A Formal Total Synthesis of Fostriecin by a Convergent Approach

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Abstract: A formal total synthesis of fostriecin has been accomplished in 20 steps. Our method features the derivation of two of the four chiral centers from commercial diethyl D-(+)-malate. The key steps involve the Julia–Kocienski olefination, the Sharpless asymmetric dihydroxylation, and the Stille coupling.

Key words: fostriecin, chiral pool, Julia–Kocienski olefination, Sharpless asymmetric dihydroxylation, Stille coupling

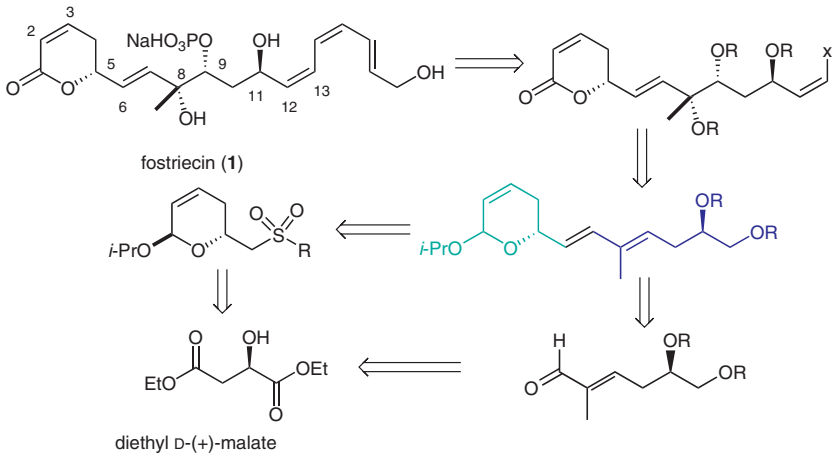
Fostriecin (**1**, CI-920), isolated from *Streptomyces pulveraceus*, is the most selective serine/threonine protein phosphatase 2A (PP2A) inhibitor known to date (PP2A/PP4 vs PP1 selectivity 10^4).[1] It displays potent cytotoxic activity in vitro against a range of cancer cell lines, and in vivo antitumor activity toward lymphoid leukemias.[2] The Phase I clinical trial of fostriecin had been investigated at NCI, but the study was later halted due to the issues involving purity and stability.[3] However, its remarkable biological activity has attracted the interest of many researchers in search of more potent and stable analogues.

Since the stereochemistry of fostriecin was established in 1997,[4] several excellent total synthesis had been reported along with a number of synthetic studies.[5] Preliminary structure–activity relationship (SAR) studies of fostrecin were also undertaken by Boger[6] and others.[5f] As a part of our chemical biology program, we aim to further optimize the structural aspects of fostriecin to improve its metabolic stability and other pharmaceutical properties. Herein we report a stereocontrolled route to fostriecin by using diethyl D-(+)-malate as the starting material.

In the total synthesis of natural product, chiral pools are often used to introduce chiral centers. As shown in Scheme 1, the chiral centers at C5 and C11 were both introduced from diethyl D-(+)-malate, making it a distinctive feature of our approach; while the other chiral centers at C8 and C9 were controlled via a Sharpless asymmetric dihydroxylation reaction. A Julia–Kocienski olefination was applied to construct the C6–C7 double bond, and the conjugated *Z*,*Z*,*E*-trienol unit was expected to be built up by Stille coupling of vinyl iodide and a stannane.[5b–g,7]

As envisaged, the synthesis began with the reduction of diethyl D-(+)-malate (**2**) to diol **3** with sodium acetoxyborohydride[8] in 82% yield (Scheme 2). Protection of the resulting diol **3** with TBSCl led to the formation of silyl ether **4**. But when **4** was treated with lithium aluminum hydride, diol **5′** was obtained instead of the desired alcohol **5**, while the reduction of **4** with Red-Al at –70 to –40 °C resulted in the formation of **5** in excellent yield (95%).

Alcohol **5** was transformed to alcohol **6** according to the reported procedure.[9] Compound **6** was converted into sulfone **7** (87% for 2 steps) through a Mitsunobu reaction followed by oxidation with hydrogen peroxide in the presence of a catalytic amount of Na_2WO_4.[10]



Scheme 1 Retrosynthetic analysis

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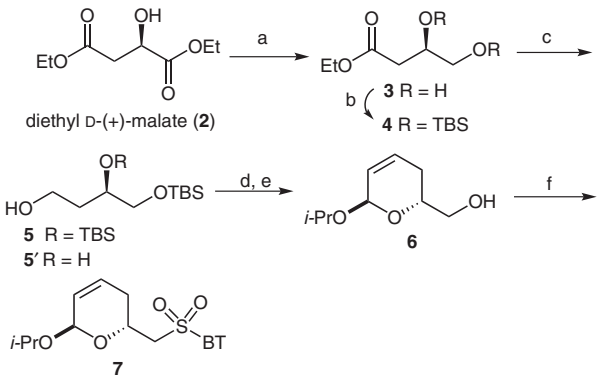
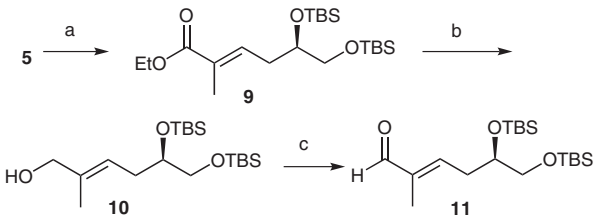


Scheme 2 *Reagents and conditions*: (a) $NaBH_4$, AcOH, THF, 0 °C to r.t., 82%; (b) TBSCl, imidazole, DMF, 86%; (c) Red-Al, THF, –70 to –40 °C, 95%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (e) ref. 9; (f) (1) DIAD, Ph_3P, BT-SH, THF; (2) Na_2WO_4, H_2O_2, MeCN, 89% for 2 steps.

Meanwhile, the α,β-unsaturated ester **9** was synthesized from alcohol **5** via Swern oxidation followed by Wittig reaction in 90% yield and excellent selectivity (*E*/*Z* = 50:1 determined by ^{1}H NMR spectroscopy) (Scheme 3). Reduction of ester **9** with lithium aluminum hydride at 0 °C gave the allyl alcohol **10**,[5e] which was then subjected to Swern oxidation to afford the α,β-unsaturated aldehyde **11** in nearly quantitative yield (98%).

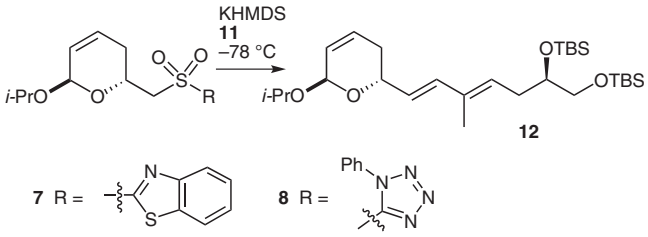


Scheme 3 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; then $Ph_3P{=}CMeCO_2Et$, 0 °C, 90%; (b) $LiAlH_4$, 0 °C, Et_2O, 96%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 98%.

Having obtained both the fragments **7** and **11**, the feasibility of using the Julia–Kocienski olefination to construct the *E*-olefin at C6–C7 was investigated by examining several reaction conditions.[11] It was found that the R group and solvent influenced the *E*/*Z* selectivity and yield as shown in Table 1. When the R group was 1-phenyl-1*H*-tetrazol-5-yl (PT) and DME was used as solvent at –78 °C, conjugated diene **12** was obtained with a 5:1 *E*/*Z* ratio and a low yield (36%) (Table 1, entry 1). Changing the R group from PT to benzothiazol-2-yl (BT), a good yield (76%) was achieved accompanied by a slight increase in *E*/*Z* ratio (7:1) (entry 2). However, when THF instead of DME was used as the solvent, a satisfactory selectivity (*E*/*Z* = 15:1) was obtained in very good yield (82%) (entry 3).

The stereocenters at C8 and C9 were built by a Sharpless asymmetric dihydroxylation reaction (AD). Since Sharpless AD reaction was prone to occur at the most electron-rich and sterically less hindered olefin,[5c,12] the sterically

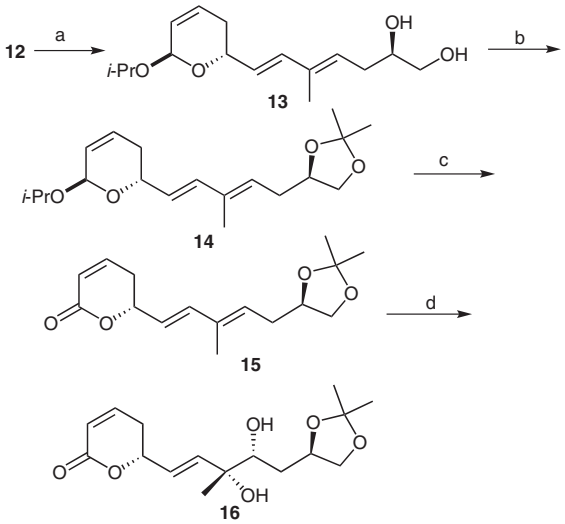
Table 1 Optimization of Julia–Kocienski Olefination Conditions



Entry	R	Solvent	Temp (°C)	*E*/*Z*[a]	Yield (%)[b]
1	PT	DME	–78	5:1	36
2	BT	DME	–78	7:1	76
3	BT	THF	–78	15:1	82

[a] Determined by ^{1}H NMR spectroscopy.
[b] Isolated yield.

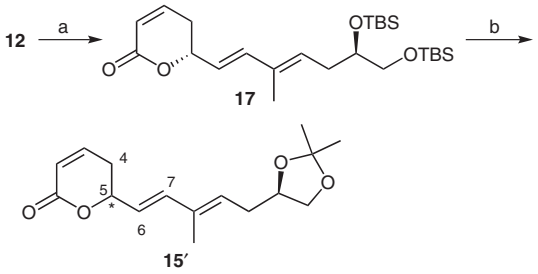
bulky TBS group in compound **12** was replaced with an acetal by treating **12** with TBAF and acetalizing the resulting diol **13** with 2-methoxypropene (MOP) in isopropyl alcohol. The acetalized intermediate **14** was then oxidized using PCC. Since the α,β-unsaturated lactone tend to decrease the election density at the C6–C7 double bond,[13] we expected a desired formation of the diol **16** from dihydroxylation of **15** using $(DHQD)_2PHAL$ as a chiral ligand. Indeed, the reaction achieved excellent regioselectivity (95:5, determined by HPLC) and a very good yield (85%) (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) TBAF, THF, 92%; (b) 2-methoxypropene, PPTS, *i*-PrOH, 91%; (c) PCC, $CaCO_3$, CH_2Cl_2, 0 °C, 62%; (d) $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0 °C, 85%.

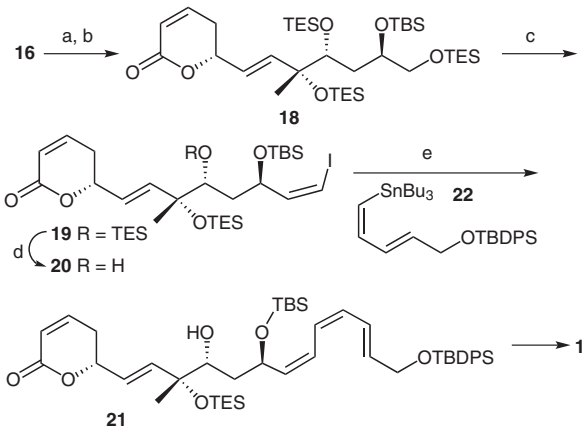
It is worth noting that compound **15** was acid-sensitive. This was verified in an alternative approach to compound **15** (Scheme 5). Silyl ether **12** was converted into the α,β-unsaturated lactone **17** by using PCC as oxidant. Treatment of lactone **17** with HF in acetone in dark gave acetal **15′** as a diasteromeric mixture. The ^{13}C NMR signals (δ =

137.93 and 137.81 for C7, 129.22 and 129.13 for C6, 78.37 and 78.28 for C5, 32.67–32.61 for C4) and a low optical rotation value {$[\alpha]_D^{25}$ +5 vs $[\alpha]_D^{25}$ +45.5 for **15**} suggested a racemization of **15′** at C5.



Scheme 5 *Reagents and conditions*: (a) PCC, $CaCO_3$, CH_2Cl_2, 0 °C, 53%; (b) HF, acetone, 85%.

After deprotection of the acetonide of compound **16**, a fully protected compound **18** was provided by selectively protecting the primary hydroxy group with triethylchlorosilane (TESCl),[14] the C11 secondary hydroxy groups with TBSOTf, and the remaining two hydroxy groups with TESOTf. According to a modification of Imanishi's procedure,[5e] **18** was subjected to Swern oxidation,[15] followed by an iodomethylenation reaction[16] to yield the vinyl iodide **19** with the *Z*-isomer as the major product (*Z*/*E* = 9:1 determined by ^{1}H NMR spectroscopy) (58% isolated yield for 2 steps). Selective removal of the more labile TES group at C9 position with PPTS in methanol at 5 °C led to the formation of vinyl iodide **20** under 80% yield.[5e] Stille coupling of compound **20** with stannane **22**[17] under ligand-free condition furnished the key intermediate **21** (Scheme 6). Further, the optical rotation and the spectral data of **21** were in agreement with those reported in the literatures,[5b–e,n] while the conversion of **21** into fostriecin has been confirmed by Jacobsen,[5b] Hatakeyama,[5c] Imanishi,[5e] and McDonald.[5n] Thus, the formal total synthesis of fostriecin (**1**) was completed.



Scheme 6 *Reagents and conditions*: (a) MeOH, cation resin; (b) TESCl, TBSOTf, TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 79% for 2 steps; (c) 1. $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2; 2. $ICH_2Ph_3P^+I^-$, NaHMDS, HMPA, THF, 58% for 2 steps; (d) PPTS, MeOH, 5 °C, 80%; (e) $Pd(MeCN)_2Cl_2$, **22**, DMF, 80%.

In conclusion, we have accomplished a formal synthesis of fostriecin using diethyl D-(+)-malate to introduce two of the four chiral centers. The total synthesis and the biological evaluation of fostriecin analogues are currently in progress in our laboratory.

Reagent and solvents were purchased from commercial suppliers and purified by standard techniques when necessary. Petroleum ether (PE) refers to the fraction boiling in the range 60–90 °C. Oxygen-sensitive and moisture-sensitive reactions were carried out under argon or N_2. Optical rotations were measured on a precision automated polarimeter. ^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer and ^{13}C NMR on a 100 MHz NMR spectrometer with complete proton decoupling. Low- and high-resolution mass spectra were recorded using electrospray ionization (ESI) and electron impact (EI) mode, and samples were used as MeOH solutions and M^+ refers to the molecular ion peak.

Diol 3

To a suspension of $NaBH_4$ (127 mg, 3.4 mmol) in anhyd THF (30 mL) was added dropwise a solution of AcOH (0.24 mL, 3.4 mmol) in anhyd THF (0.6 mL) at 0 °C over a period of 10 min and the mixture was stirred for 1 h. A solution of ester **2** (0.5 g, 2.6 mmol) in anhyd THF (2 mL) was added dropwise at 0 °C over a period of 10 min. The resulting mixture was stirred at 5–10 °C for 2 h. The mixture was quenched by slow addition of MeOH (10 mL) and evaporated to dryness on a rotary evaporator under reduced pressure. The residue was dissolved in MeOH (20 mL) and evaporated to dryness again. This process was repeated twice. The residue was treated with EtOAc (20 mL) and filtered. The solid was washed with EtOAc (25 mL). The filtrate was evaporated to dryness and purified by silica gel chromatography eluting with PE–EtOAc (1:1 to 1:2) to yield **3** (0.32 g, 82%) as a colorless oil; $[\alpha]_D^{25}$ +16.4 (*c* 7.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (q, *J* = 7.2 Hz, 2 H), 4.13–4.09 (m, 1 H), 3.67 (dd, *J* = 3.4, 11.4 Hz, 1 H), 3.52 (dd, *J* = 6.2, 11.4 Hz, 1 H), 3.27 (br s, 2 H), 2.54 (dd, *J* = 8.4, 16.4 Hz, 1 H), 2.47 (dd, *J* = 4.0, 16.4 Hz, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

MS (ESI): *m*/*z* = 149.1 $(M + H)^+$.

Silyl Ether 4

To a solution of alcohol **3** (4.0 g, 27.0 mmol) and imidazole (5.5 g, 81.0 mmol) in DMF (15 mL) was added TBDMSCl (10.2 g, 67.5 mmol) at r.t. After the disappearance of the starting material (TLC), the reaction mixture was diluted with Et_2O (70 mL) and washed with H_2O (3 × 25 mL), sat. aq $NaHCO_3$ (2 × 25 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was loaded on a silica gel column and eluted with PE–EtOAc (10: 1) to yield **4** (8.77 g, 86%) as a colorless oil; $[\alpha]_D^{25}$ +24.3 (*c* 10, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20–4.06 (m, 3 H), 3.58 (dd, *J* = 5.2, 9.8 Hz, 1 H), 3.41 (dd, *J* = 7.0, 9.8 Hz, 1 H), 2.62 (dd, *J* = 4.3, 14.8 Hz, 1 H), 2.35 (dd, *J* = 8.0, 14.8 Hz, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.88 (d, *J* = 2.9 Hz, 9 H), 0.86–0.84 (m, 9 H), 0.06 (d, *J* = 2.9 Hz, 3 H), 0.04 (d, *J* = 2.2 Hz, 9 H).

MS (ESI): *m*/*z* = 377.2 $(M + H)^+$.

Alcohol 5

To a solution of Red-Al (1.14 g, 70% in toluene) in THF (20 mL) was added dropwise a solution of silyl ether **4** (1.0 g, 2.65 mmol) in THF (5 mL) slowly at –70 °C. After the addition, the temperature of the mixture was gradually raised to –40 °C and stirred overnight. Aq NH_4OH (0.6 mL) was added to quench the reaction. The resulting mixture was allowed to warm to r.t. and filtered. The filtrate was evaporated to dryness and loaded on a silica gel column and eluted

with PE–EtOAc (20:1) to yield **5** (0.84 g, 95%) as a colorless oil; $[\alpha]_D^{25}$ +15.8 (*c* 5.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90–3.84 (m, 1 H), 3.79–3.69 (m, 2 H), 3.59 (dd, *J* = 4.8, 10.0 Hz, 1 H), 3.49 (dd, *J* = 7.2, 10.0 Hz, 1 H), 2.78 (t, *J* = 5.4 Hz, 1 H), 1.87 (m, 1 H), 1.72 (m, 1 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.075 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

MS (ESI): *m*/*z* = 335.1 $(M + H)^+$.

Alcohol 6[9]

Alcohol **6** was prepared from **5** according to the reported procedure;[9] $[\alpha]_D^{25}$ +38.2 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (dd, *J* = 5.2, 10.0 Hz, 1 H), 5.72 (d, *J* = 10.0 Hz, 1 H), 5.10 (s, 1 H), 4.08 (m 1 H), 4.00 (hept, *J* = 6.0 Hz, 1 H), 3.73 (m 1 H), 3.60 (m, 1 H), 2.14 (m, 1 H), 1.93–1.85 (m, 2 H), 1.25 (d, *J* = 6.0 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H).

MS (ESI): *m*/*z* = 195.1 $(M + Na)^+$.

Sulfone 7

To a solution of alcohol **6** (0.200 g, 1.16 mmol), benzothiazol-2-thiol (BT-SH) (0.233 g, 1.39 mmol), and Ph_3P (0.365 g, 1.39 mmol) in anhyd THF (15 mL) was added DEAD (0.3 mL, 1.5 mmol) at 0 °C. After 1 h, the temperature was raised to r.t., and the reaction mixture was stirred for 5 h. The mixture was concentrated, and the residue was treated with Et_2O (15 mL) and filtered. The filtrate was evaporated to dryness. The residue was then dissolved in MeCN (10 mL) and treated with a mixture of $Na_2WO_4{\cdot}2H_2O$ (57 mg, 0.17 mmol) and 30% aq H_2O_2 (1.4 g, 11.6 mmol). After 24 h, the mixture was diluted with CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (PE–EtOAc, 5:1) provided **7** (0.367 g, 89%) as a colorless syrup; $[\alpha]_D^{25}$ +15.6 (*c* 3.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (ddd, *J* = 0.8, 1.2, 8.0 Hz, 1 H), 8.00 (ddd, *J* = 0.8, 1.2, 8.0 Hz, 1 H), 7.63 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1 H), 7.58 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1 H), 5.96–5.89 (m, 1 H), 5.67 (ddd, *J* = 2.0, 4.8, 10.0 Hz, 1 H), 4.98 (d, *J* = 2.0 Hz, 1 H), 4.63 (ddd, *J* = 4.8, 7.6, 14.4 Hz, 1 H), 4.00 (hept, *J* = 6.0 Hz, 1 H), 3.90 (dd, *J* = 7.6, 14.8 Hz, 1 H), 3.73 (dd, *J* = 4.8, 14.8 Hz, 1 H), 2.19–2.13 (m, 2 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 1.07 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 152.6, 136.7, 128.0, 127.6, 127.1, 126.2, 125.4, 122.4, 91.8, 68.8, 61.1, 59.2, 30.0, 23.4, 21.2.

MS (ESI): *m*/*z* = 376.1 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}NO_4S_2$ + Na $(M + Na)^+$: 376.0648; found: 376.0657.

Compound 8

To a solution of alcohol **6** (0.2 g, 1.16 mmol), PT-SH (0.269 g, 1.5 mmol), and Ph_3P (0.396 g, 1.5 mmol) in THF (15 mL) was added DEAD (0.322 mL, 1.624 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was warmed to r.t. and stirred for 5 h. The resulting mixture was evaporated and treated with Et_2O (5 mL) and filtered. The filtrate was evaporated to dryness. The residue was dissolved in MeCN (10 mL) and treated with a mixture of $Na_2MoO_4{\cdot}2H_2O$ (56 mg, 0.23 mmol) and 30% aq H_2O_2 (1.4 g, 11.6 mmol) overnight and then diluted with CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Purification on a silica gel column (PE–EtOAc 5:1) provided **8** (0.19 g, 45%) as a colorless syrup; $[\alpha]_D^{25}$ +3.6 (*c* 1.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.53 (m, 5 H), 5.90 (m, 1 H), 5.64 (ddd, *J* = 2.2, 4.6, 10.0 Hz, 1 H), 4.92 (s, 1 H), 4.61 (m, 1 H), 3.92 (dd, *J* = 7.6, 14.2 Hz, 1 H), 3.86 (dd, *J* = 4.4, 14.2 Hz, 1 H), 3.79 (hept, *J* = 6.2 Hz, 1 H), 2.15–2.06 (m, 2 H), 1.06 (d, *J* = 6.0 Hz, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 133.0, 131.5, 129.7, 126.8, 126.2, 125.3, 91.7, 68.7, 61.1, 60.3, 29.5, 23.3, 21.1.

MS (ESI): *m*/*z* = 287.1 $(M + Na)^+$.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{20}O_4N_4S$: 364.1204; found: 364.1200.

Ester 9

To a solution of oxalyl chloride (0.58 mL, 6.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of DMSO (0.63 mL, 8.8 mmol) in CH_2Cl_2 (4 mL) at –78 °C. After 15 min, alcohol **5** (1.35 g, 4.0 mmol) in CH_2Cl_2 (5 mL) was added slowly. The white slurry was stirred for 1 h at –78 °C before Et_3N (2.45 mL, 17.6 mmol) was added slowly. The solution was allowed to warm to r.t. and stirred for an additional 30 min. The Wittig reagent 2-(triphenyl-5-phosphanylidene)propionic acid ethyl ester (PPh_3=$CMeCO_2Et$) (1.34 g, 4.0 mmol) was added to the reaction mixture, and stirred at 0 °C for 1 h. The mixture was diluted with Et_2O (50 mL), and the Et_2O layer was washed with H_2O (3 × 20 mL), sat. aq $NaHCO_3$ (2 × 20 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by using silica gel chromatography eluting with PE–Et_2O (50:1) to yield **9** (1.52 g, 90%) as a colorless oil; $[\alpha]_D^{25}$ +14 (*c* 5.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (t, *J* = 7.2 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 3.80–3.72 (m, 1 H), 3.55 (dd, *J* = 4.8, 10.0 Hz, 1 H), 3.40 (dd, *J* = 6.8, 10.0 Hz, 1 H), 2.48 (ddd, *J* = 5.2, 6.8, 15.2 Hz, 1 H), 2.28 (dt, *J* = 7.2, 15.2 Hz, 1 H), 1.84 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 138.9, 129.0, 72.4, 67.1, 60.3, 33.9, 25.9, 25.8, 18.3, 18.1, 14.3, 12.5, –4.5, –4.8, –5.4, –5.4.

MS (ESI): *m*/*z* = 439.2 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{44}O_4Si_2$ + Na $(M + Na)^+$: 439.2670; found: 439.2679.

Alcohol 10

To a mixture of $LiAlH_4$ (1.1 g, 28.8 mmol) and Et_2O (60 mL) was added dropwise a solution of ester **9** (10.0 g, 24.0 mmol) in Et_2O (20 mL) at 0 °C. After stirring for 2.5 h, the reaction mixture was quenched by slowly adding H_2O (1 mL) followed by 10% aq NaOH (5 mL). The resulting mixture was filtered. The filtrate was evaporated and the residue was purified by silica gel chromatography eluting with PE–EtOAc (1:1) to yield **10** (8.68 g, 96%) as a colorless syrup; $[\alpha]_D^{25}$ +7.4 (*c* 5.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52–5.45 (m, 1 H), 4.01 (d, *J* = 6.0 Hz, 2 H), 3.72–3.67 (m, 1 H), 3.50 (dd, *J* = 5.2, 10.0 Hz, 1 H), 3.41 (dd, *J* = 6.4, 10.0 Hz, 1 H), 2.32 (ddt, *J* = 0.8, 6.0, 14.4 Hz, 1 H), 2.17 (dt, *J* = 7.2, 14.4 Hz, 1 H), 1.67 (s, 3 H), 1.26 (t, *J* = 6.0 Hz, 1 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.05–0.04 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3, 120.4, 71.2, 66.9, 65.0, 30.6, 24.0, 23.9, 16.4, 16.2, 11.9, –6.4, –6.7, –7.3, –7.3.

MS (ESI): *m*/*z* = 397.2 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{42}O_3Si_2$ + Na $(M + Na)^+$: 397.2565; found: 397.2560.

Aldehyde 11

To a solution of oxalyl chloride (2.0 mL, 23.6 mmol) in CH_2Cl_2 (150 mL) was added dropwise a solution of DMSO (2.58 mL, 36.28 mmol) in CH_2Cl_2 (5 mL) at –78 °C. After 30 min, alcohol **10** (6.8 g, 18.14 mmol) in CH_2Cl_2 (10 mL) was added slowly. The white slurry was stirred for 1 h at –78 °C before Et_3N (8.8 mL, 63.49 mmol) was added slowly. The solution was allowed to warm to r.t. and washed

with H_2O (3 × 30 mL), sat. aq $NaHCO_3$ (2 × 30 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography eluting with PE–Et_2O (50:1 to 20:1) to yield **11** (6.65 g, 98%) as a colorless oil; $[\alpha]_D^{25}$ +9.5 (*c* 9.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 6.61 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1 H), 3.87–3.80 (m, 1 H), 3.56 (dd, *J* = 5.2, 10.0 Hz, 1 H), 3.39 (dd, *J* = 7.6, 10.0 Hz, 1 H), 2.61 (ddt, *J* = 0.8, 6.4, 14.8 Hz, 1 H), 2.51 (dt, *J* = 7.2, 14.8 Hz, 1 H), 1.74 (s, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 151.3, 140.5, 72.0, 66.8, 34.1, 25.9, 25.8, 18.3, 18.0, 9.4, –4.4, –4.8, –5.4, –5.4.

MS (ESI): *m*/*z* = 373.2 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{40}O_3Si_2$ + Na $(M + Na)^+$: 395.2408; found: 395.2401.

Compound 12

To a solution of the sulfone **7** (5.78 g, 16.4 mmol) and the aldehyde **11** (5.30 g, 14.2 mmol) in anhyd THF (300 mL) at –78 °C was added KHMDS (0.5 M in toluene, 34.1 mL, 17.1 mmol) over a period of 1 h. The resulting mixture was stirred for an additional 3 h at this temperature, and then allowed to warm to r.t. and evaporated. The residue was loaded on silica gel column and eluted with PE–EtOAc (50:1 to 20:1) to give **12** (6.03 g, 82%) as a pale-yellow syrup; $[\alpha]_D^{25}$ +24.5 (*c* 1.05, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (d, *J* = 16.0 Hz, 1 H), 6.00 (dd, *J* = 5.2, 10.0 Hz, 1 H), 5.72 (ddt, *J* = 1.2, 2.8, 10.0 Hz, 1 H), 5.59 (dd, *J* = 6.4, 16.0 Hz, 1 H), 5.56 (t, *J* = 7.6 Hz, 1 H), 5.11 (s, 1 H), 4.51–4.46 (m, 1 H), 4.01 (hept, *J* = 6.4 Hz, 1 H), 3.74–3.68 (m, 1 H), 3.50 (dd, *J* = 5.2, 10.0 Hz, 1 H), 3.41 (dd, *J* = 6.4, 10.0 Hz, 1 H), 2.41 (dt, *J* = 6.4, 14.4 Hz, 1 H), 2.26 (dt, *J* = 7.2, 14.4 Hz, 1 H), 2.12–2.08 (m, 1 H), 2.05–1.99 (m, 1 H), 1.75 (s, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.04–0.02 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 134.3, 129.7, 128.6, 126.3, 126.1, 93.3, 73.2, 69.5, 67.1, 67.0, 33.4, 31.0, 26.0, 25.9, 23.9, 22.1, 18.3, 18.1, 12.5, –4.5, –4.8, –5.3, –5.4.

MS (ESI): *m*/*z* = 533.3 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{54}O_4Si_2$ + Na $(M + Na)^+$: 533.3453; found: 533.3478.

Diol 13

A solution of the TBS-protected diol **12** (5.5 g, 10.76 mmol) in THF (50 mL) was treated with a 1.0 M solution of TBAF in THF (24.7 mL, 24.7 mmol) at r.t. The reaction mixture was stirred overnight at r.t. and then evaporated. The residue was loaded on a silica gel column and eluted with PE–EtOAc (2:1 to 1:1) to afford **13** (2.8 g, 92%) as a pale-yellow oil; $[\alpha]_D^{25}$ +46 (*c* 2.3, $CHCl_3$).

^{1}H NMR (400 MHz, CD_3OD): δ = 6.32 (d, *J* = 15.6 Hz, 1 H), 6.02–5.98 (m, 1 H), 5.68 (dd, *J* = 2.0, 10.0 Hz, 1 H), 5.62 (dd, *J* = 6.4, 15.6 Hz, 1 H), 5.59 (t, *J* = 7.2 Hz, 1 H), 5.10 (s, 1 H), 4.45–4.30 (m, 1 H), 3.99 (hept, *J* = 6.0 Hz, 1 H), 3.65 (pent, *J* = 6.0 Hz, 1 H), 3.50 (dd, *J* = 4.4, 11.2 Hz, 1 H), 3.44 (dd, *J* = 6.0, 11.2 Hz, 1 H), 2.39 (dt, *J* = 6.4, 15.2 Hz, 1 H), 2.27 (dt, *J* = 7.6, 15.2 Hz, 1 H), 2.06–2.04 (m, 2 H), 1.77 (s, 3 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 135.6, 134.6, 128.6, 128.1, 126.4, 125.8, 93.3, 71.9, 69.6, 67.1, 65.48, 32.1, 30.7, 22.8, 21.0, 11.3.

MS (ESI): *m*/*z* = 305.1 $(M + Na)^+$.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{26}O_4$: 282.1826; found: 282.1811.

Acetal 14

To a solution of diol **13** (0.55 g, 1.95 mmol) and 2-methoxypropene (MOP) (0.9 mL, 9.7 mmol) in *i*-PrOH (40 mL) was added PPTS (95 mg, 0.39 mmol) at r.t. The reaction mixture was stirred for 1.5 h at r.t. before Et_3N (0.3 mL) was added to quench the reaction. The resulting mixture was evaporated, and the residue was loaded on a silica gel column and eluted with PE–EtOAc (20:1) to give **14** (0.57 g, 91%) as a colorless oil; $[\alpha]_D^{25}$ +24 (*c* 1.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (d, *J* = 16.0 Hz, 1 H), 5.99 (dd, *J* = 5.6, 10.0 Hz, 1 H), 5.71 (d, *J* = 10.0 Hz, 1 H), 5.63 (dd, *J* = 6.4, 16.0 Hz, 1 H), 5.48 (t, *J* = 7.4 Hz, 1 H), 5.10 (s, 1 H), 4.51–4.42 (m, 1 H), 4.14 (pent, *J* = 6.4 Hz, 1 H), 4.04–3.97 (m, 2 H), 3.55 (t, *J* = 7.4 Hz, 1 H), 2.53–2.46 (m, 1 H), 2.41–2.34 (m, 1 H), 2.11 (dd, *J* = 10.8, 18.0 Hz, 1 H), 2.01 (dt, *J* = 4.4, 18.0 Hz, 2 H), 1.76 (s, 3 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 1.23 (d, *J* = 6.0 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.52, 135.48, 128.4, 127.4, 127.2, 126.1, 109.0, 93.1, 75.5, 69.4, 69.1, 66.8, 32.7, 30.9, 26.9, 25.6, 23.9, 22.0, 12.6.

MS (ESI) *m*/*z* = 345.1 $(M + Na)^+$.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{30}O_4$: 322.2157; found: 322.2139.

Lactone 15

A mixture of PCC (10.0 g, 46.5 mmol), $CaCO_3$ (20.0 g), and CH_2Cl_2 (100 mL) was stirred for 30 min before a solution of acetal **14** (3.0 g, 9.3 mmol) in CH_2Cl_2 (150 mL) was added at 5 °C. The reaction mixture was stirred overnight at this temperature and filtered. The filtrate was evaporated, and the residue was loaded on a silica gel column and eluted with PE–EtOAc (4:1) to give **15** (1.6 g, 62%) as a pale-yellow syrup; $[\alpha]_D^{25}$ +45.5 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (dt, *J* = 4.4, 10.0 Hz, 1 H), 6.33 (d, *J* = 15.6 Hz, 1 H), 6.01 (d, *J* = 10.0 Hz, 1 H), 5.64 (dd, *J* = 6.8, 15.6 Hz, 1 H), 5.53 (t, *J* = 7.2 Hz, 1 H), 4.94 (dd, *J* = 7.0, 15.0 Hz, 1 H), 4.12 (pent, *J* = 6.4 Hz, 1 H), 4.00 (dd, *J* = 6.0, 7.6 Hz, 1 H), 3.53 (t, *J* = 7.6 Hz, 1 H), 2.51–2.33 (m, 4 H), 1.74 (s, 3 H), 1.39 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 144.7, 137.8, 134.8, 129.1, 123.5, 121.6, 109.0, 78.5, 75.3, 68.9, 53.4, 32.6, 29.9, 26.9, 25.6, 12.5.

MS (ESI): *m*/*z* = 279.1 $(M + H)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{22}O_4$ + Na $(M + Na)^+$: 301.1410; found: 301.1423.

Compound 16

A mixture of $(DHQD)_2PHAL$ (220 mg, 0.28 mmol), $K_2OsO_2(OH)_4$ (42 mg, 0.113 mmol), $K_3Fe(CN)_6$ (3.95 g, 12.0 mmol), K_2CO_3 (1.66 g, 12.0 mmol), $NaHCO_3$ (1.01 g, 12.0 mmol), and $MeSO_2NH_2$ (0.393 g, 4.13 mmol) in *t*-BuOH–H_2O (1:1, 37 mL) was stirred at r.t. till both phases were clear, and then the reaction mixture was cooled to 0 °C. A solution of the lactone **15** (1.05 g, 3.76 mmol) in *t*-BuOH (4 mL) was added. The resulting mixture was stirred vigorously for 10 h at this temperature and treated with 2 M aq citric acid (10 mL, 20 mmol) and Na_2SO_3 (5.6 g). The resulting mixture was extracted with EtOAc (4 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was loaded on a silica gel column and eluted with PE–EtOAc (2:1 to 1:1) to afford **16** (0.855 g, 85%) as a colorless syrup. The unreacted starting material was recovered (100 mg); $[\alpha]_D^{25}$ +78.5 (*c* 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.04 (ddd, *J* = 2.8, 5.6, 10.0 Hz, 1 H), 6.00 (ddd, *J* = 1.2, 2.4, 10.0 Hz, 1 H), 5.98 (dd, *J* = 0.8, 15.6 Hz, 1 H), 5.89 (dd, *J* = 6.0, 15.6 Hz, 1 H), 5.04–4.98 (m, 1 H), 4.29–4.23 (m, 1 H), 4.06 (dd, *J* = 6.0, 8.0 Hz, 1 H), 3.56 (dd, *J* = 1.6, 10.8 Hz, 1 H), 3.53 (t, *J* = 7.6 Hz, 1 H), 2.56 (dddd, *J* = 1.2, 4.8, 5.6, 18.4 Hz, 1 H), 2.45 (ddt, *J* = 2.8, 10.8, 18.4 Hz, 1 H), 1.87 (ddd, *J* = 1.6,

8.0, 14.0 Hz, 1 H), 1.41 (ddd, *J* = 4.8, 10.8, 14.0 Hz, 1 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 165.2, 146.6, 137.7, 126.2, 120.1, 108.2, 78.2, 74.4, 74.1, 74.0, 69.6, 35.1, 29.4, 26.0, 24.7, 23.1.

MS (ESI): *m*/*z* = 335.1 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{24}O_6$ + Na $(M + Na)^+$: 335.1465; found: 335.1473.

Compound 17

A mixture of PCC (0.4 g, 1.96 mmol), $CaCO_3$ (2.0 g), and CH_2Cl_2 (15 mL) was stirred at r.t. Thirty min later, compound **12** (0.2 g, 0.39 mmol) in CH_2Cl_2 (2 mL) was added dropwise at 15 °C and stirred overnight. The resulting mixture was filtered. The filtrate was evaporated and purified by chromatography over silica gel eluting with PE–EtOAc (10:1–5:1) to yield **17** (0.1 g, 53%), $[\alpha]_D^{25}$ +24.2 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (td, *J* = 9.6, 4.2 Hz, 1 H), 6.35 (d, *J* = 15.6 Hz, 1 H), 6.06 (td, *J* = 9.6, 1.8 Hz, 1 H), 5.68–5.59 (m, 2 H), 4.98 (dd, *J* = 14.4, 7.2 Hz, 1 H), 3.75–3.69 (m, 1 H), 3.51 (dd, *J* = 10.0, 5.2 Hz, 1 H), 3.39 (dd, *J* = 10.0, 6.8 Hz, 1 H), 2.50–2.37 (m, 3 H), 2.34–2.24 (m, 1 H), 1.74 (s, 3 H), 0.89 (s, 11 H), 0.87 (s, 9 H), 0.04 (s, 9 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 144.8, 138.5, 133.8, 131.6, 122.6, 121.7, 78.7, 72.9, 66.9, 33.4, 30.1, 26.0, 25.9, 18.4, 18.1, 12.5, –4.4, –4.7, –5.30, –5.34.

MS (ESI): *m*/*z* = 489.2 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{47}O_4Si_2$ $(M + H)^+$: 467.3007; found: 467.3012.

Silyl Ether 18

A mixture of acetal **16** (65 mg, 0.21 mmol), cationic exchange resin [001 × 7 (strong acidic styrene cation exchange resin), 0.1 g] and MeOH (10 mL) was stirred for 6 h and filtered. The filtrate was evaporated to dryness, and the residue was dissolved in 2,6-lutidine (0.5 mL) and CH_2Cl_2 (10 mL). The mixture was cooled to –78 °C and TESCl (56 μL, 0.33 mmol) was added. After stirring for 2 h, TBSOTf (67 μL, 0.29 mmol) was added and after 30 min, TESOTf (0.42 mL, 1 M in CH_2Cl_2) was added to the reaction mixture, which was stirred for 2 h before quenching with sat. aq $NaHCO_3$ (10 mL). The resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel (PE–EtOAc, 50:1 to 20:1) to give **18** (120 mg, 79%) as a colorless syrup; $[\alpha]_D^{25}$ +19.7 (*c* 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (ddd, *J* = 4.0, 4.4, 10.0 Hz, 1 H), 6.05 (td, *J* = 1.6, 10.0 Hz, 1 H), 5.89 (dd, *J* = 1.0, 15.6 Hz, 1 H), 5.73 (dd, *J* = 6.4, 15.6 Hz, 1 H), 4.96–4.90 (m, 1 H), 3.82–3.76 (m, 1 H), 3.65 (dd, *J* = 2.8, 8.4 Hz, 1 H), 3.51 (dd, *J* = 6.0, 10.0 Hz, 1 H), 3.39 (dd, *J* = 4.8, 10.0 Hz, 1 H), 2.44–2.40 (m, 2 H), 1.67 (ddd, *J* = 2.8, 8.8, 14.4 Hz, 1 H), 1.33 (s, 3 H) 1.32 (ddd, *J* = 1.8, 8.4, 14.4 Hz, 4 H), 0.98–0.92 (m, 27 H), 0.87 (s, 9 H), 0.67–0.55 (m, 18 H), 0.08 (s, 3 H), 0.077(s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 144.4, 138.6, 125.8, 121.8, 77.9, 77.8, 77.1, 71.4, 67.8, 38.8, 29.8, 26.0, 24.8, 18.3, 7.2, 7.1, 6.9, 6.8, 5.7, 4.4, –3.6, –4.2.

MS (ESI) *m*/*z* = 751.3 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{37}H_{76}O_6Si_4$ + Na $(M + Na)^+$: 751.4611; found: 751.4631.

Vinyl Iodide 19

To a solution of oxalyl chloride (50 μL, 0.59 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DMSO (65 μL, 0.92 mmol) in CH_2Cl_2 (0.2 mL) at –78 °C. Ten min later, silyl ether **18** (26 mg, 0.035 mmol) in CH_2Cl_2 (0.3 mL) was added slowly. After stirring for 10 min at –78 °C, the temperature of the reaction mixture was allowed to rise to –40 °C and stirred at this temperature for 1.5 h. The mixture was then cooled to –78 °C and DIPEA (0.45 mL, 2.59 mmol) was added. The mixture was allowed to warm to r.t. and diluted with Et_2O (30 mL), washed with a phosphate buffer (pH 6.86) (3 × 5 mL). The organic phase was dried ($MgSO_4$) and concentrated to give the intermediate crude aldehyde, which was used in next step without further purification. To a mixture of $ICH_2Ph_3P^+I^-$ (218 mg, 0.41 mmol) and anhyd THF (5 mL) was added a 2 M solution of NaHMDS in THF (0.185 mL, 0.37 mmol) at r.t. and stirred for 3 min. The resulting mixture was cooled to –60 °C, and HMPA (0.1 mL) was added. The mixture was cooled to –78 °C and the aldehyde, prepared as described above, in THF (1 mL) was added. The reaction mixture was stirred at this temperature for 2 h and then diluted with Et_2O (40 mL), the Et_2O layer was washed with a phosphate buffer (pH 6.86) (15 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by preparative TLC on silica gel plates (PE–EtOAc, 5:1) to yield **19** (15 mg, 58%) as a colorless oil together with the *E*-isomer **19′** (2 mg, 8%).

19

$[\alpha]_D^{25}$ +22.5 (*c* 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.02 (ddd, *J* = 3.2, 5.6, 10.0 Hz, 1 H), 6.36 (d, *J* = 7.6 Hz, 1 H), 6.21 (t, *J* = 7.6 Hz, 1 H), 6.00 (d, *J* = 10.0 Hz, 1 H), 5.94 (d, *J* = 15.6 Hz, 1 H), 5.80 (dd, *J* = 6.0, 15.6 Hz, 1 H), 5.05–5.00 (m, 1 H), 4.53–4.48 (m, 1 H), 3.83 (d, *J* = 8.4 Hz, 1 H), 2.60–2.52 (m, 1 H), 2.45–2.37 (m, 1 H), 1.94–1.88 (m, 1 H), 1.38 (s, 3 H), 1.14 (ddd, *J* = 2.8, 8.8, 14.0 Hz, 1 H), 1.03 (t, *J* = 8.0 Hz, 9 H), 0.99 (t, *J* = 8.0 Hz, 9 H), 0.91 (s, 9 H), 0.78 (q, *J* = 8.0 Hz, 6 H), 0.65 (q, *J* = 8.0 Hz, 7 H), 0.16 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 164.9, 145.9, 144.7, 137.9, 126.6, 120.3, 79.2, 77.8, 77.7, 75.8, 73.0, 41.2, 29.3, 25.2, 23.2, 17.6, 6.6, 6.5, 6.3, 6.2, 5.6, –4.0, –4.8.

19′

^{1}H NMR (400 MHz, CD_3OD): δ = 7.03 (ddd, *J* = 3.2, 5.6, 9.6 Hz, 1 H), 6.55 (dd, *J* = 7.6, 14.4 Hz, 1 H), 6.35 (d, *J* = 14.4 Hz, 1 H), 6.03–5.95 (m, 1 H), 5.94 (d, *J* = 15.7 Hz, 1 H), 5.81 (dd, *J* = 6.0, 15.7 Hz, 1 H), 5.06–5.01 (m, 1 H), 4.29–4.24 (m, 1 H), 3.70 (dd, *J* = 4.0, 6.8 Hz, 1 H), 2.62–2.54 (m, 1 H), 2.46–2.37 (m, 1 H), 1.95 (ddd, *J* = 4.0, 8.4, 14.0 Hz, 1 H), 1.39 (s, 3 H), 1.28–1.21 (m, 1 H), 1.01 (t, *J* = 8.0 Hz, 9 H), 1.00 (t, *J* = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.72–0.63 (m, 12 H), 0.06 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, D_3OD): δ = 166.3, 151.1, 147.3, 138.9, 128.2, 121.7, 79.4, 79.2, 77.8, 77.3, 74.7, 44.2, 30.8, 26.5, 25.6, 19.1, 8.0, 7.6, 7.4, 6.7, –3.4, –3.9.

MS (ESI): *m*/*z* = 759.3 $(M + Na)^+$.

HRMS (ESI): *m*/*z* calcd for $C_{32}H_{61}IO_5Si_3$ + Na $(M + Na)^+$: 759.2764; found: 759.2773.

Vinyl Iodide 20

A solution of **19** (8 mg, 0.01 mmol) and PPTS (16 mg, 0.06 mmol) in MeOH (3 mL) was stirred at 5 °C for 5 h. After quenching the reaction with Et_3N (0.1 mL), the mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (0.1 mL) and purified by preparative TLC on silica gel plates (PE–EtOAc, 5:1) to yield **20** (5 mg, 80%) as a colorless oil. The unreacted starting material was recovered (1.5 mg); $[\alpha]_D^{25}$ +40.0 (*c* 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (dt, *J* = 4.0, 10.0 Hz, 1 H), 6.33 (t, *J* = 7.6 Hz, 1 H), 6.22 (d, *J* = 7.6 Hz, 1 H), 6.06 (d, *J* = 10.0 Hz, 1 H), 5.90 (d, *J* = 15.6 Hz, 1 H), 5.80 (dd, *J* = 6.0, 15.6 Hz, 1 H), 4.97 (dd, *J* = 6.4, 14.8 Hz, 1 H), 4.68–4.63 (m, 1 H), 3.63 (d,

J = 10.8 Hz, 1 H), 3.01 (s, 1 H), 2.50–2.40 (m, 2 H), 1.71 (dd, J = 7.6, 14.0 Hz, 1 H), 1.42–1.35 (m, 1 H), 1.34 (s, 3 H), 0.94 (t, J = 8.0 Hz, 9 H), 0.88 (s, 9 H), 0.58 (q, J = 8.0 Hz, 6 H), 0.11 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 144.4, 144.2, 138.2, 127.1, 122.1, 79.7, 77.7, 77.5, 75.1, 74.3, 37.5, 29.9, 26.0, 22.8, 18.2, 7.2, 7.1, –4.2, –4.7.

MS (ESI): m/z = 645.3 $(M + Na)^+$.

Compound 22[17]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 6.4 Hz, 4 H), 7.45–7.37 (m, 6 H), 7.11 (t, J = 12.0 Hz, 1 H), 6.40–6.28 (m, 1 H), 6.08 (d + dd, J = 12.8, 63.2 Hz, 1 H), 5.81 (dt, J = 4.6, 15.2 Hz, 1 H), 4.29 (d, J = 2.8 Hz, 2 H), 1.60–1.42 (m, 6 H), 1.35–1.26 (m, 6 H), 1.10 (s, 9 H), 0.99–0.95 (m, 6 H), 0.89 (t, J = 7.2 Hz, 9 H).

MS (ESI): m/z = 613.1 $(M + H)^+$.

Compound 21

To a solution of **20** (4.0 mg, 0.0064 mmol) and stannane **22** (15 mg, 0.025mmol) in DMF (1 mL), which had been degassed previously, was added $Pd(MeCN)_2Cl_2$ (1.0 mg, 0.0039 mmol) The reaction mixture was stirred at r.t. in the dark for 24 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (0.1 mL) and purified by preparative TLC on silica gel plates (PE–CH_2Cl_2, 1:3) to yield **21** (4.2 mg, 80%) as a colorless oil; $[\alpha]_D^{25}$ –1.8 (c 0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 6.8 Hz, 4 H), 7.44–7.36 (m, 6 H), 6.89 (dt, J = 4.0, 9.6 Hz, 1 H), 6.76 (dd, J = 12.0, 14.4 Hz, 1 H), 6.34 (t, J = 11.4 Hz, 1 H), 6.15 (t, J = 11.4 Hz, 1 H), 6.07–6.02 (m, 2 H), 5.91–5.77 (m, 3 H), 5.53 (t, J = 10.0 Hz, 1 H), 4.99–4.91 (m, 2 H), 4.29 (d, J = 4.8 Hz, 2 H), 3.68 (d, J = 10.8 Hz, 1 H), 3.03 (d, J = 1.6 Hz, 1 H), 2.46–2.43 (m, 2 H), 1.68–1.62 (m, 1 H), 1.38–1.33 (m, 1 H), 1.32 (s, 1 H), 1.07 (s, 9 H), 0.92 (t, J = 8.0 Hz, 9 H), 0.88 (s, 9 H), 0.57 (q, J = 8.0 Hz, 6 H), 0.07 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 144.2, 138.3, 135.8, 135.8, 134.5, 134.0, 130.3, 129.8, 127.9, 127.1, 124.9, 123.5, 122.6, 122.1, 77.7, 77.4, 75.2, 67.3, 64.5, 39.4, 29.9, 27.1, 26.1, 22.5, 19.5, 18.3, 7.2, 7.0, –4.1, –4.8.

MS (ESI): m/z = 839.3 $(M + Na)^+$.

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