Asymmetric Synthesis of the Enantiopure C28–C41 Segment of the Phorboxazoles A and B

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Abstract. The phorboxazoles A and B are a new class of biologically highly active macrolides. The enantiopure C28–C41 segment containing four stereogenic centers, an *E*-configurated trisubstituted double bond and the 2,4-difunctionalized oxazole moiety has been prepared in 16 steps in 10% overall yield. The synthesis represents advances in strategy and methodology.

Key words: oxazoles, marine natural products, oxabicyclic ketones, cytotoxicity, HWE reaction, *E*,*E*-selectivity

The phorboxazoles A and B first described by Molinski in 1995,[1] are two new macrolides with an unprecedented molecular skeleton. The structural assignment has resulted from exhaustive NMR studies and comparison of synthetic samples with derivatized fragments of the phorboxazoles after degradation.[2] Together with the altohyrtins[3] and the bryostatins[4] they are amongst the most cytotoxic natural products as they inhibit growth of tumor cells at sub-nanomolar concentrations in vitro (mean GI_{50} 1.58×10^{-9} M).[2b] Unlike antimitotic natural products such as Taxol[5] or the epothilones[6] the phorboxazoles arrest the cell cycle during S phase.

Only a few synthetic approaches towards the total synthesis have been published so far including a total synthesis of phorboxazole A by Forsyth and his co-workers.[7,8] The side chain beginning with C27 contains four *E*-configurated double bonds, five stereogenic centers and a 2,4-disubstituted oxazole moiety.

As part of our program towards the total synthesis of the phorboxazoles A and B we considered the approach from 8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**) as outlined in the Figure.

The efficient synthesis of enantiopure methoxyacetal ester **2** from oxabicyclic ketone **1** has been described by us recently in gram quantities.[9] Starting from α-methoxyacetal ester **2** we first aimed to prepare the 2,4-disubstituted oxazole moiety. Among several procedures to install this 5-membered heterocycle the biomimetic pathway using L-serine as the nitrogen source seemed to be the method of choice. The α-methoxyacetal ester **2** was quantitatively hydrolyzed to the acid **3**, converted into the mixed anhydride using isobutyl chloroformate and subsequently coupled with L-serine methyl ester to the *N*-acylserine ester **4** in good yield. Cyclodehydration (**4** → **5**) to the oxazoline occurred smoothly in the presence of the Burgess reagent.[10] The oxidative aromatisation of oxazolines to oxazoles has been a difficult step for a long time.[11] An inexpensive and efficient method has been developed at Bristol-Myers Squibb using a $CuBr_2$/HMTA/DBU complex.[12] This method proved to be very useful in the presence of the electron-withdrawing ester functionality at the 4-position of the oxazoline. Treating oxazoline **5** under these conditions we obtained oxazole ester **6** in a fast and

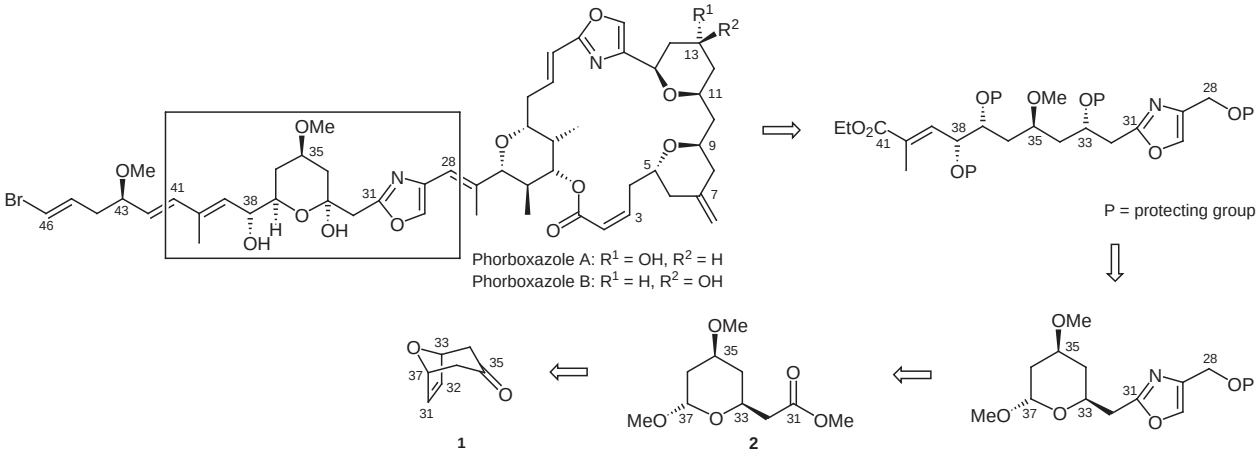
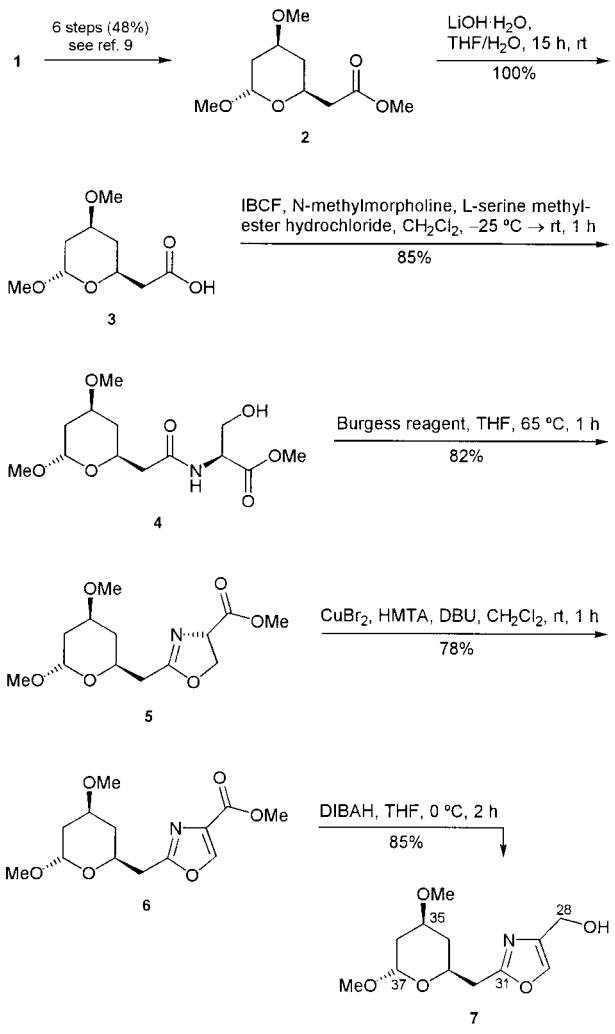


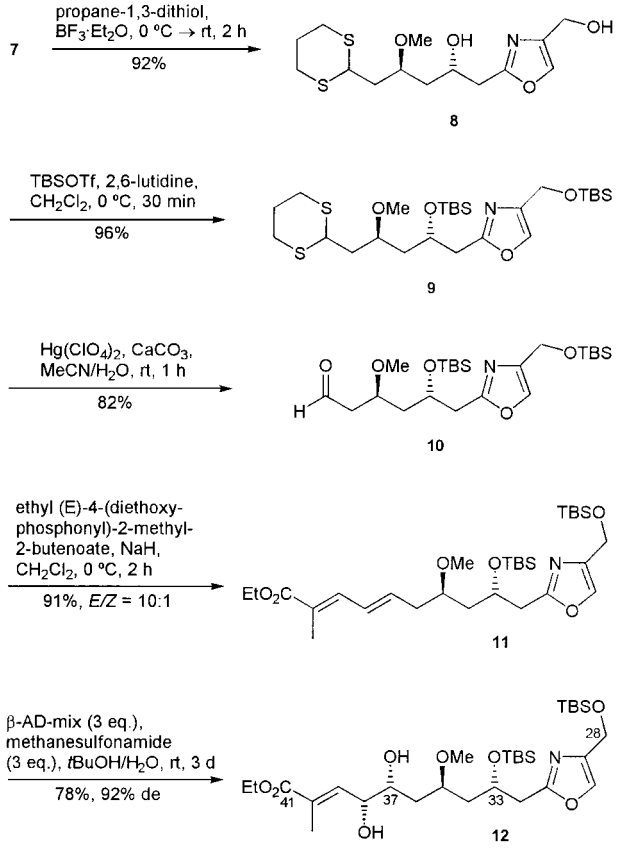
Figure 1 Retrosynthetic analysis of the side chain

high yielding reaction without any side products. DIBAH reduction of the oxazole ester **6** to oxazole alcohol **7** concluded the synthesis of the C28–C37 building block.



Scheme 1

The opening of the methoxyacetal ring of alcohol **7** is shown in Scheme 2. Lewis acid mediated transthioacetalisation of tetrahydropyran methoxyacetals affords polyketides in high yields.[13] When oxazole alcohol **7** was treated with propane-1,3-dithiol in the presence of boron trifluoride–diethyl ether complex anti 1,3-diol oxazole **8** (with one alcohol group methylated) was obtained in excellent yield. Protection of both hydroxy groups in one step under standard procedures with TBS-triflate/2,6-lutidine in dichloromethane afforded O-diprotected oxazole **9**. Removal of a dithiane moiety can sometimes be tedious. After optimization on a model compound the dithiane **9** was converted into the aldehyde **10** rapidly and under mild reaction conditions by treatment with mercuric perchlorate in aqueous acetonitrile, the pH being controlled with solid calcium carbonate.[14] Coupling of aldehyde **10** with the BASF phosphonoester ethyl [(E)-4-(diethoxyphosphonyl)-2-methylbut-2-enoate][15] in the presence of sodium hydride in dichloromethane at 0 °C gave the (2*E*,4*E*)-deca-2,4-dienoic ester **11** in excellent yield and with good E,E-stereocontrol (E:Z > 10:1) of both disubstituted and trisubstituted alkenic double bonds. Asymmetric dihydroxylations of polyalkenated carbonyl compounds usually give diols in high yields and with excellent diastereoselectivity whilst conjugation of the π system is generally retained.[16] Treatment of deca-2,4-dienoic ester **11** with three equivalents of β-AD-mix in the presence of methanesulfonamide in *t*-BuOH/H_2O at room temperature was site-selective and provided the C28–C41 segment **12** in good chemical yield and with excellent asymmetric induction.



Scheme 2

In summary, we have described a highly diastereoselective and efficient de novo synthesis of the C28–C41 segment **12** of the phorboxazoles A and B. The synthesis consists of only 16 steps, most of which have been optimized with respect to stereocontrol and chemical yields, and proceeds in 10% overall yield. Further synthetic approaches to the other segments of the phorboxazole A and B and towards a convergent total synthesis are in progress.[17]

IR spectra were recorded on a Perkin-Elmer 1710 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated $CHCl_3$ unless otherwise stated,

with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 312 (70 eV) or a VG Autospec spectrometer at r.t. unless otherwise stated. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30–60 μm). Analytical TLC was carried out on aluminium-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). THF was distilled over Na and benzophenone before use. CH_2Cl_2 was distilled over CaH_2 before use. DMF was dried over BaO and distilled over CaH_2 before use. *tert*-Butyl methyl ether (MTBE), EtOAc and light petroleum (PE, bp 40–60 °C) were distilled before use.

(2*S*,4*S*,6*S*)-(4,6-Dimethoxytetrahydropyran-2-yl)acetic Acid (3)

To a solution of ester **2** (1.09 g, 5 mmol) in THF (5 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (450 mg, 5 mmol) and the mixture was stirred for 15 h at r.t. The mixture was acidified with concd HCl (pH 1) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layer was dried ($MgSO_4$) and evaporated to afford acid **3** (1.02 g, 100%) as a colourless oil. $[\alpha]_D^{20}$ = +100.1 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 4.88 (d, ^3J = 2.9 Hz, 1 H, H-37), 4.22–4.16 (m, 1 H, H-33), 3.72–3.65 (m, 1 H, H-35), 3.36 (s, 6 H, 2 × OCH_3), 2.62–2.49 (m, 2 H, H-32, H-32'), 2.20–2.15 (m, 1 H, H-36_{eq}), 2.12–2.08 (m, 1 H, H-34_{eq}), 1.51–1.42 (m, 1 H, H-36_{ax}), 1.25 (q, ^2J = 11.7 Hz, 1 H, H-34_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 176.3 (C-31), 99.2 (C-37), 72.1 (C-35), 64.3 (C-33), 55.5 (OCHO*C*H_3), 54.7 (CHO*C*H_3), 40.7 (C-32), 37.0, 35.7 (C-34, C-36).

IR ($CHCl_3$) ν = 3000, 2936, 2832, 2748, 2676, 1712, 1448, 1412, 1384, 1348, 1304, 1268, 1228, 1188, 1152, 1124, 1080, 1044, 972, 928, 848 cm^{-1}.

MS (r.t.): *m/z* (%) = 204 (M^+, 1.2), 173 ($M^+ - OCH_3$, 13.3), 172 (43.3), 154 (30.9), 141 (100), 129 (17.3), 112 (33.6), 103 (30.9), 97 (19.1), 87 (48.0), 81 (70.1), 71 (54.9).

HRMS calcd for $C_8H_{13}O_4$ ($M^+ - OCH_3$) 173.0813, found 173.0804.

Methyl (2*S*)-2-[2-(2*S*,4*S*,6*S*)-(4,6-Dimethoxytetrahydropyran-2-yl)acetylamino]-3-hydroxypropanoate (4)

To a solution of acid **3** (1.1 g, 5.4 mmol) in CH_2Cl_2 (10 mL) was added *N*-methylmorpholine (0.7 mL, 0.62 g, 6.1 mmol) followed by *iso*-butyl chloroformate (0.72 mL, 0.76 g, 5.4 mmol) at –25 °C. The mixture was stirred for 15 min, then L-serine methyl ester hydrochloride (1.0 g, 6.4 mmol) and *N*-methylmorpholine (1.4 mL, 1.24 g, 12.2 mmol) were added. The mixture was stirred for 30 min at –25 °C and then allowed to reach r.t. slowly and stirred for a further hour. Sat. aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (10 × 20 mL). The combined organic layer was dried (Na_2SO_4), the solvent was removed and the crude product purified by column chromatography (silica gel; EtOAc → EtOAc/ oil. $[\alpha]_D^{20}$ = +82.1 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.15 (br d, 1 H, NH), 4.86 (d, ^3J = 2.8 Hz, 1 H, H-37), 4.68–4.64 (m, 1 H, H-29), 4.18–4.12 (m, 1 H, H-33), 4.01–3.91 (m, 2 H, H-30, H-30'), 3.79 (s, 3 H, CO_2CH_3), 3.71–3.63 (m, 1 H, H-35), 3.34 (s, 6 H, 2 × OCH_3), 3.21 (br. s, 1 H, OH), 2.54–2.44 (m, 2 H, H-32, H-32'), 2.18–2.14 (m, 1 H, H-36_{eq}), 2.11–2.05 (m, 1 H, H-34_{eq}), 1.43 (ddd, ^2J = 12.7 Hz, ^3J = 11.3 Hz, ^3J = 2.8 Hz, 1 H, H-36_{ax}), 1.29–1.20 (m, 1 H, H-34_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 170.9 (C-28), 170.8 (C-31), 99.3 (C-37), 71.9 (C-35), 64.8 (C-33), 63.1 (CH_2OH), 55.5 (OCH_3), 54.9 (OCH_3), 54.7 (C-30), 52.8 (CO_2CH_3), 42.8 (C-32), 37.1, 35.9 (C-34, C-36).

IR ($CHCl_3$): ν = 3624, 3428, 3380, 3000, 2936, 2832, 1744, 1672, 1604, 1512, 1440, 1384, 1348, 1300, 1232, 1200, 1152, 1120, 1088, 1044, 1000, 972, 924, 604, 544 cm^{-1}.

MS (140 °C): *m/z* (%) = 287 ($M^+ - H_2O$, 1.3), 274 ($M^+ - OCH_3$, 3.9), 273 (5.8), 255 (7.5), 243 (37.7), 211 (53.4), 182 (18.1), 155 (18.7), 140 (11.5), 120 (25.2), 94 (19.2), 81 (100).

HRMS calcd for $C_{12}H_{20}NO_6$ ($M^+ - OCH_3$) 274.1290, found 274.1286.

Methyl (4*S*)-2-{[(2*S*,4*S*,6*S*)-4,6-Dimethoxytetrahydropyran-2-yl]methyl}-4,5-dihydro-1,3-oxazole-4-carboxylate (5)

To a solution of amide **4** (1.30 g, 4.26 mmol) in THF (70 mL) was added Burgess reagent (1.22 g, 5.11 mmol) and the mixture was heated to reflux for 1 h. The solvent was removed and the crude yield the oxazoline **5** (1.0 g, 82%) as a colourless oil. $[\alpha]_D^{20}$ = +169.5 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 4.86 (d, ^3J = 3 Hz, 1 H, H-37), 4.76 (dd, ^3J = 10.7 Hz, ^3J = 7.8 Hz, 1 H, H-29), 4.53 (dd, ^3J = 8.7 Hz, ^3J = 7.8 Hz, 1 H, H-30), 4.39 (dd, ^3J = 10.7 Hz, ^3J = 8.8 Hz, 1 H, H-30'), 4.15–4.08, 3.68–3.60 (m, 2 H, H-35, H-33), 3.77 (s, 3 H, CO_2CH_3), 3.33, 3.31 (2 s, 6 H, OCH_3), 2.64–2.46 (m, 2 H, H-32, H-32'), 2.18–2.14 (m, 2 H, H-36_{eq}, H-34_{eq}), 1.43 (ddd, ^2J = 12.9 Hz, ^3J = 11.4 Hz, ^3J = 3.0 Hz, 1 H, H-36_{ax}), 1.31 (q, $^{2/3}J$ = 11.7 Hz, 1 H, H-34_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 171.5 (C-28), 168.0 (C-31), 99.2 (C-37), 72.1 (C-35), 69.4 (C-29), 68.1 (C-30), 65.1 (C-33), 55.5 (OCH_3), 54.6 (OCH_3), 52.6 (CO_2CH_3), 37.1, 35.9 (C-34, C-36), 34.7 (C-32).

IR ($CHCl_3$): ν = 3000, 2952, 2936, 2832, 1740, 1660, 1600, 1580, 1440, 1352, 1304, 1228, 1184, 1156, 1124, 1080, 1044, 972, 924, 868, 844 cm^{-1}.

MS (r.t.): *m/z* (%) = 287 (M^+, 3.1), 272 (14.7), 256 (17.0), 224 (24.9), 197 (19.1), 169 (54.3), 143 (100), 113 (52.4), 87 (45.9), 81 (58.0).

HRMS calcd for $C_{13}H_{21}NO_6$ (M^+) 287.1369, found 287.1369.

Methyl 2-{[(2*S*,4*S*,6*S*)-4,6-Dimethoxytetrahydro-2*H*-pyran-2-yl]methyl}-1,3-oxazole-4-carboxylate (6)

To a solution of CuBr (2.68 g, 11.84 mmol) and HMTA (1.67 g, 11.84 mmol) in oxygen-free CH_2Cl_2 (25 mL) was added DBU (1.78 mL, 11.84 mmol) dropwise. The reaction is slightly exothermic and the solution becomes dark. To this mixture was added oxazoline **5** (850 mg, 2.96 mmol) in CH_2Cl_2 (5 mL) dropwise. After being stirred for 1 h at r.t. the mixture was treated with 2 M HCl (50 mL) and EtOAc (50 mL). The mixture was stirred until the dark precipitate had dissolved. The layers were separated and the aqueous layer was extracted with EtOAc (5 × 30 mL). The combined organic layer was dried ($MgSO_4$), evaporated and the crude product purified by azole ester **6** (658 mg, 78%) as a colourless oil. $[\alpha]_D^{20}$ = +79.1 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.18 (s, 1 H, H-30), 4.82 (d, ^3J = 3 Hz, 1 H, H-37), 4.33–4.29 (m, 1 H, H-35), 3.72 (s, 3 H, CO_2CH_3), 3.70–3.62 (m, 1 H, H-33), 3.33, 3.21 (2 s, 6 H, 2 × OCH_3), 3.10–2.96 (m, 2 H, H-32, H-32'), 2.16–2.08 (m, 2 H, H-34_{eq}, H-36_{eq}), 1.44 (ddd, ^2J = 12.5 Hz, ^3J = 11.4 Hz, ^3J = 3.0 Hz, 1 H, H-36_{ax}), 1.31–1.22 (m, 1 H, H-34_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 163.0 (C-28), 161.7 (C-31), 143.9 (C-29), 133.4 (C-30), 99.2 (C-37), 72.0 (C-35), 65.7 (C-33), 55.5 (OCH_3), 54.7 (OCH_3), 52.1 (CO_2CH_3), 37.1, 35.8 (C-34, C-36), 34.7 (C-32).

IR ($CHCl_3$): ν = 2988, 2936, 2832, 1736, 1584, 1440, 1380, 1348, 1324, 1276, 1232, 1112, 1088, 1044, 1004, 976, 844 cm^{-1}.

MS (r.t.): *m/z* (%) = 285 (M^+, 0.8), 270 (0.9), 254 (11.1), 222 (21.5), 210 (8.1), 194 (7.1), 167 (24.4), 145 (39.7), 113 (100), 101 (13.1), 87 (59.7).

HRMS calcd for $C_{13}H_{19}NO_6$ (M^+) 285.1212, found 285.1212.

{2-[(2*S*,4*S*,6*S*)-4,6-Dimethoxytetrahydropyran-2-yl]methyl-1,3-oxazol-4-yl}methanol (7)

To a solution of ester **6** (0.57 g, 2 mmol) in THF (10 mL) was added DIBAH (5 mL, 6 mmol, 1.2 M solution in toluene) at –20 °C under Ar. The mixture was stirred for 2 h at 0 °C, then MeOH (1 mL) was added carefully. The mixture was treated with sat. aq potassium sodium tartrate solution (20 mL) and EtOAc (20 mL) and stirred for 30 min. The aqueous layer was extracted with EtOAc (5 × 20 mL), the combined organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (SiO_2; EtOAc) to give oxazole alcohol **7** (430 mg, 85%) as a colourless oil. $[\alpha]_D^{20}$ = +101.1 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.52 (d, ^4J = 0.9 Hz, 1 H, H-30), 4.83 (d, ^3J = 3.2 Hz, 1 H, H-37), 4.57 (2 H, s, H-28, H-28´), 4.21–4.14 (m, 1 H, H-35), 3.70–3.63 (m, 1 H, H-33), 3.33, 3.22 (2 s, 6 H, OCH_3), 3.05–2.89 (m, 2 H, H-32, H-32'), 2.17–2.09 (m, 2 H, H-36_{eq}, H-34_{eq}), 1.45 (ddd, ^2J = 13.6 Hz, ^3J = 11.5 Hz, ^3J = 3.2 Hz, 1 H, H-36_{ax}), 1.31–1.22 (m, 1 H, H-34_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 162.5 (C-31), 140.4 (C-30), 135.0 (C-29), 99.2 (C-37), 72.1 (C-35), 65.7 (C-33), 56.6 (C-28), 55.5 (OCH_3), 54.6 (OCH_3), 37.1, 35.8 (C-34, C-36), 34.8 (C-32).

IR ($CHCl_3$): ν = 3608, 3436, 3000, 2936, 2832, 1572, 1448, 1380, 1344, 1304, 1264, 1228, 1184, 1152, 1124, 1088, 1044, 960, 916, 844 cm^{-1}.

MS (r.t.): *m/z* (%) = 257 (M^+, 2.8), 242 (1.1), 226 (6.9), 220 (3.0), 194 (10.8), 176 (4.4), 166 (1.5), 145 (40.2), 113 (100), 101 (12.6), 87 (63.8), 81 (15.6).

HRMS calcd for $C_{12}H_{19}NO_5$ (M^+) 257.1263, found 257.1272.

(2*S*,4*S*)-5-[1,3]Dithian-2-yl-1-(4-hydroxymethyl-1,3-oxazol-2-yl)-4-methoxypentan-2-ol (8)

To a solution of oxazole alcohol **7** (52 mg, 0.2 mmol) and propane-1,3-dithiol (0.03 mL, 0.3 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (0.024 mL, 0.2 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at r.t. Silica gel was added and the mixure oxazole diol **7** (61 mg, 92%) as a white foam. $[\alpha]_D^{20}$ = –11.4 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.51 (s, 1 H, H-30), 5.30 (s, 2 H, H-28), 4.53 (s, 1 H, OH), 4.38–4.29 (m, 1 H, H-35), 4.18–4.10 (m, 1 H, H-37), 3.84–3.78 (m, 1 H, H-33), 3.48 (s, 1 H, OH), 3.40 (s, 3 H, OCH_3), 2.92–2.78 (m, 6 H, 2 × SCH_2, H-32, H-32'), 2.15–1.98 (2 m, 2 H, H-36, H-36'), 1.92–1.58 (m, 4 H, CH_2, H-34, H-34').

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 163.1 (C-31), 140.1 (C-29), 135.0 (C-30), 75.3 (C-33), 66.2 (C-35), 57.5 (C-28), 53.5 (OCH_3), 43.6 (C-37), 40.3, 39.8 (C-34, C-36), 36.2 (C-32), 30.4, 30.2 (2 × SCH_2), 25.9 (CH_2).

IR ($CHCl_3$): ν = 3608, 3452, 3216, 2980, 2940, 2904, 2832, 1588, 1572, 1460, 1424, 1364, 1308, 1276, 1228, 1192, 1176, 1080, 1020, 992, 908, 848, 812, 548 cm^{-1}.

MS (120 °C): *m/z* (%) = 333 (M^+, 2.5), 301 (1.2), 226 (1.9), 194 (3.0), 182 (3.7), 169 (9.7), 150 (1.6), 119 (5.6), 99 (6.6), 73 (100).

HRMS calcd for $C_{14}H_{23}NO_4S_2$ (M^+) 333.1069, found 333.1062.

2-[(2S,4S)-2-*tert*-Butyldimethylsilyloxy-5-[1,3]dithian-2-yl-4-methoxypentanyl]-4-*tert*-butyldimethylsilyloxymethyl-1,3-oxazole (9)

To a solution of diol **8** (55 mg, 0.165 mmol) and 2,6-lutidine (0.074 mL, 0.62 mmol) in CH_2Cl_2 (1 mL) was added trifluormethanesulfonic acid *tert*-butyldimethylsilyl ester (0.08 mL, 0.35 mmol) slowly dropwise at 0 °C. The mixture was stirred for 30 min at the same temperature, MTBE (2 mL) was added and the crude product was purified by column chromatography (silica gel; MTBE/PE, 1:5) to afford bis-*O*-silyl ether **9** (88 mg, 96%) as a colourless oil. $[\alpha]_D^{20}$ = –8.8 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.44 (t, ^4J = 1.3 Hz, 1 H, H-30), 4.63 (d, ^4J = 1.3 Hz, 2 H, H-28), 4.30–4.24 (m, 1 H, H-35), 4.14 (t, ^3J = 7.3 Hz, 1 H, H-37), 3.72–3.66 (m, 1 H, H-33), 3.32 (s, 3 H, OCH_3), 2.94–2.78 (m, 6 H, SCH_2, H-32, H-32'), 2.15–2.08, 2.04–1.95 (2 m, 2 H, H-36, H-36'), 1.93–1.58 (m, 4 H, CH_2, H-34, H-34'), 0.95–0.85 (m, 18 H, $Si(C(CH_3)_3)$, 0.13–0.03 (m, 12 H, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 162.1 (C-31), 141.3 (C-29), 134.7 (C-30), 73.8 (C-33), 67.7 (C-35), 58.7 (C-28), 55.7 (OCH_3), 43.7 (C-37), 42.3, 39.6 (C-34, C-36), 37.3 (C-32), 30.42, 30.36 (2 × SCH_2), 25.95 (CH_2), 25.89, 25.83 ($SiC(CH_3)_3$), 18.4, 17.9 ($SiC(CH_3)_3$), –4.60, –4.66, –5.32 ($Si(CH_3)_2$).

IR ($CHCl_3$): ν = 2956, 2928, 2900, 2856, 1600, 1568, 1472, 1424, 1380, 1360, 1256, 1180, 1096, 1004, 960, 936, 908, 836 cm^{-1}.

MS (90 °C): *m/z* (%) = 562 (M^+ + 1, 8.2), 561 (18.0) (M^+), 472 (11.9), 398 (9.2), 372 (8.5), 340 (5.5), 296 (6.7), 266 (4.0), 240 (4.7), 198 (5.1), 170 (3.0), 133 (3.3), 119 (100), 89 (14.7), 73 (30.8).

HRMS calcd for $C_{26}H_{51}NO_4Si_2S_2$ (M^+) 561.2798, found 561.2791.

(3S,5S)-5-*tert*-Butyldimethylsilyloxy-3-methoxy-6-(4-*tert*-butyldimethylsilyloxymethyl-1,3-oxazol-2-yl)hexanal (10)

To a solution of oxazole **9** (150 mg, 0.27 mmol) and $CaCO_3$ (78 mg, 0.81 mmol) in MeCN (2 mL) was added a solution of $Hg(ClO)_4{\cdot}5H_2O$ (~264 mg, ~0.54 mmol) in H_2O (0.3 mL) dropwise at 0 °C. The mixture was stirred for 1 h at r.t.. CH_2Cl_2 (1 mL) was added and a yellow solid precipitated. Silica gel was added and the resulting mixture was purified by column chromatography (silica gel; MTB/PE, 1:3) to give aldehyde **10** (104 mg, 82%) as a colourless oil. $[\alpha]_D^{20}$ = –12.3 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 9.70 (t, ^3J = 2.3 Hz, 1 H, H-37), 7.43 (t, ^4J = 1.3 Hz, 1 H, H-30), 4.62 (d, ^4J = 1.3 Hz, 2 H, H-28), 4.31–4.24 (m, 1 H, H-35), 3.93–3.87 (m, 1 H, H-33), 3.31 (s, 3 H, OCH_3), 2.92–2.88 (m, 2 H, H-32, H-32'), 2.67–2.54 (m, 2 H, H-36, H-36'), 1.85–1.78, 1.67–1.62 (2 m, 2 H, H-34, H-34'), 0.92, 0.86 (2 s, 18 H, $Si(C(CH_3)_3)$, 0.10–0.02 (m, 12 H, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 201.0 (C-37), 161.8 (C-31), 141.3 (C-29), 134.8 (C-30), 72.7 (C-33), 67.4 (C-35), 58.6 (C-28), 56.1 (OCH_3), 47.8 (C-36), 42.6 (C-34), 37.2 (C-32), 25.85, 25.75 ($SiC(CH_3)_3$), 18.3, 17.9 ($SiC(CH_3)_3$), –4.6, –4.8, –5.4 ($Si(CH_3)_2$).

IR ($CHCl_3$): ν = 2956, 2928, 2896, 2856, 2736, 1724, 1568, 1472, 1376, 1360, 1256, 1188, 1160, 1092, 1004, 936. cm^{-1}.

MS (60 °C): *m/z* (%) =456 ($M^+ - CH_3$, 4.8), 425 (1.8), 416 (29.9), 414 (92.3), 384 (32.0), 383 (100), 297 (29.8), 250 (53.9), 214 (19.2), 199 (10.6), 169 (14.4), 155 (4.3), 129 (7.0), 101 (7.2), 73 (44.9).

HRMS calcd for $C_{22}H_{42}NO_5Si_2$ ($M^+ - CH_3$) 456.2601, found 456.2594.

(2*E*,4*E*,7*R*,9*S*)-9-*tert*-Butyldimethylsilyloxy-10-(4-*tert*-butyldimethylsilyloxymethyl-1,3-oxazol-2-yl)-7-methoxy-2-methyldeca-2,4-dienoate (11)

To a solution of aldehyde **10** (65 mg, 0.138 mmol) and ethyl [(*E*)-4-(diethoxyphosphonyl)-2-methylbut-2-enoate] (80 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added NaH (12 mg, 0.3 mmol, 60% suspension in mineral oil) at 0 °C. The mixture was stirred for 2 h at the same temperature, then silica gel was added and the mixture was purified by column chromatography (silica gel; MTBE/PE, 1:4) to give ester **11** (71 mg, 91%; *E*:*Z* = 10:1) as a colourless oil. $[\alpha]_D^{20}$ = –19.5 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.45 (m, 1 H, H-30), 7.18 (d, ^3J = 11.3 Hz, 1 H, H-39), 6.42 (dd, ^3J = 15.1 Hz, ^3J = 11.3 Hz, 1 H, H-38), 6.08–6.02 (dt, ^3J = 15.1 Hz, ^3J = 7.3 Hz, 1 H, H-37), 4.63 (d,

^4J = 1.4 Hz, 2 H, H-28), 4.33–4.27 (m, 1 H, H-35), 4.22 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 3.52–3.46 (m, 1 H, H-33), 3.31 (s, 3 H, OCH_3), 2.89 (d, ^3J = 6.2 Hz, 2 H, H-32, H-32'), 2.44–2.39 (m, 2 H, H-36, H-36'), 1.93 (d, ^4J = 1.0 Hz, 3 H, CH_3), 1.70–1.56 (m, 2 H, H-34, H-34'), 1.31 (t, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 0.92, 0.86 (2 s, 18 H, $Si(C(CH_3)_3)$, 0.10–0.02 (m, 12 H, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 168.6 (C-41), 162.1 (C-31), 141.3 (C-29), 138.1, 137.7 (C-37, C-39), 134.7 (C-30), 128.4 (C-38), 125.8 (C-40), 76.4 (C-33), 67.6 (C-35), 60.5 (OCH_2CH_3), 58.7 (C-28), 56.0 (OCH_3), 42.4 (C-34), 37.4, 36.9 (C-32, C-36), 25.9, 25.8 ($SiC(CH_3)_3$), 18.4, 17.9 ($SiC(CH_3)_3$), 14.3 (OCH_2CH_3), 12.6 (CH_3), –4.6, –4.8, –5.3 ($Si(CH_3)_2$).

IR ($CHCl_3$): ν = 2956, 2928, 2856, 2736, 1696, 1636, 1608, 1568, 1464, 1368, 1256, 1160, 1108, 1004, 972, 936, 904, 836 cm^{-1}.

MS (90 °C): *m/z* (%) = 581 (M^+, 1.7), 566 (6.9), 524 (100), 428 (25.0), 361 (16.2), 296 (88.4), 240 (7.4), 198 (11.9), 168 (6.1), 124 (13.3), 89 (21.0), 73 (46.6).

HRMS calcd for $C_{30}H_{55}NO_6Si_2$ (M^+) 581.3568, found 581.3569.

(2*E*,4*R*,5*R*,7*R*,9*S*)-9-*tert*-Butyldimethylsilyloxy-10-(4-*tert*-butyldimethylsilyloxymethyl-1,3-oxazol-2-yl)-4,5-dihydroxy-7-methoxy-2-methyldec-2-enoate (12)

To a solution of ester **11** (71 mg, 0.122 mmol. *E:Z* = 10:1) in *t*-BuOH (0.15 mL) and H_2O (0.15 mL) were added AD-β-mix (170 mg) and methanesulfonamide (12 mg, 0.125 mmol) and the resulting mixture was stirred for 2 d at r.t.. The reaction was incomplete and a further portion of AD-β-mix (340 mg) and methanesulfonamide (24 mg, 0.25 mmol) was added. Stirring was continued for 24 h. The mixture was cooled to 0 °C, sodium sulfite (550 mg, 5.33 mmol) was added and the mixture was stirred for 20 min. H_2O (5 mL) and CH_2Cl_2 (10 mL) were added. The aqueous layer was extracted with MTBE (5 × 10 mL), the combined organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica gel; MTBE/PE, 2:1) to afford **12** (53 mg, 78%, 92% *de*) as a colourless oil. $[\alpha]_D^{20}$ = +2.2 (*c* = 1 in $CHCl_3$), $[\alpha]_{365}^{20}$ = +19.1 (*c* = 1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.47 (t, ^4J = 1.4 Hz, 1 H, H-30), 6.69 (dq, ^3J = 9 Hz, ^4J = 1.4 Hz, 1 H, H-39), 4.65 (d, ^4J = 1.4 Hz, 2 H, H-28), 4.27–4.17 (m, 5 H, H-6, H-29, OH, OCH_2CH_3), 3.87–3.82 (m, 1 H, H-37), 3.75–3.71 (m, 1 H, H-35), 3.68 (s, 1 H, OH), 3.38 (s, 3 H, OCH_3), 2.94 (d, ^3J = 6.2 Hz, 2 H, H-32, H-32'), 1.96 (d, ^4J = 1.5 Hz, 3 H, CH_3), 1.95–1.86 (m, 2 H, H-34, H-36), 1.63 (ddd, ^2J = 14.3 Hz, ^3J = 6.9 Hz, ^3J = 4.3 Hz, 1 H, H-34'), 1.48 (ddd, ^2J = 14.7 Hz, ^3J = 6.4 Hz, ^3J = 2.5 Hz, 1 H, H-36'), 1.33 (t, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 0.96, 0.89 (2 s, 18 H, $Si(C(CH_3)_3)$, 0.13–0.02 (m, 12 H, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 167.6 (C-41), 162.0 (C-31), 141.3 (C-29), 138.8 (C-39), 134.8 (C-30), 131.2 (C-40), 75.8 (C-35), 71.9 (C-38), 71.5 (C-37), 67.9 (C-33), 60.8 (OCH_2CH_3), 58.6 (C-28), 56.3 (OCH_3), 41.5 (C-34), 37.0 (C-32), 35.1 (C-36), 25.8, 25.7 ($SiC(CH_3)_3$), 18.3, 17.9 ($SiC(CH_3)_3$), 14.2 (OCH_2CH_3), 13.3 (CH_3), –4.6, –4.7, –5.4 ($Si(CH_3)_2$).

IR ($CHCl_3$): ν = 3556, 3524, 3488, 3464, 3436, 2956, 2928, 2896, 2856, 1708, 1652, 1568, 1472, 1388, 1256, 1188, 1092, 1004, 968, 936, 940, 908, 836, 796 cm^{-1}.

MS (110 °C): *m/z* (%) = 558 ($M^+ - C_4H_9$, 2.1), 472 (1.3), 430 (1.4), 400 (4.3), 382 (5.1), 314 (18.8), 279 (20.9), 250 (5.7), 198 (8.0), 167 (40.4), 149 (100), 113 (13.1), 71 (22.0).

HRMS calcd for $C_{26}H_{48}NO_8Si_2$ ($M^+ - C_4H_9$) 558.2919, found 558.2919.

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