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Formal Synthesis of the Anti-Angiogenic Polyketide (–)-Borrelidin under Asymmetric Catalytic Control

Ashoka V. R. Madduri and Adriaan J. Minnaard^{*,[a]}

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Experimental Details: Synthesis of the upper part of Borrelidin.

(E)-4-(*tert*-Butyl-diphenyl-silanyloxy)-but-2-enethioic acid S-ethyl ester (**3**)

To 20 mL of glycol (358 mmol) in 180 mL of dry THF was added 2.2 g (32.2 mmol) imidazole. Then 9.3 g (33.8 mmol) *tert*-butyldiphenylsilyl chloride was added to the mixture under nitrogen atmosphere. The resulting mixture was stirred for 24 h at rt, quenched with water and extracted with diethyl ether. The combined organic phases were dried over MgSO_4 , concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 4:1) to afford 8.5 g (83% yield) of monoprotected glycol **a** as a colorless oil. A solution of **a** (8.5 g, 28.3 mmol) and 1.3 equiv of iodoxybenzoic acid (IBX) (10.3 g, 36.3 mmol) in 180 mL of EtOAc was refluxed for 24 h and cooled to rt. IBX and benzoic acid were filtered off through Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give aldehyde **b** (8.3 g, 98% yield) which was used in the next step without purification. A solution of **b** (8.3 g, 27.8 mmol) and $\text{Ph}_3\text{PCHCOSEt}$ (12.2 g, 33.4 mmol) in CH_2Cl_2 (120 mL) was refluxed for 24 h. The solution was concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford α,β -unsaturated thioester **2** as a colourless oil (8.5 g, 80% yield).

^1H -NMR (400 MHz, CDCl_3): δ ppm 7.66 (dd, $J = 7.7, 1.3$ Hz, 4H), 7.43-7.35 (m, 6H), 6.89 (dt, $J = 15.3, 3.2$ Hz, 1H), 6.55 (dt, $J = 14.9, 2.3$ Hz, 1H), 4.37-4.32 (m, 2H), 2.98 (q, $J = 7.6$ Hz, 2H), 1.30 (t, $J = 7.3$ Hz, 3H), 1.08 (s, 9H).

^{13}C -NMR (100.6 MHz, CDCl_3): δ 190.07 (s), 142.70 (d), 135.40 (d), 132.86 (s), 129.86 (d), 127.80 (d), 126.73 (d), 62.77 (t), 26.74 (q), 23.35 (t), 19.45 (s), 14.80 (q).

HRMS, calcd for $\text{C}_{18}\text{H}_{19}\text{O}_2\text{SSi}$ (*M*-*tert*-butyl) 327.0875 found 327.0875.

(-)-(S)-4-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-thiobutyric acid S-ethyl ester (3**)**

(R,S_{Fe})-Josiphos 4•CuBr complex (67.7 mg, 0.091 mmol, 1 mol%) was dissolved in *t*-BuOMe (50 mL) under nitrogen. The solution was cooled to -78 °C and methylmagnesium bromide (3.64 mL, 10.93 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester **2** (3.5 g, 9.11 mmol) in *t*-BuOMe (15 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at -75 °C for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford **3** as a colourless oil (3.50 g, 96% yield, 98% ee)

1,4- addition on 15 g scale:

For the experimental procedure see the paper.

$[\alpha]_D^{25} = -8.5$ ($c = 1.7$, CHCl₃).

¹H-NMR (400 MHz, CDCl₃): δ 7.66 (dd, $J = 6.8, 1.4$ Hz, 4H), 7.47-7.35 (m, 6H), 3.54 (dd, $J = 10.0, 5.3$ Hz, 1H), 3.46 (dd, $J = 9.9, 6.3$ Hz, 1H), 2.88 (q, $J = 7.4$ Hz, 2H), 2.83 (dd, $J = 14.5, 5.3$ Hz, 1H), 2.38 (dd, $J = 14.5, 8.4$ Hz, 1H), 2.28 (m, 1H), 1.25 (t, $J = 7.4$ Hz, 3H), 1.15 (s, 9H), 0.97 (d, $J = 6.6$ Hz, 3H).

¹³C-NMR (100.6 MHz, CDCl₃): 199.2 (s), 135.62 (d), 133.63 (s), 129.58 (d), 127.50 (d), 67.90 (t), 47.75 (t), 33.76 (d), 26.84 (q), 23.27 (t), 19.28 (s), 16.40 (q), 14.86 (q).

HRMS, calcd for C₁₉H₂₃O₂SSi (M-*tert*-butyl) 343.1188 found 343.1183.

E.e. and absolute configuration of **3** were determined by removal of the tert-butyldiphenylsilyl group. To 20 mg (0.05 mmol) of **3** 0.5 mL of THF was added under nitrogen and to the mixture (0.1 mmol, 2 eq) of TBAF were added and stirred for 3-4 h. The reaction mixture was filtered over a silica plug (eluent pentane/ether 2:1) to afford **3a**. The enantiomeric excess was determined by GC analysis [Chiraldex AT-A (30.0 m x 0.25 mm), 1.0 mL/min, initial temp. 50 °C then 5 °C/min to final temp. 170 °C, 19.5 min (major), 19.7 (minor), shows 98% *ee*].¹

An alternative method for e.e determination: To **3** (103 mg, 0.25 mmol) in 4 mL THF, LiAlH₄ (1M in THF, 3 eq, 0.77 mL) was added at 0 °C and the reaction mixture stirred for at rt and quenched with water and aq. NaOH solution. Upon filtration through the Buchner funnel and the solid waste was washed twice with EtOAc. The filtrate was dried over MgSO₄, concentrated under reduced pressure, to afford a crude **3b**. To **3b** in 2 mL pyridine, benzoyl chloride (3.5 eq, 126 mg) was added and the reaction mixture was heated to reflux for 4 h. It was then allowed to cool down to rt continued to stir for 2h. To this, 5 mL of toluene was added, concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/ether 50:3) to afford **3c** as a colorless oil. Determination of enantiomeric excess was achieved by HPLC (Chiralcel OB, 250*4.6, 10 μm), Eluent 95/5 heptane/IPA, 23.38 min (major), 28.78 min (minor) 98% *ee*.

¹. B. ter Horst, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2007**, *9*, 3013.

HPLC Shimadzu-System.
 Column: Chiralcel OB, 250*4.6, 10 um.
 Eluent: 95/5 Heptane/IPA.

1: 215
 nm, 2 nm
 Results

Pk #	Name	Retention Time	Area	Area Percent
1	1	23,868	37236209	49,793
2	2	28,692	37545575	50,207
Totals			74781784	100,000

HPLC Shimadzu-System.
 Column: Chiralcel OB, 250*4.6, 10 um.
 Eluent: 95/5 Heptane/IPA.

1: 215
 nm, 2 nm
 Results

Pk #	Name	Retention Time	Area	Area Percent
1	1	23,380	135230055	99,152
2	2	28,788	1156875	0,848
Totals			136386930	100,000

(-)-(E)-(S)-6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-2-enethioic acid S-ethyl ester (6)

To a stirred mixture of **3** (2.78 g, 6.95 mmol) in CH_2Cl_2 (100 mL) was added DIBALH (9.03 mL, 9.03 mmol, 1.0 M solution in CH_2Cl_2) at -65°C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched in 100 mL saturated aqueous Rochelle salt (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure to yield crude aldehyde which was purified by flash chromatography (eluent pentane/ether 40:1) to give **5** in turn was used in the next step without complete removal of the eluent.

A solution of $(\text{EtO})_2\text{POCH}_2\text{COSEt}$ (2.5 g, 10.42 mmol, 1.5 eq) dissolved in THF (40 mL) under nitrogen and cooled to 0°C , (5.21 mL, 8.34 mmol, 1.2 eq) n-butyllithium (1.6 M in hexane) was added slowly at 0°C . The reaction mixture was stirred for 10 min at rt. Then the aldehyde **5** was dissolved in 5 mL THF was slowly added and the reaction mixture stirred at rt for 10 h. the reaction mixture was washed with distilled water and extracted with diethyl ether. The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure to yield crude olefin. Purification by flash chromatography (eluent pentane/ether 40:1) afforded α,β -unsaturated thioester **6** as a colourless oil (2.4 g, 81% yield over 2 steps)

$[\alpha]_D^{25} = -6.25$ (c = 1.81, CHCl_3).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.65 (d, $J = 7.9$ Hz, 4H), 7.49-7.35 (m, 6H), 6.87 (dt, $J = 15.4$, 7.6 Hz, 1H), 6.11 (dt, $J = 15.5$, 1.4 Hz, 1H), 3.53 (dd, $J = 10.0$, 5.4 Hz, 1H), 3.46 (dd, $J = 10.0$, 6.4 Hz, 1H), 2.95 (q, $J = 7.4$ Hz, 2H), 2.44 (m, 1H), 2.05 (m, 1H), 1.92-1.84 (m, 1H), 1.29 (t, $J = 7.4$ Hz, 3H), 1.06 (s, 9H), 0.93 (d, $J = 6.8$ Hz, 3H).

$^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3): 190.1 (s), 143.89 (d), 135.60 (d), 133.70 (s), 129.95 (d), 129.61 (d), 127.64 (d), 68.07 (t), 35.97 (t), 35.42 (d), 26.86 (q), 23.03 (t), 19.29 (s), 16.46 (q), 14.91 (q).

HRMS, calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2\text{SSi}$ (M-*tert*-butyl) 369.1331 found 369.1345.

(-)-(3*R*,5*S*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-3,5-dimethyl-hexanethioic acid S-ethyl ester (7a)

(*R,S*_{Fe})-Josiphos 4•CuBr complex (70 mg, 0.095 mmol, 1 mol%) was dissolved in *t*-BuOMe (45 mL) under nitrogen. The mixture was cooled to $-75\text{ }^{\circ}\text{C}$ and methylmagnesium bromide 3.81 mL (11.4 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester **6** (4.05 g, 9.51 mmol) in *t*-BuOMe (18 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at $-75\text{ }^{\circ}\text{C}$ for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl was added, and after phase separation and extraction of the aqueous phase with 3 portions of diethyl ether, the combined organic phases were dried over MgSO_4 , concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford **7b** as a colourless oil (3.75 g, 90% yield)

syn/anti ratio by NMR = 98:2

$[\alpha]_{\text{D}}^{25} = -4.86$ ($c = 1.53$, CHCl_3).

^1H -NMR (400 MHz, CDCl_3): δ 7.68 (dd, $J = 7.6, 1.5$ Hz, 4H), 7.41 (m, 6H), 3.50 (dd, $J = 9.9, 5.5$ Hz, 1H), 3.43 (dd, $J = 9.9, 6.4$ Hz, 1H), 2.87 (q, $J = 7.4$ Hz, 2H), 2.52 (dd, $J = 14.4, 5.1$ Hz, 1H), 2.25 (dd, $J = 14.4, 8.8$ Hz, 1H), 2.08 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.24 (t, $J = 7.4$ Hz, 3H), 1.06 (s, 9H), 1.03 (m, 1H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H).

^{13}C -NMR (100.6 MHz, CDCl_3): 199.3 (s), 135.7 (d), 133.94 (s), 129.50 (d), 127.57 (d), 68.74 (t), 51.19 (t), 40.79 (t), 33.16 (d), 28.69 (d), 26.88 (q), 23.26 (t), 20.28 (q), 19.29 (s), 17.54 (q), 14.82 (q).

HRMS, calcd for $\text{C}_{22}\text{H}_{29}\text{O}_2\text{SSi}$ (*M*-*tert*-butyl) 385.1658 found 385.1668.

(-)-(3*S*,5*S*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-3,5-dimethyl-hexanethioic acid S-ethyl ester (7b)

(*S*,*R*_{Fe})-Josiphos 4•CuBr complex (23.5 mg, 0.0317 mmol, 1 mol%) was dissolved in *t*-BuOMe (15 mL) under nitrogen. The mixture was cooled to -75 °C and methylmagnesium bromide (1.27 mL 3.81 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester **6** (1.35 g, 3.17 mmol) in *t*-BuOMe (6 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at -75 °C for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with 3 portions of diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford **7b** as a colourless oil (1.25 g, 89% yield)

anti/syn ratio by NMR = 95/5

$[\alpha]_D^{25} = -12.6$ (*c* = 0.47, CHCl₃).

¹H-NMR (400 MHz, CDCl₃): δ 7.66 (dd, *J* = 7.7, 1.6 Hz, 4H), 7.41 (m, 6H), 3.46 (m, 2H), 2.87 (q, *J* = 7.5 Hz, 2H), 2.47 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.37 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 1.28 (m, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.08 (m, 1H), 1.06 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 6H).

¹³C-NMR (100.6 MHz, CDCl₃): 199.09 (s), 135.61 (d), 134.00 (s), 129.49 (d), 127.56 (d), 69.29 (t), 52.14 (t), 40.13 (t), 33.11 (d), 28.4 (d), 26.88 (q), 23.25 (t), 19.30 (s), 19.17 (q), 16.36 (q), 14.73 (q).

HRMS, calcd for C₂₂H₂₉O₂SSi (*M*-*tert*-butyl) 385.1658 found 385.1668.

(-)-(E)-(5*R*,7*S*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-5,7-dimethyl-oct-2-enethioicacid S-ethyl ester (9)

To a stirred mixture of **7a** (1.23 g, 2.79 mmol) in CH₂Cl₂ (50 mL) was added DIBALH (3.62 mL, 3.62 mmol, 1.0 M solution in CH₂Cl₂) at -65 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched in 45 mL saturated aqueous Rochelle sat (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude aldehyde and purified by flash chromatography (eluent pentane/ether 40:1) to give **8** which was used in the next step without complete removal of the eluent.

A solution of (EtO)₂POCH₂COSEt (1.01 g, 4.186 mmol, 1.5 eq) dissolved in THF (20 mL) under nitrogen and cooled to 0 °C, (2.09 mL, 3.34 mmol, 1.2 eq) *n*-butyllithium (1.6 M in hexane) was added slowly at 0 °C. The reaction mixture was stirred for 10 min at rt. Then the aldehyde **8** was dissolved in 2 mL THF was slowly added and the reaction mixture stirred at rt for 10 h. the reaction mixture was washed with distilled water and extracted with diethyl ether. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude olefin. Purification by flash chromatography (eluent pentane/ether 40:1) afforded α,β-unsaturated thioester **9** as a colourless oil (1.1 g, 84% yield over 2 steps)

$[\alpha]_D^{25} = -7.6$ ($c = 1.97$, CHCl₃).

¹H-NMR (400 MHz, CDCl₃): δ 7.66 (dd, $J = 7.7, 1.6$ Hz, 4H), 7.41 (m, 6H), 6.83 (dt, $J = 15.4, 7.6$ Hz, 1H), 6.08 (dt, $J = 15.5, 1.4$ Hz, 1H), 3.50 (dd, $J = 9.8, 5.3$ Hz, 1H), 3.42 (dd, $J = 9.8, 6.3$ Hz, 1H), 2.94 (q, $J = 7.4$ Hz, 2H), 2.18 (m, 1H), 1.92 (m, 1H), 1.69 (m, 2H), 1.39 (m, 1H), 1.28 (t, $J = 7.4$ Hz, 3H), 1.06 (s, 9H), 1.02 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H).

¹³C-NMR (100.6 MHz, CDCl₃): 189.97 (s), 144.07 (d), 135.59 (d), 133.93 (s), 129.84 (d), 129.51 (d), 127.57 (d), 68.61 (t), 40.76 (t), 39.45 (t), 33.08 (d), 29.96 (d), 26.86 (q), 23.01 (t), 20.12 (q), 19.28 (s), 17.59 (q), 14.81 (q).

HRMS, calcd for C₂₄H₃₁O₂SSi (*M-tert-butyl*) 411.1814 found 411.1812.

(-)-(3*S*,5*R*,7*S*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-3,5,7-trimethyl-octanethioic acid S-ethyl ester (10)

(*R,S_{Fe}*)-Josiphos 4•CuBr complex (15.5 mg, 0.0209 mmol, 1 mol%) was dissolved in *t*-BuOMe (4 mL) under nitrogen. The mixture was cooled to $-75\text{ }^{\circ}\text{C}$ and methylmagnesium bromide (0.836 mL, 2.05 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester **9** (980 mg, 2.09 mmol) in *t*-BuOMe (6 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at $-75\text{ }^{\circ}\text{C}$ for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl was added and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO_4 , concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford **10** as a colourless oil (890 mg, 87% yield)

syn/anti ratio by NMR = > 98:2

$[\alpha]_{\text{D}}^{25} = -6.8$ ($c = 1.13$, CHCl_3).

^1H -NMR (400 MHz, CDCl_3): δ 7.67 (dd, $J = 1.7, 7.7$ Hz, 4H), 7.41 (m, 6H), 3.46 (dd, $J = 9.8, 5.1$ Hz, 1H), 3.41 (dd, $J = 9.8, 6.5$ Hz, 1H), 2.87 (q, $J = 7.4$ Hz, 2H), 2.52 (dd, $J = 5.0, 14.3$ Hz, 1H), 2.23 (dd, $J = 8.8, 14.3$ Hz, 1H), 2.10 (m, 1H), 1.72 (m, 1H), 1.49 (m, 1H), 1.35 (m, 1H), 1.25 (t, $J = 7.4$ Hz, 3H), 1.21 (m, 1H), 1.06 (s, 12H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.92 (m, 2H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.84 (d, $J = 6.5$ Hz, 3H).

^{13}C -NMR (100.6 MHz, CDCl_3): 199.22 (s), 135.60 (d), 134.03 (s), 129.47 (d), 127.54 (d), 68.74 (t), 50.93 (t), 44.71 (t), 41.18 (t), 33.08 (d), 28.59 (d), 27.61 (d), 26.88 (q), 23.24 (t), 20.53 (q), 20.46 (q), 19.29 (s), 17.98 (q), 14.80 (q).

HRMS, calcd for $\text{C}_{25}\text{H}_{35}\text{O}_2\text{SSi}$ (*M*-*tert*-butyl) 427.2127 found 427.2142.

(-)-(6*R*,8*S*,10*S*,*E*)-11-(*tert*-butyldiphenylsilyloxy)-6,8,10-trimethylundec-3-en-2-one (12**)**

To a stirred mixture of **10** (1.50 g, 3.10 mmol) in CH₂Cl₂ (60 mL) was added DIBALH (4.01 mL, 4.01 mmol, 1.0 M solution in CH₂Cl₂) at -65 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched in 45 mL saturated aqueous Rochelle salt (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude aldehyde which was purified by flash chromatography (eluent pentane/ether 40:1) to give **11** which in turn was used in the next step without complete removal of the eluent.

A solution of (EtO)₂POCH₂COMe (902.1 mg, 4.648 mmol, 1.5 eq) dissolved in THF (20 mL) under nitrogen and cooled to 0 °C, (2.32 mL, 3.718 mmol, 1.2 eq) *n*-butyllithium (1.6 M in hexane) was added slowly at 0 °C. The reaction mixture was stirred for 10 min at rt. Then the aldehyde **11** was dissolved in 3 mL THF was slowly added and the reaction mixture stirred at rt for 10 h. the reaction mixture was washed with distilled water and extracted with diethyl ether. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude **12**. Purification by flash chromatography (eluent pentane/ether 40:1) afforded α,β -unsaturated ketone **12** as a colourless oil (1.32 g, 92% yield over 2 steps)

$[\alpha]_D^{25} = -9.2$ ($c = 1.12$, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, $J = 7.9, 1.6$, 4H), 7.45 – 7.34 (m, 6H), 6.74 (s, 1H), 6.05 (d, $J = 15.9$, 1H), 3.46 (ddd, $J = 16.2, 9.8, 5.8$, 2H), 2.23 (s, 3H), 1.98 – 1.88 (m, 1H), 1.72 (dd, $J = 12.0, 6.6$, 2H), 1.58 – 1.50 (m, 1H), 1.35 (d, $J = 6.7$, 1H), 1.20 (s, 1H), 1.05 (s, 9H), 0.96 – 0.77 (m, 13H).

¹³C NMR (101 MHz, CDCl₃) δ 198.50, 147.42, 135.75, 134.13, 132.61, 129.65, 127.70, 68.83, 44.96, 41.36, 39.58, 33.30, 30.06, 27.77, 27.04, 20.88, 20.59, 19.44, 18.16.

HRMS, calcd for C₃₀H₄₄O₂Si ($M+Na^+$) 487.3008, found 487.2988.

(–)- (4*S*,6*R*,8*S*,10*S*)-11-(*tert*-butyldiphenylsilyloxy)-4,6,8,10-tetramethylundecan-2-one (13a)

For the experimental procedure and spectroscopic data of **13a** see the paper.

(–)- (4*S*,6*R*,8*S*,10*S*)-11-(*tert*-butyldiphenylsilyloxy)-4,6,8,10-tetramethylundecan-2-one (13b)

(*S*,*R*_{Fe})-Josiphos (4)•CuBr complex (18.5 mg, 0.0249 mmol, 1 mol%) was dissolved in *t*-BuOMe (5 mL) under nitrogen. The mixture was cooled to –80 °C and methylmagnesium bromide (0.996 mL 2.44 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester **12** (1.2 g, 2.49 mmol) in *t*-BuOMe (7.2 mL) was added via syringe pump over 1.5 h. The reaction mixture was stirred at –80 °C for 18 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford **13b** as a colourless oil (1.05 g, 88% yield)

syn/anti ratio by NMR = > 99/1

$[\alpha]_D^{25} = -10.6$ ($c = 0.47$, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, $J = 7.2$, 4H), 7.39 (d, $J = 7.3$, 6H), 3.47 (dt, $J = 15.8$, 9.6, 2H), 2.41 (d, $J = 11.3$, 1H), 2.10 (d, $J = 9.6$, 4H), 1.72 (s, 1H), 1.51 (s, 2H), 1.28 (ddd, $J = 40.1$, 16.4, 10.4, 7H), 1.05 (s, 9H), 0.96 – 0.79 (m, 18H).

¹³C NMR (101 MHz, CDCl₃) δ 209.42, 135.84, 134.34, 129.69, 127.76, 68.87, 51.08, 45.68, 44.91, 41.32, 33.39, 30.66, 27.78, 27.10, 21.01, 19.53, 18.43.

HRMS, calcd for C₃₁H₄₈O₂Si ($M + Na^+$) 503.3321 found 503.3313.

(-)- (2*S*,4*R*,6*S*,8*S*)-9-(*tert*-butyldiphenylsilyloxy)-2,4,6,8-tetramethylnonan-1-ol (15)

To a stirred mixture of **13a** (2.0 g, 4.16 mmol) in CHCl₃ (30 mL) was added *m*CPBA (2.86 g, 16.6 mmol) at rt. After stirring 12 h at 60 °C the reaction mixture was cooled to rt. The solvent was evaporated and the crude reaction mixture was purified by flash chromatography (eluent pentane/ether 40:1) to afford **14** as a colorless oil (1.55 g, 75 % yield + 400 mg recovered starting material). Repeating the above procedure for recovered starting material to afford **14** in an overall yield of 1.75 g, 85% yield.

To a stirred solution of **14** (1.7 g 3.42 mmol) in 4 mL of methanol was added potassium carbonate (520 mg, 3.76 mmol). The reaction was stirred at rt for 3 h and the diluted with water. After phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 40:4) to afford **15** as a colourless oil (1.5 g, 97% yield) Spectral data of **15** were consistent with those reported in the literature.²

$[\alpha]_D^{25} = -9.4$ ($c = 1.39$, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, $J = 7.1$, 4H), 7.47 – 7.35 (m, 6H), 4.55 (s, 1H), 3.55 – 3.40 (m, 4H), 1.79 – 1.50 (m, 4H), 1.07 (s, 9H), 0.97 – 0.75 (m, 18H).

¹³C NMR (101 MHz, CDCl₃) δ 135.83, 134.28, 129.68, 127.76, 69.47, 69.03, 46.34, 41.71, 40.15, 33.32, 27.61, 27.26, 27.11, 20.81, 20.52, 19.53, 18.25, 16.30.

HRMS, calcd for C₂₉H₄₆O₂Si (M+Na⁺) 477.3165 found 477.3159.

(-)- (2*S*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethyl-9-(tetrahydro-2H-pyran-2-yloxy)nonan-1-ol (17)

To a stirred mixture of **15** (1.4 g, 3.1 mmol) in CH₂Cl₂ (30 mL) were added dihydropyran (2.78 mL, 30.8 mmol) and PPTS (77 mg, 0.31 mmol). The resulting solution was stirred at rt for 4 h. The reaction was quenched with sat. aq. NaHCO₃ and after phase separation and extraction of the aqueous phase with CH₂Cl₂, the combined organic phases were dried over MgSO₄, concentrated

² T. Novak, Z. Tan, B. Liang, , E.-I. Negishi, *J. Am. Chem. Soc.* **2005**, *127*, 2838.

under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:2) to afford **16** as a colourless oil (1.62 g, 98% yield)

To a stirred mixture of **16** (1.60 g, 2.97 mmol) in THF (25 mL) was added TBAF (1.0 M solution in THF, 8.91 mL, 8.91 mmol). The resulting solution was stirred for 5 h, quenched with sat. aq. NH₄Cl and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:8) to afford **17** as a colourless oil (856 mg, 96% yield)

$[\alpha]_D^{25} = -4.2$ ($c = 0.30$, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 4.61 – 4.52 (m, 1H), 3.91 – 3.81 (m, 1H), 3.51 (dddd, $J = 12.9, 9.3, 8.5, 5.2$, 3H), 3.41 – 3.34 (m, 1H), 3.17 (ddd, $J = 16.5, 9.4, 6.3$, 1H), 1.86 – 1.50 (m, 11H), 1.33 – 1.16 (m, 3H), 1.11 – 1.06 (m, 1H), 0.92 – 0.83 (m, 12H).

¹³C NMR (101 MHz, CDCl₃) δ 99.19, 98.74, 74.09, 73.83, 68.29, 62.37, 45.96, 41.50, 40.63, 33.21, 30.83, 27.49, 27.27, 25.66, 20.95, 20.48, 19.59, 17.64, 17.00.

HRMS, calcd for C₁₈H₃₆O₃ (M+H⁺) 301.2664 found 301.2682.

(–)- (4*S*,6*S*,8*R*,10*S*)-4-methoxybenzyl 4,6,8,10-tetramethyl-3-oxo-11-(tetrahydro-2*H*-pyran-2-yl)undecanoate (20**)**

To a stirred mixture of **17** (800 mg, 2.66 mmol) in CH₂Cl₂ (25 mL) were added molecular sieves 4Å (1.5 g), NMO (657 mg, 5.52 mmol) and TPAP (49 mg, 140 μmol). The reaction was stirred at rt for 1 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:2) to afford **18** as a colourless oil (698 mg, 88% yield).

To a stirred mixture of samarium iodide (0.1 M solution in THF, 33 mL, 3.3 mmol) were added **18** (198 mg, 0.66 mmol) and 4-methoxybenzyl 2-bromoacetate (187 mg, 0.72 mmol) in THF (3 mL) at –78 °C. The reaction was stirred for 30 min and then treated with hexane (35 mL) followed by silica gel (15 g). The mixture was allowed to warm to rt and stirred for 30 min. The mixture was filtered through a short plug of silica gel, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:10) to afford **19** as a colorless oil (284 mg, 90% yield)

To a stirred mixture of **19** (215 mg, 0.45 mmol) in CH₂Cl₂ (4.2 mL) were added molecular sieves 4Å (0.5 g), NMO (111 mg, 0.93 mmol) and TPAP (8.2 mg, 24 μmol). The reaction was stirred at rt for 2 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 55:7) to afford **20** as a colourless oil (182 mg, 85% yield).

$[\alpha]_D^{25} = -5.7$ ($c = 1.55$, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 7.31 (s, 2H), 6.89 (s, 2H), 5.10 (s, 2H), 4.57 (s, 1H), 3.80 (s, 4H), 3.50 (s, 3H), 3.17 (d, $J = 30.7$, 1H), 2.74 (s, 1H), 1.69 (d, $J = 91.5$, 11H), 1.26 (s, 1H), 1.09 (s, 6H), 0.87 (s, 10H).

¹³C NMR (101 MHz, CDCl₃) δ 206.51, 172.80, 159.90, 130.35, 127.66, 114.07, 99.22, 98.81, 73.80, 67.01, 65.66, 62.26, 55.31, 47.82, 46.26, 45.93, 44.40, 41.18, 40.84, 40.34, 37.55, 30.93, 27.97, 27.23, 25.68, 20.60, 20.26, 19.68, 17.10.

HRMS, calcd for C₂₈H₄₄O₆ ($M^+ Na^+$) 499.3036 found 499,3031.

(–)- (3*S*,4*S*,6*S*,8*R*,10*S*)-4-methoxybenzyl 3-hydroxy-4,6,8,10-tetramethyl-11-(tetrahydro-2H-pyran-2-yloxy)undecanoate (21**)**

For the experimental procedure and spectroscopic data of **21** see the paper.

(–)- (3*S*,4*S*,6*S*,8*R*,10*S*)-3-(tert-butyldimethylsilyloxy)-4,6,8,10-tetramethyl-11-(tetrahydro-2H-pyran-2-yloxy)undecanoic acid (A**)**

To a stirred mixture of **21** (125 mg, 0.26 mmol) in CH₂Cl₂ (2.6 mL) was added 2,6-lutidine (51 μl, 0.44 mmol) followed by TBSOTf (77 μl, 0.34 mmol) at 0 °C. The mixture was stirred for 1 h and was quenched with water, after phase separation and extraction of the aqueous phase with CH₂Cl₂, the combined organic phases were dried over MgSO₄, and concentrated under reduced pressure. Crude compound **22** was employed in the next reaction without further purification.

To the stirred mixture of **22** in THF(2 mL) and H₂O (0.55 mL) at 0 °C, LiOH (12 mg, 0.51 mmol) was added and the mixture was stirred for 4 h. after quenching with water, phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:12) to afford **A** as a colourless oil (104 mg, 85% yield over 2 steps). Spectral data of **A** were consistent with those reported in the literature.³

$[\alpha]_D^{25} = -33.2$ (c = 0.25, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 4.58 (d, *J* = 11.4, 1H), 4.02 (d, *J* = 3.2, 1H), 3.86 (s, 1H), 3.61 – 3.44 (m, 2H), 3.26 – 3.07 (m, 1H), 2.47 (d, *J* = 6.2, 2H), 1.69 (dd, *J* = 62.3, 52.6, 12H), 1.37 (s, 1H), 1.25 (s, 3H), 0.89 – 0.84 (m, 21H), 0.07 (dd, *J* = 7.9, 2.8, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 178.22, 99.10, 98.74, 74.18, 74.00, 72.66, 62.26, 45.93, 40.58, 40.26, 39.47, 36.12, 31.05, 30.85, 29.88, 27.63, 27.35, 26.03, 25.70, 20.99, 20.86, 19.69, 18.24, 16.83, 15.41, -4.33, -4.46.

HRMS, calcd for C₂₆H₅₂O₅Si (M+H⁺) 473.3657 found 473.3656.

Experimental Details: Synthesis of the lower part of Borrelidin.

(–)-(1*R*, 2*R*)-methyl 2-hydroxycyclopentanecarboxylate (**24**)

For the experimental procedure and spectroscopic data of **24** see the paper.

³ T. Nagamitsu, D. Takano, T. Fukuda, K. Otoguro, I. Kuwajima, Y. Harigaya, S. Omura, *Org. Lett.* **2004**

Enantiomeric excess and absolute configuration were determined by HPLC (Chiralcel OD, 250*4.6, 10 μ m), eluent 99/1 heptane/IPA, 23.883 min (major), 29.856 min (minor) shows 97% *ee*.⁴

HPLC Shimadzu-System.
Column: Chiralcel OD, 250*4.6, 10 μ m.
Eluent: 99/1 Heptane/IPA.

1: 220 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	12.885	812713	26.50
2	2	20.341	808090	26.35
3	3	24.384	751789	24.51
4	4	28.864	694294	22.64
Totals			3066886	100.00

HPLC Shimadzu-System.
Column: Chiralcel OD, 250*4.6, 10 μ m.
Eluent: 99/1 Heptane/IPA.

1: 220 nm, 10 nm

Results

Pk #	Name	Retention Time	Area	Area Percent
1	1	23.883	5836134	98.58
2	2	29.856	83873	1.42
Totals			5920007	100.00

⁴ R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *Journal of the American Chemical Society* **1989**, *111*, 9134; K.

(-)-(1*R*,2*R*)-methyl 2-(tetrahydro-2*H*-pyran-2-yloxy)cyclopentanecarboxylate (25)

To a stirred mixture of **24** (2.0 g, 13.9 mmol) in CH₂Cl₂ (80 mL) were added dihydropyran (1.39 g, 16.7 mmol) and PPTS (349 mg, 1.4 mmol). The resulting solution was stirred at rt for 4 h. The reaction was quenched with sat. aq. NaHCO₃ solution and after phase separation and extraction of the aqueous phase with CH₂Cl₂, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 50:7) to afford **25** as a colourless oil (3.03 g, 96% yield)

$[\alpha]_D^{25} = -51.4$ ($c = 1.07$, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 4.64 (dt, $J = 19.6, 3.8$, 1H), 4.46 – 4.35 (m, 1H), 3.91 – 3.78 (m, 1H), 3.73 – 3.61 (m, 3H), 3.53 – 3.40 (m, 1H), 2.79 (d, $J = 39.1$, 1H), 2.10 – 1.86 (m, 2H), 1.81 – 1.60 (m, 6H), 1.51 (dd, $J = 11.4, 7.5$, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 175.00, 174.90, 97.65, 97.32, 80.67, 80.36, 61.91, 61.65, 51.07, 50.90, 50.48, 50.10, 33.07, 31.39, 30.45, 28.41, 27.77, 25.03, 22.91, 22.45, 19.14.

HRMS, calcd for C₁₂H₂₀O₄ (M+Na⁺) 251.1259 found 251.1253.

(-)-((1*S*,2*R*)-2-(tetrahydro-2*H*-pyran-2-yl oxy)cyclopentyl)methanol (26**)**

To LiAlH₄ (731 mg, 19.3 mmol) suspended in dry ether (65 mL) was added dropwise **25** (2.93 g, 12.8 mmol) in dry ether (17 mL) for 1 h under nitrogen. After being stirred for 10 h at rt, the reaction mixture was cooled to 0 °C and water (1.08 mL) was added carefully, followed by the addition of 15% aqueous NaOH (1.08 mL) and water (3.2 mL). The white precipitate was filtered off, and the filtrate was concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 1:1) to afford **26** as a colourless oil (2.38 g, 93% yield)

$[\alpha]_D^{25} = -16.2$ ($c = 1.09$, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 4.66 (ddd, $J = 8.4, 5.1, 2.6$, 1H), 4.04 – 3.82 (m, 2H), 3.71 – 3.42 (m, 3H), 2.48 (s, 1H), 2.20 – 2.00 (m, 1H), 1.90 – 1.45 (m, 11H), 1.26 – 1.09 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 98.29, 97.97, 81.26, 80.87, 65.10, 64.70, 63.07, 62.49, 47.75, 33.25, 31.62, 31.03, 30.88, 26.74, 25.31, 25.19, 22.81, 22.10, 19.95, 19.64.

HRMS, calcd for C₁₁H₂₀O₃ (M-H⁻) 199.1412, found 199.1328.

(-)-2-((1*R*,2*S*)-2-((4-methoxybenzyloxy)methyl)cyclopentyl oxy)tetrahydro-2*H*-pyran (27**)**

To a stirred mixture of **26** (2.25 g, 11.3 mmol) in DMF (60 mL) was added sodium hydride (60% in oil, 351 mg, 14.6 mmol) at -20 °C. After being stirred for 30 min, to the resulting suspension was added PMBCl (2.11 g, 13.5 mmol) and then allowed to warmed upto rt. The reaction was quenched with water, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 50:7) to afford **27** as a colourless oil (3.42 g, 95% yield)

$[\alpha]_D^{25} = -31.6$ ($c = 0.98$, CHCl₃).

^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 1.5$, 1H), 7.25 (q, $J = 2.4$, 1H), 6.89 – 6.84 (m, 2H), 4.65 – 4.59 (m, 1H), 4.45 (d, $J = 4.7$, 2H), 3.92 (dddd, $J = 20.5$, 10.2, 8.9, 4.6, 2H), 3.81 – 3.78 (m, 3H), 3.53 – 3.31 (m, 3H), 2.30 – 2.10 (m, 1H), 1.92 – 1.50 (m, 12H), 1.38 – 1.23 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 158.92, 130.61, 129.06, 113.55, 98.42, 96.47, 81.28, 78.84, 72.40, 72.11, 62.73, 61.93, 55.05, 45.95, 33.39, 31.26, 30.97, 27.76, 27.41, 25.47, 22.94, 22.77, 20.03, 19.41.

HRMS, calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4$ ($\text{M} + \text{Na}^+$) 343.1885 found 343.1875.

(+)-(1R,2S)-2-((4-methoxybenzyloxy)methyl)cyclopentanol (28**)**

To a stirred mixture of **27** (3.52 g, 11.0 mmol) in EtOH (100 mL) was added PPTS (400 mg, 1.59 mmol), and the resulting solution was stirred at 50 °C. After 12 h, the reaction was diluted with water, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO_4 , concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:12) to afford **28** as a colourless oil (2.49 g, 96% yield)

$[\alpha]_{\text{D}}^{25} = +1.2$ ($c = 1.15$, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, $J = 0.7$, 1H), 7.24 (s, 1H), 6.92 – 6.81 (m, 2H), 4.50 – 4.42 (m, 2H), 3.97 (q, $J = 6.9$, 1H), 3.81 (s, 3H), 3.56 (dd, $J = 8.9$, 5.3, 1H), 3.33 (t, $J = 9.1$, 1H), 2.20 (s, 1H), 2.07 – 1.70 (m, 4H), 1.58 (ddd, $J = 15.9$, 9.1, 5.3, 2H), 1.28 – 1.08 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.21, 130.41, 129.26, 113.83, 77.85, 73.55, 72.90, 55.26, 47.60, 34.05, 26.69, 21.92.

HRMS, calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ ($\text{M} - \text{H}^+$) 235.1412, found 235.1328.

(–)-(1R,2S)-2-((4-methoxybenzyloxy)methyl)cyclopentyl 4-methylbenzenesulfonate (29**)**

To a stirred mixture of **28** (805 mg, 3.40 mmol) and pyridine (3 mL), was added tosyl chloride (1.29 g, 6.8 mmol) at rt under nitrogen, and the mixture was stirred for 12 h. The reaction mixture was

concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:20) to afford **29** as a colourless oil (1.29 g, 98% yield)

$[\alpha]_D^{25} = -23.5$ ($c = 1.18$, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.6$, 2H), 7.28 (s, 1H), 7.26 (s, 1H), 7.17 (d, $J = 8.2$, 2H), 6.87 (d, $J = 8.7$, 2H), 4.77 (dd, $J = 8.8$, 4.4, 1H), 4.34 – 4.26 (m, 2H), 3.84 – 3.77 (m, 3H), 3.23 (d, $J = 5.9$, 2H), 2.42 (s, 3H), 1.90 – 1.56 (m, 6H), 1.32 (ddd, $J = 27.8$, 17.8, 10.2, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.21, 144.50, 134.36, 130.50, 129.81, 129.15, 127.92, 113.82, 86.66, 72.63, 70.36, 55.39, 46.04, 32.79, 26.94, 22.95, 21.73.

HRMS, calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{S}$ ($\text{M} + \text{Na}^+$) 413.1399 found 413.1385.

(+)-(1S,2R)-2-((4-methoxybenzyloxy)methyl)cyclopentanecarbonitrile (30)

To a stirred mixture of **29** (1.22 g, 3.14 mmol) in DMSO (15 mL), was added NaCN (0.310 g, 6.29 mmol) and the resulting solution was stirred at 50 °C. After 12 h, the reaction was diluted with water, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO_4 , concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 50:10) to afford **30** as a colourless oil (615 mg, 80% yield)

$[\alpha]_D^{25} = +36.8$ ($c = 1.05$, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.27 (m, 2H), 6.91 – 6.85 (m, 2H), 4.55 – 4.41 (m, 2H), 3.80 (s, 3H), 3.65 – 3.51 (m, 2H), 3.05 (td, $J = 7.4$, 4.7, 1H), 2.42 – 2.31 (m, 1H), 2.04 – 1.83 (m, 4H), 1.73 – 1.60 (m, 1H), 1.52 – 1.40 (m, 1H), 1.25 (d, $J = 11.1$, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.15, 130.18, 129.34, 121.08, 113.69, 73.07, 71.23, 55.13, 42.52, 32.13, 30.84, 27.39, 23.51.

HRMS, calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ ($\text{M} + \text{Na}^+$) 268.1313 found 268.1306.

(-)-(1*R*,2*R*)-2-((4-methoxybenzyloxy)methyl)cyclopentanecarbaldehyde (31**)**

For the experimental procedure and spectroscopic data of **31** see the paper.

(+)-(S)-1-((1*R*,2*R*)-2-((4-methoxybenzyloxy)methyl)cyclopentyl)but-3-en-1-ol (32**)**

To a stirred mixture of **31** (1.2 g, 4.8 mmol) in CH₂Cl₂ (40 mL) was added allyltrimethylsilane (1.17 mL, 1.77 mmol) and magnesium bromide diethyl etherate (1.24 g, 4.83 mmol) at 0 °C. The reaction was stirred for 10 h at 0 °C, then quenched with 2M HCl and stirred for 1 h, after phase separation and extraction of the aqueous phase with CH₂Cl₂, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/Ether 55:10) to afford **30** as a colourless oil (1.2 g, 86% yield). Spectral data of **32** were consistent with those reported in the literature.³

$$[\alpha]_D^{25} = +6.3 \text{ (c = 0.32, CHCl}_3\text{)}.$$

¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.21 (m, 2H), 6.86 (ddd, *J* = 7.5, 4.7, 2.3, 2H), 6.05 – 5.89 (m, 1H), 5.15 – 5.03 (m, 2H), 4.48 (qd, *J* = 11.8, 4.3, 2H), 4.33 (s, 1H), 3.82 – 3.75 (m, 3H), 3.50 (dt, *J* = 8.8, 4.4, 1H), 3.43 – 3.34 (m, 1H), 3.18 (td, *J* = 10.0, 4.4, 1H), 2.37 (dd, *J* = 10.1, 3.9, 1H), 2.16 – 2.00 (m, 2H), 1.82 – 1.41 (m, 5H), 1.23 (td, *J* = 12.3, 5.5, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 159.36, 135.87, 129.50, 116.48, 113.90, 75.06, 74.35, 72.96, 55.26, 51.73, 43.98, 40.56, 31.08, 30.03, 24.62.

HRMS, calcd for C₁₈H₂₆O₃ (M-H⁺) 289.1882, found 289.1798.

(+)-(S,2E,4E)-2-bromo-7-hydroxy-7-((1R,2R)-2-((4 methoxybenzyloxy)methyl) cyclopentyl) hepta-2,4-dienitrile (B)⁵

For the experimental procedure and spectroscopic data of **B** see the paper.

Spectral data of **B** were consistent with those reported in the literature.³

Final steps in the synthesis of Borrelidin (1).

The coupling of **A** and **B** above scheme as described by Omura *et al* results in **1**.³

⁵ B. R. Iorga, L. Savignac. P, *J. Chem. Soc., Perkin Trans. I* **2000**, 3311.

NMR Spectra: Upper part of Borrelidin.

¹H-NMR

¹³C-NMR and APT

¹H-NMR

¹³C-NMR and APT

¹H-NMR

¹³C-NMR and APT

¹H-NMR

¹³C-NMR and APT

¹H-NMR

¹³C-NMR and APT

^1H -NMR

^{13}C -NMR and APT

¹H-NMR

¹³C-NMR and APT

¹H-NMR

¹³C-NMR and APT

¹H-NMR

^{13}C -NMR and APT

¹H-NMR ^{13}C -NMR and APT

¹H-NMR ^{13}C -NMR and APT

^1H -NMR

^{13}C -NMR and APT

^1H -NMR

^{13}C -NMR and APT

¹H-NMR ^{13}C -NMR and APT

¹³C-NMR

¹H-NMR

Upper part of Borrelidin.

^{13}C -NMR and APT

NMR Spectra: Lowerpart of Borrelidin.

^1H -NMR

^{13}C -NMR and APT

¹H-NMR

¹³C-NMR and APT

¹H-NMR

¹³C-NMR and APT

^1H -NMR

^{13}C -NMR and APT

^1H -NMR

^{13}C -NMR and APT

$^1\text{H-NMR}$

$^{13}\text{C-NMR}$ and APT

¹H-NMR

¹³C-NMR and APT

NOE Experiment of Cis and Trans 2-((4 methoxybenzyloxy) methyl) cyclopentanecarbonitrile.

¹H-NMR

¹³C-NMR and APT

$^1\text{H-NMR}$

$^{13}\text{C-NMR}$ and APT

¹H-NMR

Lower part of Borrelidin.

¹³C-NMR and APT