Total Synthesis of Xestodecalactone C from L-Malic Acid

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Abstract: An efficient total synthesis of the ten-membered macrolide, xestodecalactone C is described. The synthetic sequence uses Barbier-allylation, $LiAlH_4$/LiI-mediated *syn*-stereoselective 1,3-asymmetric reduction, and intramolecular Friedel–Crafts acylation as key steps.

Key words: xestodecalactone C, Barbier allylation, stereoselective reduction, intramolecular Friedel–Crafts acylation

Xestodecalactones A, B, and C (**1**, **2**, and **3**, respectively) were isolated from the fungus *Penicillium cf. mantanense* obtained from the marine sponge *Xestospongia exigua*.[1] Structurally these natural products constitute ten-membered macrolides with a fused 1,3-dihydroxybenzene ring, that are related to a number of compounds isolated from terrestrial fungi such as sporostatin (**4**)[2] and curvularins **5**, **6a**, and **6b**.[3] The absolute stereochemistry of xestodecalactones B and C was determined by Xinfu Pan et al. by their stereoselective synthesis.[4] Xestodecalactone A–C have been found to exhibit antibacterial and antifungal activities.[5] Considering its selective biological profile and structural features, several syntheses of xestodecalactones A, B, and C have been well reported (Figure 1).[6]

As a part of our interest in the total synthesis of biologically active natural products, we herein report a total synthesis of xestodecalactone C (**3**) using a commercially available and inexpensive starting material, L-malic acid. This strategy mainly relies on Barbier allylation, *syn*-stereoselective 1,3-asymmetric reduction, and intramolecular Friedel–Crafts acylation as the key steps. Retrosynthetic analysis reveals that target molecule **3** could be easily synthesized from alcohol **8** (Scheme 1), which in turn could be prepared from commercially available starting material L-malic acid (**9**) as outlined in Scheme 1.

Accordingly, the precursor **8** was prepared from L-malic acid.[7] Thus, the resulting primary alcohol **8** was treated with 2-iodoxybenzoic acid in dimethyl sulfoxide–dichloromethane to give aldehyde **10**, which on further treatment with allyl bromide and activated zinc in tetrahydrofuran–aqueous ammonium chloride solution under Barbier reaction conditions,[8] gave the homoallyl alcohol **11** as a diastereomeric mixture (Scheme 2). Oxidation of secondary alcohol **11** with 2-iodoxybenzoic acid in dimethyl sulfoxide–dichloromethane afforded the ketone **12**. A highly *syn*-stereoselective 1,3-asymmetric reduction was carried out using lithium aluminum hydride–lithium iodide in diethyl ether at –100 °C to provide the desired *syn*-diol **13** in good yield (*syn*/*anti* 95:5).[9] The secondary hydroxy group was protected as its benzyl ether to give **14**, which was subjected to acid-catalyzed hydrolysis in aqueous methanol to give diol **15a**. Chemoselective tosylation (TsCl, Et_3N, DMAP, CH_2Cl_2) of **15a** gave the monotosylated compound **15b**.

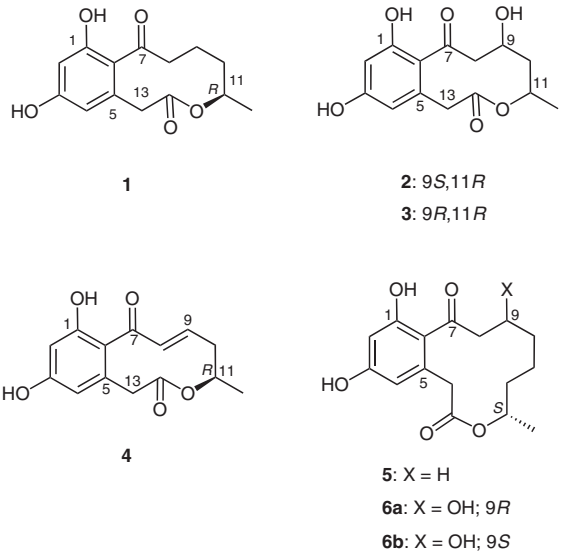
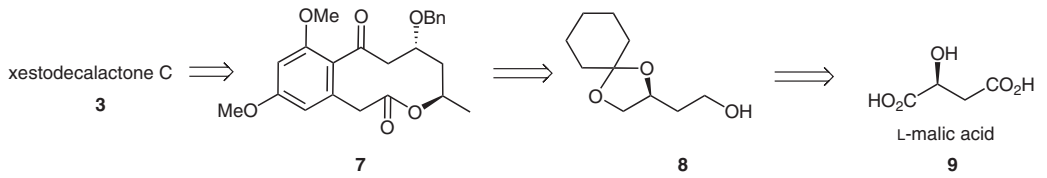


Figure 1 Xestodecalactones A, B, and C (**1**, **2**, and **3**), sporostatin (**4**), curvularins **5**, **6a**, and **6b**



Scheme 1 Retrosynthetic analysis of xestodecalactone C

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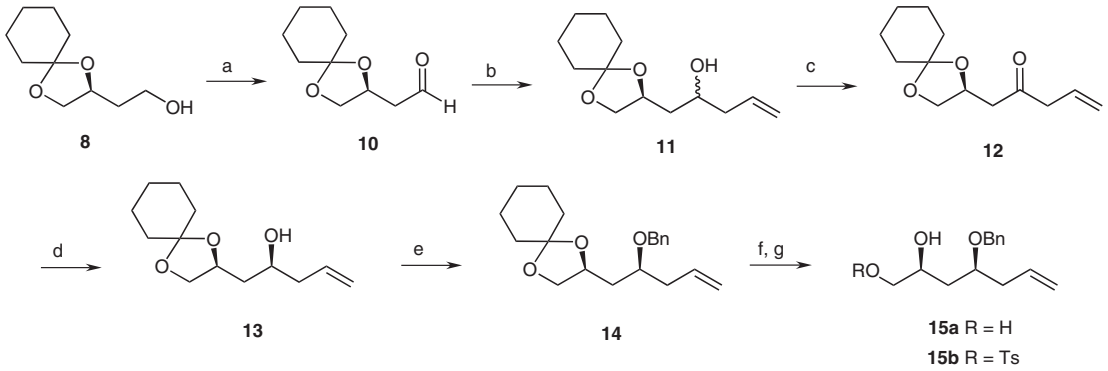
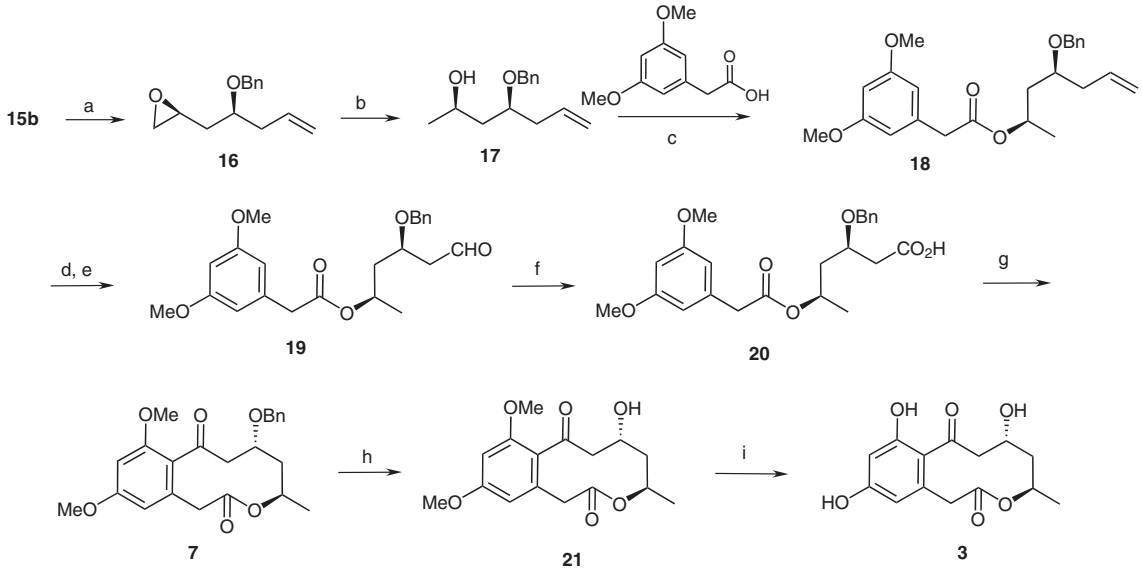


Scheme 2 *Reagents and conditions*: (a) IBX, DMSO, CH_2Cl_2, 3 h, 90%; (b) allyl bromide, activated Zn, THF–aq NH_4Cl, 0 °C to r.t., 4 h, 90%; (c) IBX, DMSO, CH_2Cl_2, 3 h, 86%; (d) $LiAlH_4$/LiI (1:1, 3 equiv), Et_2O, –100 °C, 92%; (e) BnBr, NaH, THF, r.t., 6 h, 85%; (f) PTSA, MeOH, r.t., 30 min, 90%; (g) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, r.t., 3 h, 75%.



Scheme 3 *Reagents and conditions*: (a) K_2CO_3, MeOH, r.t., 1 h, 81%; (b) $LiAlH_4$, THF, 0 °C to r.t., 2 h, 90%; (c) DCC, DMAP, CH_2Cl_2, r.t., 2 h, 90%; (d) OsO_4, NMO, acetone–H_2O (8:2), r.t., 2 h, 90%; (e) $NaIO_4$, THF–H_2O (2:1), 0 °C to r.t., 1 h, 80%; (f) $NaClO_2$, $NaH_2PO_4 \cdot 2\,H_2O$, 2-methylbut-2-ene, *t*-BuOH–H_2O (4:1), 0 °C to r.t., 12 h, 85%; (g) TFA, TFAA, r.t., 8 h, 40%; (h) H_2, Pd/C, EtOAc, r.t., 90%; (i) AlI_3, TBAI, benzene, 10 °C, 94%.

Monotosylated compound **15b** was treated with potassium carbonate in methanol to afford the epoxide **16**. Terminal epoxide **16** was subjected to regioselective reductive opening with lithium aluminum hydride in tetrahydrofuran to afford the secondary alcohol **17**, which upon treatment with 3,5-dimethoxyphenylacetic acid using *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine gave the ester **18**,[10] which was further converted into aldehyde **19** by dihydroxylation followed by sodium periodate mediated cleavage. Then aldehyde **19** was oxidized to carboxylic acid **20** under Pinnicks reaction conditions.[11] The desired macrolide **7** was obtained in 40% yield by intramolecular Friedel–Crafts reaction of the carboxylic acid **20** with a mixture of trifluoroacetic acid and trifluoroacetic anhydride.[12] The benzyl group of macrolide **7** was cleaved by hydrogenation using palladium-on-carbon in ethyl acetate to furnish compound **21**. Finally, demethylation of **21** was performed using freshly prepared aluminum(III) iodide to give the target molecule **3** in good yield.[13] The spectral and analytical data of natural product **3** were in agreement with the literature (Scheme 3).[1]

In conclusion, an efficient total synthesis of xestodecalactone C was accomplished by means of a versatile strategy, wherein L-malic acid was used as inexpensive starting material for accessing the natural product.

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H and ^{13}C NMR spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Room temperature = 25 °C.

1-[(2*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-en-2-ol (11)

To a stirred soln of IBX (11.3 g, 40.32 mmol) in anhyd DMSO (40 mL), was added a soln of **8** (5.0 g, 26.8 mmol) in CH_2Cl_2 (50 mL) at r.t. The resulting mixture was stirred at this temperature for 3 h.

Then the mixture was filtered and diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated to give **10** (4.45 g, 90%) as a colorless liquid, which was as used for the next reaction without purification.

To a stirred soln of **10** (4.45 g, 24.1 mmol) in THF (40 mL) was added Zn (3.14 g, 48.3 mmol) and allyl bromide (4.1 mL, 48.3 mmol) at 0 °C. Then a soln of sat. NH_4Cl (80 mL) was added and the resulting mixture was allowed to stir at this temperature for 4 h. After completion, the mixture was quenched with H_2O (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 1:4) to afford **11** (5.13 g, 90%) as a colorless liquid.

$[\alpha]_D^{20}$ +2.8 (*c* 0.5, $CHCl_3$).

IR (neat): 3448, 3059, 2918, 1580, 1050 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.90–5.73 (m, 1 H), 5.13–5.04 (m, 1 H), 4.29–4.18 (m, 1 H), 4.15–3.98 (m, 1 H), 3.96–3.80 (m, 1 H), 3.50 (t, *J* = 6.7 Hz, 1 H), 3.10–3.02 (m, 1 H), 2.32–2.14 (m, 2 H), 1.74–1.51 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.2, 118.1, 75.5, 70.4, 69.1, 42.0, 40.1, 36.5, 35.1, 25.4, 23.9.

MS (ESI): *m*/*z* = 227 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.95; H, 9.70.

(2*S*)-1-[(2*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-en-2-ol (13)

A soln of IBX (7.11 g, 25.42 mmol) in anhyd DMSO (30 mL) at r.t. was stirred for 30 min, then a soln of **11** (4 g, 16.94 mmol) in CH_2Cl_2 (50 mL) was added. The resulting mixture was allowed to stir at r.t. for 3 h. Then the mixture was filtered and diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL).The combined organic layers were washed with brine (20 mL), dried (anhyd Na_2SO_4) and evaporated to give **12** (3.41 g, 86%) as a colorless liquid, which was used for the next reaction.

To a stirred soln of **12** (3.41 g, 14.5 mmol) in anhyd Et_2O (10 mL) was added a soln of LiI (5.85 g, 43.7 mmol) in Et_2O at 0 °C and the mixture was stirred for 10 min. Then $LiAlH_4$ (1.66 g, 43.7 mmol) was added at –78 °C and the resulting mixture was stirred for 10 min after which the temperature was decreased to –100 °C and stirred for 30 min. Upon completion, the mixture was quenched with sat. aq KOH (10 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 1:9) to afford **13** (3.16 g, 92%) as a colorless syrup.

$[\alpha]_D^{20}$ +12.2 (*c* 1.0, $CHCl_3$).

IR (neat): 3440, 3050, 2920, 1590, 1054 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.90–5.73 (m, 1 H), 5.13–5.04 (m, 1 H), 4.29–4.18 (m, 1 H), 4.05 (q, *J* = 8.3, 6.0 Hz, 1 H), 3.90–3.80 (m, 1 H), 3.52 (t, *J* = 6.7 Hz, 1 H), 3.10 (br s, 1 H), 2.32–2.14 (m, 2 H), 1.74–1.51 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.2, 118.1, 75.5, 70.4, 69.1, 42.0, 40.1, 36.5, 35.1, 25.4, 23.9.

MS (ESI): *m*/*z* = 227 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.90; H, 9.78.

(2*S*)-2-(Benzyloxy)-1-[(2*S*)-1,4-dioxaspiro[4.5]decan-2-yl]pent-4-ene (14)

To a stirred soln of **13** (3.0 g, 12.7 mmol) in anhyd THF (40 mL) was added NaH (1.0 g, 25.42 mmol, 60% w/w in paraffin oil) at 0 °C. After 30 min, BnBr (1.66 mL, 13.98 mmol) was added at 0 °C and the mixture was stirred for 6 h. Then the mixture was quenched with sat. aq NH_4Cl (20 mL) at 0 °C and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure and the resulting crude product was purified by column chromatography (60–120 silica gel, EtOAc–hexanes, 1:40) to afford **14** (3.41 g, 85%) as a pale yellow liquid.

$[\alpha]_D^{20}$ +4.28 (*c* 1.2, $CHCl_3$).

IR (neat): 750, 1100, 1250, 1700, 2950, 3050 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.40 (m, 2 H), 1.48–1.68 (m, 9 H), 1.88–2.00 (m, 1 H), 2.26 (m, 2 H), 3.39–3.62 (m, 2 H), 3.85–3.94 (m, 1 H), 4.10–4.35 (m, 1 H), 4.50 (q, *J* = 11.2, 23.0 Hz, 2 H), 5.08 (dd, *J* = 6.6, 17.0 Hz, 2 H), 5.71–5.92 (m, 1 H), 7.28 (m, 5 H).

MS (EI): *m*/*z* = 317 $[M + H]^+$.

(2*S*,4*S*)-4-(Benzyloxy)hept-6-ene-1,2-diol (15a)

To a stirred soln of **14** (2.0 g, 6.32 mmol) in MeOH was added a catalytic amount of PTSA (0.107 g, 0.632 mmol) and the mixture was stirred at r.t. for 30 min. The mixture was neutralized with Et_3N (3 mL) and the solvent was evaporated. The crude residue was purified by column chromatography (60–120 silica gel, EtOAc–hexanes, 1:1) to afford **15** (1.33 g, 90%) as a syrup.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.58–1.78 (m, 2 H), 2.36–2.46 (m, 2 H), 3.28–3.85 (m, 4 H), 4.60 (ABq, *J* = 11.1 Hz, 2 H), 5.03–5.22 (m, 2 H), 5.64–5.84 (m, 1 H), 7.26–7.40 (m, 5 H).

MS (EI): *m*/*z* = 237 $[M + H]^+$.

(2*S*,4*S*)-4-(Benzyloxy)-1-tosylhept-6-en-2-ol (15b)

To a soln of **15** (1.3 g, 5.55 mmol) in anhyd CH_2Cl_2 (15.0 mL) was added Et_3N (1.55 mL, 11.11 mmol) at 0 °C. Then TsCl (1.16 g, 6.11 mmol) and was added over 2 h and then DMAP (cat.) was added. The resulting mixture was allowed to warm to r.t. and stirred for 3 h. Then the mixture was treated with aq 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were washed with sat. $NaHCO_3$ (15 mL) and H_2O (15 mL), dried (anhyd Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the crude product afforded **15b** (1.57 g, 75%) as a gummy liquid; R_f = 0.5 (silica gel, 80% EtOAc–hexane).

$[\alpha]_D^{20}$ +14.2 (*c* 0.8, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.6 (m, 3 H), 2.24–2.40 (m, 2 H), 2.42 (s, 3 H), 3.71–4.11 (m, 4 H), 4.52 (ABq, *J* = 11.3 Hz, 2 H), 5.04–5.12 (m, 2 H), 5.66–5.84 (m, 1 H), 7.26–7.27 (m, 7 H), 7.69–7.9 (m, 2 H).

MS (EI): *m*/*z* = 390 $[M]^+$.

(*S*)-2-[(*S*)-2-(Benzyloxy)pent-4-enyl]oxirane (16)

To a stirred soln of **15b** (1.5 g, 3.96 mmol) in anhyd MeOH (20 mL), was added K_2CO_3 (1.64 g, 11.9 mmol) and the mixture was stirred at r.t. for 1 h. Then the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (10 mL), washed with H_2O, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give **16** (0.701 g, 81%) as a pale yellow liquid.

$[\alpha]_D^{20}$ 24.23 (*c* 0.2, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.55 (m, 1 H), 1.76–1.86 (m, 1 H), 2.34–2.40 (m, 2 H), 2.44 (q, *J* = 3.0 Hz, 1 H), 2.75 (q, *J* = 3.7 Hz, 1 H), 3.65–3.73 (m, 2 H), 4.58 (ABq, *J* = 11.3 Hz, 2 H), 5.03–5.12 (m, 2 H), 5.72–5.88 (m, 1 H), 7.2–7.32 (m, 5 H).

MS (EI): *m*/*z* = 219 $(M + H)^+$.

(2*R*,4*S*)-4-(Benzyloxy)hept-6-en-2-ol (17)

To a stirred soln of $LiAlH_4$ (366 mg, 9.63 mmol) in anhyd THF (10 mL) at 0 °C, was added slowly a soln of **16** (700 mg, 3.21 mmol) in anhyd THF (5 mL) and the mixture was stirred at r.t. for 2 h. After completion, the mixture was quenched with sat. aq NH_4Cl (20 mL) at 0 °C and stirred for 1 h and then extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography (60–120 silica gel, EtOAc–hexane, 1:40) to afford **17** (632 mg, 90%) as a colorless liquid.

$[\alpha]_D^{20}$ –33.1 (*c* 0.61, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5 H), 5.85–5.70 (m, 1 H), 5.13–5.03 (m, 2 H), 4.56 (ABq, *J* = 11.5 Hz, 2 H), 4.11–4.01 (m, 1 H), 3.72–3.68 (m, 1 H), 2.50–2.25 (m, 2 H), 1.65–1.57 (m, 2 H), 1.15 (d, *J* = 6.2 Hz, 3 H).

MS (EI): *m*/*z* = 221 $[M + H]^+$.

(2*R*,4*S*)-4-(Benzyloxy)hept-6-en-2-yl 2-(3,5-Dimethoxyphenyl)acetate (18)

To a stirred soln of **17** (500 mg, 2.28 mmol) in anhyd CH_2Cl_2 at 0 °C was added DMAP (557 mg, 4.56 mmol), DCC (940.7 mg, 4.56 mmol), and 3,5-dimethoxyphenylacetic acid (492 mg, 2.51 mmol) and the resulting mixture was stirred at r.t. for 2 h. The mixture was filtered, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes–EtOAc, 10:1) to afford the **18** (815 mg, 90%) as a yellow oil.

$[\alpha]_D^{20}$ –77.0 (*c* 1.15, $CHCl_3$).

IR (KBr): 2934, 2839, 1730, 1597, 1459, 1431, 1350, 1205 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 5 H), 6.38 (d, *J* = 2.2 Hz, 2 H), 6.28 (t, *J* = 2.2 Hz, 1 H), 5.78–5.62 (m, 1 H), 5.08–4.96 (m, 2 H), 4.22 (ABq, *J* = 11.3, 10.5 Hz, 2 H), 3.78–3.67 (m, 7 H), 3.42 (s, 2 H), 3.30–3.18 (m, 1 H), 2.32–2.11 (m, 2 H), 1.72–1.51 (m, 2 H), 1.22 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.71, 160.73, 138.39, 136.41, 134.20, 128.30, 127.89, 127.48, 117.39, 107.23, 99.09, 74.77, 71.39, 68.57, 55.19, 42.21, 41.17, 38.29, 20.57.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{30}NaO_5$: 421.1990; found: 421.2004.

(3*R*,5*R*)-3-(Benzyloxy)-5-[2-(3,5-dimethoxyphenyl)acetoxy]hexanoic Acid (20)

To a stirred soln of **18** (800 mg, 2.01 mmol) in acetone–H_2O (8:2) at r.t. was added OsO_4 (cat.). After 15 min, NMO (258 mg, 2.21 mmol) was added and stirring was continued for 2 h. Acetone was removed under reduced pressure and the mixture was quenched with $NaHSO_3$ soln at 0 °C and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting crude diol (780 mg, 90%) was used in next reaction without further purification.

To a stirred soln of diol in a mixture of THF–H_2O (2:1) at 0 °C was added $NaIO_4$ (774 mg, 3.61 mmol) and stirring was continued at r.t. for 1 h. Then the mixture was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4). Removal of solvent followed by purification gave the crude aldehyde **19** (577 mg, 80%) which was used in next reaction without further purification.

To a stirred soln of crude **19** in *t*-BuOH (3 mL) was added 2-methylbut-2-ene (1.2 mL) in *t*-BuOH (2 mL). The mixture was cooled to 0 °C and then treated with a soln of $NaClO_2$ (196 mg, 2.16 mmol) and NaH_2PO_4 (338 mg, 2.17 mmol) in H_2O (1 mL). After 12 h, the mixture was diluted with brine (5 mL) and extracted with Et_2O (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo and purified by flash chromatography to afford **20** (511 mg, 85%).

$[\alpha]_D^{20}$ –33.5 (*c* 1.05, $CHCl_3$).

IR (neat): 3675, 3468, 2928, 2852, 1731, 1597, 1459, 1431, 1350, 1205, 1066 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 5 H), 6.41 (d, *J* = 2.2 Hz, 2 H), 6.31 (t, *J* = 2.2 Hz, 1 H), 5.78–5.62 (m, 1 H), 4.27 (ABq, *J* = 11.3, 10.5 Hz, 2 H), 3.78–3.65 (s, 6 H), 3.47 (s, 2 H), 2.64–2.39 (m, 2 H), 1.83–1.74 (m, 1 H), 1.42–1.30 (m, 2 H), 1.27 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.92, 170.89, 160.85, 137.66, 137.20, 136.24, 128.41, 128.06, 127.83, 107.26, 99.26, 72.41, 72.15, 68.37, 55.28, 42.18, 41.63, 39.48, 20.57.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{28}NaO_7$: 439.1732; found: 439.1723.

(4*R*,6*R*)-6-(Benzyloxy)-9,11-dimethoxy-4-methyl-4,5,6,7-tetrahydro-2*H*-3-benzoxecine-2,8(1*H*)-dione (7)[12]

Reddish oil.

$[\alpha]_D^{20}$ –5.90 (*c* 1.01, $CHCl_3$).

IR (KBr): 2925, 1730, 1638, 1603, 1456, 1336, 1239, 1157, 1092 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5 H), 6.37 (d, *J* = 1.5 Hz, 1 H), 6.21 (d, *J* = 1.5 Hz, 1 H), 4.91–4.81 (m, 1 H), 4.56 (ABq, *J* = 12.8, 11.3 Hz, 2 H), 4.27–4.17 (m, 1 H), 4.01–3.89 (m, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.38–3.28 (m, 1 H), 3.15–3.06 (m, 2 H), 2.10–2.01 (m, 1 H), 1.80–1.74 (m, 1 H), 1.20 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.59, 168.75, 161.33, 159.02, 138.24, 134.40, 128.36, 127.65, 124.19, 107.75, 96.94, 71.70, 70.72, 55.65, 55.36, 52.35, 43.66, 40.31, 29.62, 20.84.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{26}NaO_6$: 421.1627; found: 421.1620.

(4*R*,6*R*)-6-Hydroxy-9,11-dimethoxy-4-methyl-4,5,6,7-tetrahydro-2*H*-3-benzoxecine-2,8(1*H*)-dione (21)

To a stirred soln of **7** (0.150 mg, 0.37 mmol) in EtOAc (4 mL), was added 10% Pd/C (catalytic) under a H_2 atmosphere and stirred for 6 h. Then the mixture was filtered through a pad of Celite and concentrated in vacuo. The crude residue thus obtained was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 1:4) to afford **21** (104 mg, 90%) as colorless syrup.

$[\alpha]_D^{20}$ +13.5 (*c* 0.3, $CHCl_3$).

IR (KBr): 3350, 2925, 1730, 1638, 1603, 1456, 1239, 1157, 1092 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.39 (s, 1 H), 6.27 (s, 1 H), 5.38–5.09 (m, 1 H,), 4.29–4.11 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.51–3.40 (d, *J* = 13.5 Hz, 1 H), 3.09 (s, 2 H), 2.39–2.21 (m, 1 H), 2.19–1.91 (m, 1 H), 1.82–1.4 (m, 1 H), 1.19 (d, *J* = 6.4 Hz, 3 H).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}NaO_6$: 331.1157; found: 331.1155.

(4*R*,6*R*)-6,9,11-Trihydroxy-4-methyl-4,5,6,7-tetrahydro-2*H*-3-benzoxecine-2,8(1*H*)-dione (3)[13]

White solid; mp 166–168 °C.

$[\alpha]_D^{20}$ +22.5 (*c* 0.8, MeOH).

IR (KBr): 3345, 2923, 1739, 1630, 1461, 1370 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 9.92 (s, 1 H), 9.71 (s, 1 H), 6.27 (d, *J* = 1.6 Hz, 1 H), 6.10 (s, 1 H), 4.75 (d, *J* = 4.0 Hz, 1 H), 4.72

(dd, *J* = 11.2, 5.6 Hz, 1 H), 3.96 (br s, 1 H), 3.80 (d, *J* = 19.0 Hz, 1 H), 3.48 (d, *J* = 19.0 Hz, 1 H), 3.08 (dd, *J* = 14.8, 10.4 Hz, 1 H), 2.81 (d, *J* = 14.5 Hz, 1 H), 1.83 (d, *J* = 13.0 Hz, 1 H), 1.63 (dd, *J* = 14.8, 11.2 Hz, 1 H), 1.08 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO): δ = 204.51, 167.75, 159.15, 157.02, 134.44, 121.80, 110.0, 101.25, 70.64, 67.78, 55.17, 45.99, 20.73.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}NaO_6$: 303.0844; found: 303.0844.

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References

(1) Edrada, R. A.; Heubes, M.; Brauers, G.; Wray, V.; Berg, A.; Gräfe, U.; Wohlfarth, M.; Mühlbacher, J.; Schaumann, K.; Sudarsono; Bringmann, G.; Proksch, P. *J. Nat. Prod.* **2002**, *65*, 1598.

(2) Kinoshita, K.; Sasaki, T.; Awata, M.; Takada, M.; Yaginuma, S. *J. Antibiot.* **1997**, *50*, 961.

(3) (a) Musgrave, O. C. *J. Chem. Soc.* **1956**, 4301. (b) Lai, S.; Shizuri, Y.; Yamamura, S.; Kawai, K.; Terada, Y.; Furukuwa, H. *Tetrahedron Lett.* **1989**, *30*, 2241. (c) Robeson, D. J.; Strobel, G. A.; Strange, R. N. *J. Nat. Prod.* **1985**, *48*, 139. (d) Ghisalberti, E. L.; Rowland, C. Y. *J. Nat. Prod.* **1993**, *56*, 2175.

(4) Liang, Q.; Zhang, J.; Quan, W.; Sun, Y.; She, X.; Pan, X. *J. Org. Chem.* **2007**, *72*, 2694.

(5) Bringmann, G.; Proksch, P.; Edrada, R. A.; Heubes, M.; Sudarsono; Gunther, E. US 2003,216,354, **2003**.

(6) (a) Bringmann, G.; Lang, G.; Michel, M.; Heubes, M. *Tetrahedron Lett.* **2004**, *45*, 2829. (b) Yoshino, T.; Ng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 14185. (c) Yadav, J. S.; Thrimurtulu, N.; Uma Gayathri, K.; Subba Reddy, B. V.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 6617.

(7) Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.

(8) (a) Petrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910. (b) Luche, J.-L.; Einhorn, C. *J. Organomet. Chem.* **1987**, *322*, 177.

(9) (a) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783. (b) Sabitha, G.; Sudhakar, K.; Mallikarjun Reddy, N.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567.

(10) Baker, P. M.; Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc. C* **1967**, 1913.

(11) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(12) Bracher, F.; Schulte, B. *Liebigs Ann./Recl.* **1997**, 1979.

(13) Kreipl, A. T.; Reid, C.; Steglich, W. *Org. Lett.* **2002**, *4*, 3287.