for 20 min. The reaction was quenched by the addition of EtOAc (10 mL), and the mixture was washed with aq Rochelle salt (3 × 10 mL), followed by brine (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (1% EtOAc–hexane) to give **11**; yield: 210 mg (91%); colourless oil; R_f = 0.43 (10% EtOAc–hexane); $[\alpha]_D^{21}$ +0.34 (*c* 1.3, $CHCl_3$).

IR (neat): 3582, 2954, 2926, 2855 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (m, 4 H, CH, *o*-Ph), 7.44 (m, 6 H, CH, *m*,*p*-Ph), 3.70 (m, 2 H, H-1), 3.52 (m, 1 H, H-2), 2.53 (s, 1 H, OH), 1.35 (s, 22 H, H-3 to H-13), 1.11 (s, 9 H, *t*-C_4H_9, TBDPS), 0.91 (t, *J* = 6.4 Hz, 3 H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.58 (CH, *o*-Ph), 133.28 (C, Ph), 129.81 (CH, *m*-Ph), 127.79 (CH, *p*-Ph), 72.01 (CH-2), 68.09 (CH_2-1), 32.82–29.38 (7 CH_2), 26.89 (CH_3-*t*-C_4H_9, TBDPS), 25.54 (CH_2), 22.71 (CH_2), 19.27 (C-*t*-C_4H_9, TBDPS), 14.14 (CH_3).

MS (ESI^+): *m*/*z* (%) = 491.33 ($[M + Na]^+$, 100), 391.30 (8), 226.95 (4).

HRMS (ESI^+): *m*/*z* calcd for $C_{30}H_{48}O_2Si$ + Na: 491.3315; found: 491.3334.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)tetradecanal (12)

To a solution of **11** (106 mg, 0.227 mmol) in CH_2Cl_2 (4 mL) was added BAIB (84 mg, 0.261 mmol) and a catalytic amount of TEMPO. The reaction mixture was stirred at r.t. for 6 h. Evaporation gave a residue, which was dissolved in *t*-BuOMe (5 mL), and washed with a 10% aq $Na_2S_2O_3$ (3 × 5 mL) and sat. aq $NaHCO_3$ (3 × 5 mL). After drying (Na_2SO_4) and solvent evaporation under reduced pressure, the residue was purified by chromatography on silica gel (1% EtOAc–hexane) to afford **12**; yield: 91 mg (86%); orange oil; R_f = 0.83 (10% EtOAc–hexane); $[\alpha]_D^{22}$ –3.8 (*c* 1.0, $CHCl_3$).

IR (neat): 2954, 2926, 2855, 1736 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.63 (s, 1 H, H-1), 7.66 (m, 4 H, CH, *o*-Ph), 7.44 (m, 6 H, CH, *m*,*p*-Ph), 4.08 (t, *J* = 5.8 Hz, 1 H, H-2), 1.65 (m, 2 H, H-3), 1.31 (s, 20 H, H-4 to H-13), 1.17 (s, 9 H, *t*-C_4H_9, TBDPS), 0.93 (t, *J* = 6.8 Hz, 3 H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.04 (CH-1), 135.86 (CH, *o*-Ph), 133.26 (C, Ph), 130.04 (CH, *m*-Ph), 127.83 (CH, *p*-Ph), 78.10 (CH-2), 32.92–29.42 (5 CH_2), 27.00 (CH_3-*t*-C_4H_9, TBDPS), 24.09 (CH_2), 22.75 (CH_2), 19.41 (C-*t*-C_4H_9, TBDPS), 14.19 (CH_3).

MS (ESI+): *m*/*z* (%) = 489.31 ([M + Na]$^+$, 31), 467.33 ([M + 1]$^+$, 86), 403.25 (60), 389.28 (35).

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{48}O_6$ + Na: 467.3343; found: 467.3339.

(*S*)-5-(*tert*-Butyldiphenylsilyloxy)-1,1-diethoxyheptadec-2-yn-4-ol (14)

To a solution of 3,3-diethoxyprop-1-yne (**13**; 29 μL, 0.204 mmol) in THF (4.2 mL) cooled to –78 °C was added dropwise *n*-BuLi (2.5 M in hexane, 82 μL, 0.204 mmol) and the solution was stirred for 1 h at 0 °C. To the yellow solution cooled to –78 °C was added dropwise compound **12** (87 mg, 0.186 mmol) dissolved in THF (2.8 mL). The mixture was stirred at r.t. for 90 min. Evaporation gave a residue, to which was added H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL).The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (5% EtOAc–hexane) affording **14** as a mixture of two diastereoisomeric alcohols; yield: 110 mg (99%); yellow oil; R_f = 0.25 (10% EtOAc–hexane).

IR (neat): 3566, 2925, 2854 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (m, 8 H, CH, *o*-Ph), 7.45 (m, 12 H, CH, *m*,*p*-Ph), 5.34 (s, 2 H, H-1), 4.39 (m, 2 H, H-4), 3.79 (m, 4 H, H-1′), 2.54 (d, *J* = 7.7 Hz, 1 H, H-5), 2.44 (d, *J* = 7.8 Hz, 1 H, H-5), 1.58 (m, 4 H, H-6), 1.25 (m, 26 H, H-2′, H-7 to H-16), 1.11 (s, 9 H, *t*-C_4H_9, TBDPS), 0.92 (t, *J* = 6.8 Hz, 3 H, H-17).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.83 (CH, *o*-Ph), 133.69 (C, Ph), 129.02 (CH, *m*-Ph), 127.83 (CH, *p*-Ph), 91.36 (CH-1), 83.45 (C-2), 81.61 (C-3), 76.06 (CH-5), 66.08 (CH-4), 64.85 (CH-4), 60.96 (CH_2-1′), 60.83 (CH_2-1′), 33.04, 29.67, 29.62, 29.51, 29.42, 29.35, 25.24, 22.73 (CH_2-6 to -16), 27.06 (CH_3-*t*-C_4H_9, TBDPS), 19.49 (C-*t*-C_4H_9, TBDPS), 15.11 (CH_3), 14.16 (CH_3).

MS (ESI$^+$): *m*/*z* (%) = 574.37 (36), 573.37 (100), 263.14 (64).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{41}H_{49}O_2$: 573.3727; found: 573.3729.

(*S*)-*tert*-Butyl[1-(furan-2-yl)tridecyloxy]diphenylsilane (16)

Commercially available Lindlar catalyst (14 mg) was added to a solution of **14** (69 mg, 0.115 mmol) in MeOH (3 mL) at r.t. The resulting suspension was stirred for 18 h under an atmosphere of H_2. The catalyst was filtered off through a pad of Celite, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (5 mL) and washed with a solution 3 M aq HCl (3 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (100% hexane) to afford **16**; yield: 42 mg (73%); colourless oil; R_f = 0.86 (10% EtOAc–hexane); $[\alpha]_D^{22}$ –58.3 (*c* 0.9, $CHCl_3$).

IR (neat): 3071, 2925, 2854, 2360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 6.7 Hz, H-5, 2 H, CH, *o*-Ph), 7.54 (d, *J* = 7.2 Hz, 2 H, CH, Ph), 7.45 (m, 5 H, CH, Ph), 7.31 (m, 2 H, CH, Ph), 6.23 (d, *J* = 1.9 Hz, 1 H, H-4), 5.97 (d, *J* = 3.0 Hz, 1 H, H-3), 4.68 (t, *J* = 6.5 Hz, 1 H, H-1′), 1.85 (dt, *J* = 6.4, 12.9 Hz, 2 H, H-2′), 1.26 (m, 20 H, H-3′ to H-12′), 1.08 (s, 9 H, *t*-C_4H_9, TBDPS), 0.94 (t, *J* = 6.7 Hz, 3 H, H-13′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.67 (C-2), 141.12 (CH-5), 135.79 (CH, *o*-Ph), 133.85 (C, Ph), 129.34 (CH, *m*-Ph), 127.31 (CH, *p*-Ph), 109.82 (CH-4), 106.40 (CH-3), 69.12 (CH-1′), 36.51–29.36 (9 CH_2), 26.97 (CH_3-*t*-C_4H_9, TBDPS), 25.05 (CH_2), 22.76 (CH_2), 19.42 (C-*t*-C_4H_9, TBDPS), 14.19 (CH_3).

MS (ESI+): *m*/*z* (%) = 527.33 ([M + Na]$^+$, 100), 503.23 ([M – 1]$^+$, 5), 413.26 (25), 394.34 (64), 226.94 (28).

HRMS (ESI+): *m*/*z* calcd for $C_{33}H_{48}O_2Si$ + Na: 527.3315; found: 527.3313.

(*S*)-5-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)tridecyl]furan-2(5*H*)-one (17)

To a solution of **16** (62 mg, 0.122 mmol) in anhyd MeOH (5 mL) was added Rose Bengal (3 mg) and the resulting pink solution was cooled to –78 °C. At this temperature, DIPEA (89 μL, 0.513 mmol) was added dropwise and the solution was stirred for 1 h under an atmosphere of O_2 and irradiated with a 200 W lamp. Evaporation gave a residue, which was dissolved in CH_2Cl_2 (5 mL) and a solution of oxalic acid (77 mg in 6.6 mL H_2O) was added. The mixture was stirred for 2 h and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford 4-hydroxybutenolide **16a** (107 mg). To a solution of 4-hydroxybutenolide **16a** in anhyd MeOH (5 mL) were added $CeCl_3·7H_2O$ (2 mg, 0.006 mmol) and $NaBH_4$ (18 mg, 0.488 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was acidified by adding concd HCl (pH 2) and stirred 17 h at r.t. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (3% EtOAc–hexane) to give **17**; yield: 48 mg (75%); orange oil; R_f = 0.71 (30% EtOAc–hexane); $[\alpha]_D^{20}$ –32.2 (*c* 1.0, $CHCl_3$).

IR (neat): 3727, 3071, 2926, 2855, 2360, 2342, 1760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 1.7, 7.7 Hz, 1 H, H-4), 7.69 (m, 3 H, CH, Ph), 7.41 (m, 7 H, CH, Ph), 6.13 (dd, *J* = 2.0, 5.8 Hz, 1 H, H-3), 4.98 (td, *J* = 1.8, 3.7 Hz, 1 H, H-5), 4.01 (dd, *J* = 6.0, 10.1 Hz, 1 H, H-1′), 1.54 (m, 2 H, H-2′), 1.29 (s, 20 H, H-3′ to H-12′), 1.08 (s, 9 H, *t*-C_4H_9, TBDPS), 0.92 (t, *J* = 6.8 Hz, 3 H, H-13′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.98 (C=O), 154.31 (CH-4),135.96 (CH, *o*-Ph), 133.42 (C, Ph), 130.08 (CH, *m*-Ph), 127.73 (CH, *p*-Ph), 122.71 (CH-3), 84.72 (CH-5), 72.62 (CH-1′), 32.81–29.43 (CH_2), 27.03 (CH_3-*t*-C_4H_9, TBDPS), 26.62–19.72 (CH_2), 19.48 (C-*t*-C_4H_9, TBDPS), 14.17 (CH_3).

MS (ESI+): *m*/*z* (%) = 543.32 ([M + Na]$^+$, 100), 538.37 (55), 521.34 ([M + 1]$^+$, 6), 403.25 (32), 394.34 (29), 379.21 (10), 245.08 (11), 146.06 (18).

HRMS (ESI+): *m*/*z* calcd for $C_{39}H_{43}O_2$: 543.3257; found: 543.3251.

(*S*)-5-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)tridecyl]dihydrofuran-2(3*H*)-one (18)

Pd/C (10%, 6 mg) was added to a solution of **17** (48 mg, 0.09 mmol) in MeOH (6 mL) at r.t. The reaction mixture was stirred under an atmosphere of H_2 for 48 h after which time it was filtered and concentrated in vacuo to give **18**; yield: 40 mg (82%); colourless oil; R_f = 0.66 (30% EtOAc–hexane); $[\alpha]_D^{20}$ +8.5 (*c* 1.0, $CHCl_3$).

IR (neat): 2923, 2852, 1742, 1456 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (m, 4 H, CH, *o*-Ph), 7.43 (m, 6 H, CH, *m*,*p*-Ph), 4.54 (m, 1 H, H-5), 3.63 (m, 2 H, H-1′, H-3), 2.52 (m, 3 H, H-3, H-4), 2.17 (m, 2 H, H-2′), 1.16 (m, 29 H, H-3′ to H-12′, *t*-C_4H_9, TBDPS), 0.91 (t, *J* = 6.6 Hz, 3 H, H-13′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.40 (C=O), 135.90 (CH, *o*-Ph), 133.90 (C, Ph), 129.72 (CH, *m*-Ph), 127.71 (CH, *p*-Ph), 81.07 (CH-5), 74.90 (CH-1′), 32.59–28.58 (6 CH_2), 27.04 (CH_3-*t*-C_4H_9, TBDPS), 26.58–22.71 (4 CH_2), 19.53 (C-*t*-C_4H_9, TBDPS), 14.14 (CH_3).

MS (ESI+): *m*/*z* (%) = 545 ([M + Na]$^+$, 100), 521 ([M – 1]$^+$, 9), 510 (64), 279 (63), 445 (60).

HRMS (ESI+): *m*/*z* calcd for $C_{33}H_{50}O_3Si$ + Na: 545.3421; found: 545.3438.

(*S*)-5-[(*S*)-1-Hydroxytridecyl]dihydrofuran-2(3*H*)-one [1, (+)-Muricatacin]

To a solution of **18** (40 mg, 0.077 mmol) in THF (2 mL) was added TBAF (1 M in THF, 77 μL). The reaction mixture was stirred at r.t. for 24 h. Evaporation gave a residue, which was purified by chromatography on silica gel (30% EtOAc–hexane) to afford (+)-muricatacin (**1**); yield: 20 mg (90%); white solid; mp 68–69 °C; R_f = 0.19 (30% EtOAc–hexane); $[\alpha]_D^{23}$ +26.7 (*c* 1.8, $CHCl_3$).

IR (NaCl, neat): 3445, 2916, 2845, 1746, 1463 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (m, 1 H, H-5), 3.60 (m, 1 H, H-1′), 2.68 (m, 2 H, H-3), 2.20 (m, 2 H, H-4), 1.55 (m, 2 H, H-2′), 1.30 (s, 20 H, H-3′ to H-12′), 0.90 (t, *J* = 6.6 Hz, 3 H, H-13′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C=O), 82.9 (CH-5), 73.7 (CH-1′), 33.0–21.1 (13 CH_2), 14.1 (CH_3).

MS (ESI+): *m*/*z* (%) = 307 ([M + Na]$^+$, 100), 285 ([M + 1]$^+$, 20), 308 (18), 201 (16).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{33}O_3$: 285.2424; found: 285.2426.

O-(2*R*,3*S*,5*S*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl)]-5-[(4-fluorophenoxy)methyl]tetrahydrofuran-3-yl-1*H*-imidazole-1-carbothioate (20)

To a solution of alcohol **19** (108 mg, 0.218 mmol) in THF (6 mL) was added 1,1′-thiocarbonyldiimidazole (78 mg, 0.436 mmol) and the mixture was heated to 70 °C for 1 day. EtOAc (5 mL) was added and the organic layer was washed with brine (3 × 10 mL), dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was chromatographed on silica gel using 15% EtOAc–hexane to afford **20**; yield: 109 mg (83%); yellow oil; R_f = 0.45 (30% EtOAc–hexane); $[\alpha]_D^{24}$ –16.97 (*c* 0.6, $CHCl_3$).

IR (neat): 3060, 2938, 2862, 1742, 1598, 1505 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 $H_{imidazolyl}$, H-2), 7.70 (dd, *J* = 1.1, 6.7 Hz, 4 H, CH, *o*-Ph), 7.62 (s, 1 $H_{imidazolyl}$, H-5), 7.43 (m, 6 H, CH, *p*,*m*-Ph), 7.07 (s, 1 $H_{imidazolyl}$, H-4), 6.99 (t, *J* = 8.5 Hz, 2 H, H-2″), 6.86 (m, 2 H, H-3″), 5.80 (d, *J* = 6.5 Hz, 1 H, H-5), 4.65 (t, *J* = 6.6 Hz, 1 H, H-2), 4.50 (qd, *J* = 5.2, 10.3 Hz, 1 H, H-3), 4.07 (dd, *J* = 5.6, 9.7 Hz, 1 H, C*H*$_2$OPh), 3.97 (dd, *J* = 5.0, 9.7 Hz, 1 H, C*H*$_2$OPh), 3.88 (m, 2 H, H-2′), 2.73 (m, 1 H, H-4), 2.27 (m, 1 H, H-4), 1.87 (m, 2 H, H-1′), 1.09 (s, 9 H, *t*-C_4H_9, TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.16 (C=S), 158.69, 156.32 (d, *J* = 238.6 Hz, C-4″), 154.70 (C-1″), 136.89 (CH-2, imidazolyl), 135.61, 135.59 (CH, *o*-Ph), 133.55, 133.48 (C, Ph), 131.03 (CH-4, imidazolyl), 129.74 (CH, *m*-Ph), 127.73 (CH, *p*-Ph), 117.84 (CH-5, imidazolyl), 116.06, 115.83 (d, *J* = 23.1 Hz, CH-3″), 115.70, 115.62 (d, *J* = 8.0 Hz, CH-2″), 87.29 (CH-3), 80.94 (CH-2), 75.67 (CH-5), 70.73 (*C*H_2OPh), 60.20 (CH_2-2′), 35.08, 33.71 (CH_2-4 and -1′), 26.89 (CH_3-*t*-C_4H_9, TBDPS), 19.20 (C-*t*-C_4H_9, TBDPS).

MS (ESI+): *m*/*z* (%) = 689.26 (32), 623.22 (43), 607.25 (42), 605.21 ([M + 1]$^+$, 13), 564.28 (33), 563.27 (100).

HRMS (ESI+): *m*/*z* calcd for $C_{33}H_{38}FN_2O_4SSi$: 605.2260; found: 605.2177.

(2*S*,5*S*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-[(4-fluorophenoxy)methyl]tetrahydrofuran (21)

To a degassed solution of **20** (271 mg, 0.448 mmol) in toluene (12 mL) was added, *n*-Bu_3SnH (144 μL, 0.537 mmol) and AIBN (17 μL, 0.035 mmol). The mixture was heated to 120 °C for 3 h. The solution was allowed to reach r.t. and the solvent evaporated. The resulting residue was chromatographed on silica gel using 3% EtOAc–hexane to afford **21**; yield: 191 mg (89%); colourless oil; R_f = 0.86 (30% EtOAc–hexane); $[\alpha]_D^{24}$ –15.58 (*c* 0.33, $CHCl_3$).

IR (neat): 3060, 2935, 2865, 1505 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 4 H, CH, *o*-Ph), 7.41 (m, 6 H, CH, *p*,*m*-Ph), 6.95 (m, 2 H, H-3″), 6.87 (m, 2 H, H-2″), 4.35 (m, 1 H, H-5), 4.23 (dt, *J* = 6.3, 12.5 Hz, 1 H, C*H*$_2$OPh), 3.92 (m, 2 H, H-2′), 3.81 (m, 2 H, H-2 and C*H*$_2$OPh), 2.12 (m, 2 H, H-4, H-3), 1.95 (qd, *J* = 6.1, 12.6 Hz, 1 H, H-3), 1.79 (m, 2 H, H-1′, H-4), 1.63 (m, 1 H, H-1′), 1.07 (s, 9 H, *t*-C_4H_9, TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.46, 156.10 (d, *J* = 237.9 Hz, C-4″), 155.10 (C-1″), 135.60 (CH, *o*-Ph), 133.94, 133.85 (C, Ph), 129.59 (CH, *m*-Ph), 127.74, 127.64 (CH, *p*-Ph), 115.83, 115.63 (d, *J* = 10.6 Hz, CH-3″), 115.60, 115.55 (d, *J* = 5.01 Hz, CH-2″), 77.00 (CH-5), 76.50 (CH-2), 71.39 (*C*H_2OPh), 61.32 (CH_2-2′), 38.50 (CH_2-1), 31.93 (CH_2-3), 28.65 (CH_2-4), 26.58 (CH_3-*t*-C_4H_9, TBDPS), 19.22 (C-*t*-C_4H_9, TBDPS).

MS (ESI+): *m*/*z* (%) = 480.23 (3), 479.23 ([M – 1]$^+$, 31), 478.23 ([M]$^+$, 100).

HRMS (ESI+): *m*/*z* calcd for $C_{29}H_{35}FO_3Si$: 478.2339; found: 478.2333.

(2*S*,5*S*)-5-[(4-Fluorophenoxy)methyl]-2-[1′-hydroxyethyl]tetrahydrofuran (22)

To compound **21** (240 mg, 0.501 mmol) was added a 1 M solution of TBAF in THF (501 μL, 0.501 mmol) and the mixture was stirred for 20 h. The mixture was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed by rotary evaporation to give a residue, which was chromatographed on silica gel using 30% EtOAc–hexane as eluent to afford **22**; yield: 88 mg (73%); colourless oil; R_f = 0.10 (30% EtOAc–hexane); $[\alpha]_D^{23}$ –4.24 (*c* 0.63, $CHCl_3$).

IR (neat): 3662, 3197, 2955, 1691, 1505 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (m, 2 H, H-3″), 6.84 (m, 2 H, H-2″), 4.37 (tt, *J* = 5.2, 6.6 Hz, 1 H, H-5), 4.20 (tt, *J* = 5.3, 8.0, 1 H, H-2), 3.90 (m, 2 H, C*H*$_2$OPh), 3.76 (t, *J* = 5.8 Hz, 2 H, H-1′), 3.00 (br s, 1 H, OH), 2.11 (m, 2 H, H-3, H-4), 1.78 (m, 3 H, H-3, H-4, H-2′), 1.62 (m, 1 H, H-2′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.48, 156.11 (d, *J* = 238.3 Hz, C-4″), 154.97 (C-1″), 115.85, 115.64 (d, *J* = 20.8 Hz, CH-3″), 115.62, 115.56 (d, *J* = 5.6 Hz, CH-2″), 79.10 (CH-5), 77.45 (CH-2), 71.13 (*C*H_2OPh), 61.10 (CH_2-1′), 37.51 (CH_2-2′), 32.04 (CH_2-3), 28.23 (CH_2-4).

MS (ESI+): *m*/*z* (%) = 529.56 (6), 481.24 (15), 263.10 ([M + Na]$^+$, 1), 242.28 (100), 241.12 ([M + 1]$^+$, 4).

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{17}FO_3$ + Na: 263.1053; found: 263.1051.

(2*S*,5*S*)-2-[(4-Fluorophenoxy)methyl]-5-[2′-(iodoethyl)]tetrahydrofuran (23)

To a solution of alcohol **22** (81 mg, 0.338 mmol) in THF (4 mL) was added Ph_3P (106 mg, 0.405 mmol) and imidazole (69 mg, 1.01 mmol). The mixture was cooled to 0 °C and I_2 (94 mg, 0.372 mmol) was added. After 4 h, the mixture was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with 10% aq $Na_2S_2O_3$ (3 × 8 mL), dried (Na_2SO_4), filtered, and the solvent was removed by rotary evaporation to give a residue, which was chromatographed on silica gel using 7% EtOAc–hexane to afford **23**; yield: 118 mg (99%); yellow oil; R_f = 0.68 (30% EtOAc–hexane); $[\alpha]_D^{23}$ +6.03 (*c* 0.26, $CHCl_3$).

IR (neat): 2923, 2860, 1698, 1505 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (m, 2 H, H-3″), 6.88 (m, 2 H, H-2″), 4.37 (m, 1 H, H-5), 4.12 (tt, *J* = 5.7, 7.8 Hz, 1 H, H-2), 3.93 (qd, *J* = 5.1, 9.7 Hz, 2 H, C*H*$_2$OPh), 3.27 (m, 2 H, H-2′), 2.09 (m, 4 H, H-3, H-4), 1.84 (m, 1 H, H-1′), 1.59 (m, 1 H, H-1′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.50, 156.13 (d, *J* = 238.4 Hz, C-4″), 155.02 (C-1″), 115.87, 115.69 (d, *J* = 18.5 Hz, CH-3″), 115.64, 115.61 (d, *J* = 3.4 Hz, CH-2″), 79.40 (CH-5), 76.90 (CH-2), 71.24 (*C*H_2OPh), 39.73 (CH_2-1′), 31.24 (CH_2-3), 28.47 (CH_2-4), 2.39 (CH_2-2′).

MS (ESI+): *m*/*z* (%) = 351.02 ([M + 1]$^+$, 100), 279.09 (33), 236.01 (6), 206.18 (22).

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{17}FIO_2$: 351.0251; found: 351.0267.

(2*S*,5*S*)-2-[(4-Fluorophenoxy)methyl]-5-vinyltetrahydrofuran (24)

To a solution of iodide **23** (64 mg, 0.181 mmol) in THF (3 mL) cooled to 0 °C was added *t*-BuOK (81 mg, 0.724 mmol). The mixture was stirred at r.t. for 2 days. Then, sat. aq NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The

combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed by rotary evaporation to give a residue, which was chromatographed on silica gel using 3% EtOAc–hexane to afford **24**; yield: 40 mg (99%); yellow oil; R_f = 0.38 (10% EtOAc–hexane); $[\alpha]_D^{25}$ +4.05 (*c* 1.0, $CHCl_3$).

IR (neat): 3073, 2936, 2879, 1609, 1506 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (m, 2 H, H-3″), 6.87 (m, 2 H, H-2″), 5.88 (ddd, *J* = 6.3, 10.3, 17.0 Hz, 1 H, H-1′), 5.28 (dd, *J* = 1.2, 17.1, 1 H, H-2′), 5.13 (dd, *J* = 1.0, 10.3 Hz, 1 H, H-2′), 4.51 (m, 1 H, H-2), 4.43 (m, 1 H, H-5), 3.95 (dq, *J* = 5.1, 9.6 Hz, 2 H, C*H*$_2$OPh), 2.17 (m, 2 H, H-3, H-4), 1.87 (m, 1 H, H-3), 1.76 (m, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.48, 156.11 (d, *J* = 240.3 Hz, C-4″), 155.06 (C-1″), 138.79 (CH-1′), 115.84, 115.61 (d, *J* = 18.5 Hz, CH-3″), 115.53 (CH-2″), 115.50 (CH_2-2′), 80.52 (CH-2), 77.12 (CH-5), 71.22 (*C*H_2OPh), 32.21 (CH_2-3), 28.48 (CH_2-4).

MS (ESI+): *m*/*z* (%) = 245.09 ($[M + Na]^+$, 6), 222.09 ($[M]^+$, 31), 221.10 ($[M – 1]^+$, 100), 151.05 (95).

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{16}FO_2$: 223.1128; found: 223.1132.

(2*S*,5*S*)-2-Ethynyl-5-[(4-fluorophenoxy)methyl]tetrahydrofuran (3)

To a solution of **24** (65 mg, 0.292 mmol) in CH_2Cl_2 (20 mL) was bubbled ozone gas at –78 °C. After 5 min of stirring at that temperature, Ph_3P (101 mg, 0.386 mmol) was added and the mixture was stirred overnight at –10 °C. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using 50% EtOAc–hexane to give the expected aldehyde; colourless oil; R_f = 0.15 (30% EtOAc–hexane).

Intermediate Aldehyde

^1H NMR (400 MHz, $CDCl_3$): δ = 9.69 (d, *J* = 1.6 Hz, 1 H, H-1′), 6.95 (m, 2 H, H-3″), 6.85 (m, 2 H, H-2″), 4.45 (m, 2 H, H-5, H-2), 3.98 (m, 2 H, C*H*$_2$OPh), 2.26 (m, 1 H, H-3), 2.07 (m, 2 H, H-3, H-4), 1.91 (m, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.31 (C=O), 158.58, 156.21 (d, *J* = 235.9 Hz, C-4″), 154.80 (C-1″), 115.93, 115.70 (d, *J* = 23.21 Hz, CH-3″), 115.64, 115.56 (d, *J* = 7.87 Hz, CH-2″), 83.38 (CH-2), 78.88 (CH-5), 70.66 (*C*H_2OPh), 27.69, 27.14 (CH_2-3, -4).

To a solution of the above obtained aldehyde in MeOH (6 mL) cooled to 0 °C was added ethyl 2-diazo-2-(dimethoxyphosphoryl)acetate (630 mg, 2.92 mmol) in MeOH (6 mL) and K_2CO_3 (403 mg, 2.92 mmol), and the mixture was stirred at r.t. for 18 h. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using 3% EtOAc–hexane to give **3**; yield: 44 mg (69%, 2 steps); colourless oil; R_f = 0.85 (EtOAc); $[\alpha]_D^{22}$ –26.47 (*c* 1.0, $CHCl_3$).

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IR (neat): 3294, 3061, 2932, 2863, 1505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (m, 2 H, H-3″), 6.86 (m, 2 H, H-2″), 4.78 (m, 1 H, H-2), 4.51 (m, 1 H, H-5), 3.96 (d, *J* = 4.7 Hz, 2 H, C*H*$_2$OPh), 2.48 (d, *J* = 2.0 Hz, 1 H, H-2′), 2.29 (m, 2 H, H-3, H-4), 2.09 (m, 1 H, H-3), 1.90 (m, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.54, 156.17 (d, *J* = 238.2 Hz, C-4″), 154.94 (C-1″), 115.89, 115.66 (d, *J* = 23.3 Hz, CH-3″), 115.63, 115.55 (d, *J* = 8.1 Hz, CH-2″), 83.47 (CH-5), 77.06 (CH-2), 72.91 (C-1′), 70.60 (*C*H_2OPh), 68.61 (CH_2-2′), 33.20 (CH_2-4), 27.66 (CH_2-3).

MS (ESI+): *m*/*z* (%) = 243.08 ($[M + Na]^+$, 100), 239.12 (57), 221.09 ($[M + 1]^+$, 95), 220.11 ($[M]^+$, 13), 201.07 ($[M – F]^+$, 1), 151.05 (35).

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{14}FO_2$: 221.0972; found: 221.0977.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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