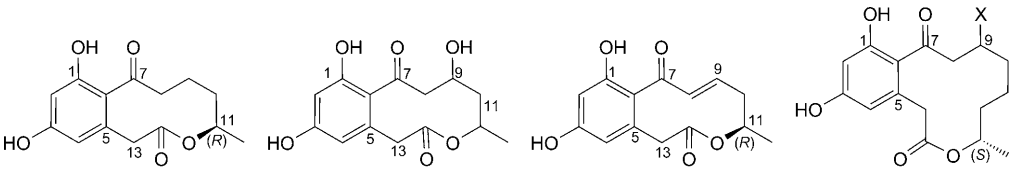
Stereoselective Total Synthesis of Xestodecalactone C

by **Karuturi Rajesh**, **Vangaru Suresh**, **Jondoss Jon Paul Selvam**, **Chitturi Bhujanga Rao**, and **Yenamandra Venkateswarlu***

Natural Products Laboratory, Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad 500007, India (phone: +91-40-27193167; fax: +91-40-27160512; e-mail: luchem@iict.res.in)

A simple and highly efficient stereoselective total synthesis of xestodecalactone C (**IIb**), a polyketide natural product, was achieved (*Scheme 2*). The synthesis involved *Keck*'s asymmetric allylation, a iodine-induced electrophilic cyclization, and an intramolecular *Friedel–Crafts* acylation as key steps.

Introduction. – Marine fungi are attracting increasing attention as a potential source of new pharmaceuticals and pharmaceutical leads [1]. In 2002, 10-membered macrolides fused to the 1,3-dihydroxybenzene ring such as xestodecalactones A (**I**), B (**IIa**), and C (**IIb**) were isolated from the fungus *Penicillium cf. mantanense* obtained from the marine sponge *Xestospongia exigua* [2]. A number of structurally related molecules such as sporostatin[1]) (**III**) [3] and the curvularins[1]) **IV**, **Va**, and **Vb** [4] were isolated from terrestrial fungi *Sporormiella* sp. and *Penicillium* sp., respectively. Xestodecalactones A–C have been shown to exhibit antibacterial and antifungal activities [5]. They are also found to be specific inhibitors of the epidermal growth factor (EGF) receptor, tyrosine kinase *in vitro*. The potential biological importance as well as the unique structural feature of these molecules sparked interest in the syntheses of these molecules [6]. *Pan* and co-workers determined the absolute configuration of xestodecalactones B and C by their stereoselective synthesis [7]. Recently, *Yadav* and co-workers reported the stereoselective total synthesis of xestodecalactone C utilizing a *Prins* cyclization for the preparation of the aliphatic segment and a *Friedel–Crafts* acylation for the construction of the macrolide [8]. In continuation of our interest on the synthesis of biologically active natural products [9], we report herein an efficient and practical total synthesis of xestodecalactone C.



I[1])

IIa (9*S*,11*R*)[1])
IIb (9*R*,11*R*)[1])

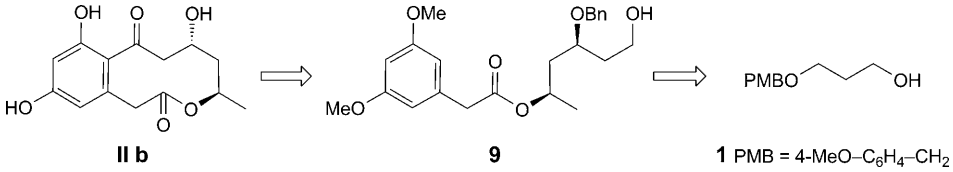
III[1])

IV x = H[1])
Va x = OH (9*R*)[1])
Vb x = OH (9*S*)[1])

[1]) Arbitrary atom numbering; for the systematic name of **IIb**, see *Exper. Part.*

Our planned approach to xestodecalactone C (**IIb)** involved an intramolecular *Friedel–Crafts* acylation for the macrolide ring formation as reported earlier [7][8], an asymmetric allylation, and a diastereoselective iodolactonization as the chirality-inducing steps starting from propane-1,3-diol (*Scheme 1*).

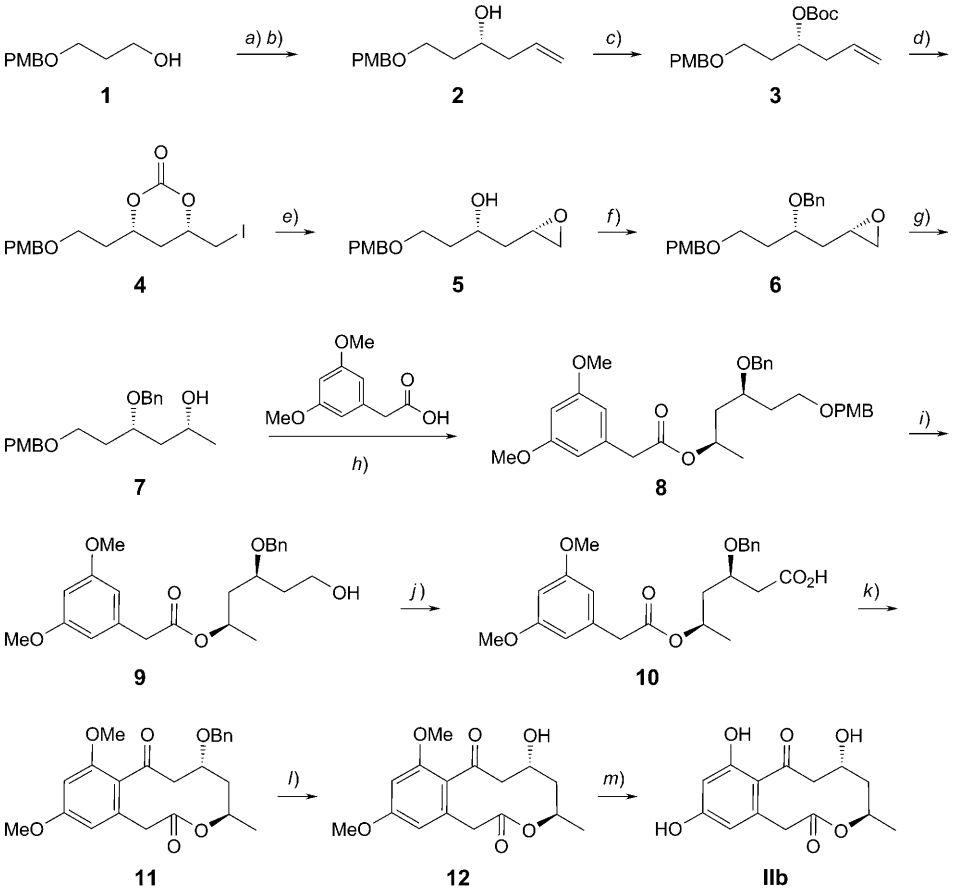
Scheme 1. *Retrosynthetic Approach to Xestodecalactone C* (**IIb**)



Results and Discussion. – The synthesis of xestodecalactone C (**IIb)** started with commercially available propane-1,3-diol (*Scheme 2*), which was protected with *p*-methoxybenzyl (PMB) bromide to yield the corresponding propan-1-ol **1**. The primary alcohol in **1** was oxidized with 2-iodoxybenzoic acid (=2-iodylbenzoic acid = IBX; 2-(O_2I)-C_6H_4–COOH) in DMSO to afford the corresponding aldehyde, which was subjected to the catalytic asymmetric allylation with an allylstannane developed by *Keck* and co-workers [10] to furnish the homoallyl alcohol **2** in 80% yield with excellent enantioselectivity (95% ee by HPLC). The homoallyl alcohol **2** was treated with di(*tert*-butyl) dicarbonate ($(Boc)_2O$) in the presence of DMAP in MeCN [11] to afford the homoallyl *tert*-butyl carbonate **3**. The latter was subjected to the diastereoselective iodolactonization [12] with I_2 in dry MeCN at $-20°$ to furnish the cyclic iodocarbonate **4** in 85% yield as a single diastereoisomer (as determined by ^{1}H-NMR analysis). Iodocarbonate **4**, upon exposure to a basic MeOH solution [12], gave the desired '*syn*'-epoxy alcohol **5** in 90% yield. The epoxy alcohol **5** was protected as benzyl ether **6** by treatment of **5** with benzyl bromide/NaH. Then, the terminal epoxide **6** was subjected to regioselective reduction with $LiAlH_4$ [13] in THF to afford the secondary alcohol **7** which was esterified with 3,5-(dimethoxyphenyl)acetic acid in the presence of DCC and DMAP [14] to give ester **8**. The latter, on treatment with DDQ in CH_2Cl_2/H_2O, afforded the primary alcohol **9** which was oxidized with *Jones* reagent (5 equiv.) in acetone at 0° for 15 min to afford the acid **10** in 86% yield [15]. The desired macrolide **11** was obtained in 40% yield by an intramolecular *Friedel–Crafts* acylation reaction of the carboxylic acid **10** in the presence of $CF_3COOH/(CF_3CO)_2O$ [8][16]. The benzyl protecting group of **11** was removed by using 5% Pd/C under H_2 in AcOEt to afford **12**. Finally, the MeO groups were removed by reaction with freshly prepared AlI_3 [17] to furnish the natural product **IIb**. The spectroscopic and analytical data of **IIb** are in good agreement with the data reported for the natural product.

In conclusion, an efficient and straightforward total synthesis of xestodecalactone C (**IIb**) was achieved. The initial *Keck* asymmetric allylation of an aldehyde for the introduction of chirality and the subsequent diastereoselective I_2-induced electrophilic cyclization constitute the key reactions for the construction of the '*syn*'-1,3-diol moiety. The synthetic strategy described here has significant potential for the synthesis of a variety of other biologically important substituted 1,3-diol-containing natural products.

Scheme 2



PMB = 4-MeO–C_6H_4–CH_2

a) 2-Iodoxybenzoic acid, DMSO, CH_2Cl_2, 3 h; 90%. *b*) (+)-(*R*)-BINOL ((+)-(1*R*)-[1,1′-binaphthalene]-2,2′-diol), 4 Å molecular sieves, Ti(^{i}PrO)$_4$, allyltributylstannane, CH_2Cl_2, −78° to −20°. *c*) $(Boc)_2O$, DMAP (*N*,*N*-dimethylpyridin-4-amine), MeCN, r.t., 5 h; 95%. *d*) I_2, MeCN, −20°, 12 h; 85%. *e*) K_2CO_3, MeOH, 0° to r.t., 30 min; 90%. *f*) BnBr, NaH, THF, r.t., 6 h; 85%. *g*) $LiAlH_4$, THF, 0° to r.t., 2 h; 90%. *h*) DCC (dicyclohexylcarbodiimide), DMAP, r.t., Et_2O; 95%. *i*) DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile), CH_2Cl_2/H_2O 19:1, r.t., 1 h; 80%. *j*) *Jones* reagent, 0°, 15 min; 86%. *k*) $CF_3COOH/(CF_3CO)_2O$, reflux; 40%. *l*) H_2, Pd/C, AcOEt, r.t.; 90%. *m*) AlI_3, $(Bu_4N)I$, benzene, r.t.; 96%.

Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros* and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried over anh. Na_2SO_4 and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (*Acme*'s 60–120 mesh). HPLC: *Eurocel 01* (250 × 4.6 mm, 5 μm); mobile phase hexane/i-PrOH 90:10, flow rate 1 ml/

min; detection by PDA (photo diode array). Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300*; at 25°. IR Spectra: *Perkin-Elmer-IR-683* spectrophotometer with NaCl optics. ^{1}H- (200 and 300 MHz) and ^{13}C-NMR (50 and 75 MHz) Spectra: *Varian-Gemini-FT-200* and *Bruker-Avance-300* instruments; Me_4Si as internal standard in $CDCl_3$; *J* values in Hz. MS: *Agilent Technologies 1100* series (*Agilent Chemistation* software); in *m/z* (rel. %).

1-[(4-Methoxybenzyl)oxy]hex-5-en-3-ol (**2**). To a stirred soln. of 2-iodoxybenzoic acid (3.2 g, 11.47 mmol) in dry DMSO (5 ml), a soln. of 3-[(4-methoxybenzyl)oxy]propan-1-ol (**1**; 1.5 g, 7.6 mmol) in CH_2Cl_2 (50 ml) was added at r.t. and stirred for 5 h at r.t. After completion of the reaction, the mixture was filtered, diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layer was washed with brine (20 ml), dried (Na_2SO_4), and evaporated to give the crude aldehyde which was purified by CC (hexane/AcOEt 1:9): aldehyde (1.36 g, 92%) as a colorless liquid. Separately, a mixture of (+)-(*R*)-BINOL (0.2 g, 0.7 mmol) and $Ti(^iPrO)_4$ (0.2 g, 0.7 mmol) in CH_2Cl_2 (30 ml) in the presence of 4 Å molecular sieves (2 g) was stirred under reflux. After 1 h, the mixture was cooled to r.t., the previously prepared aldehyde (1.36 g, 7 mmol) was added, and the resulting mixture was stirred for 10 min. Then, the mixture was cooled to −78°, and allyltributylstannane (2.7 g, 8.4 mmol) was added and the stirring continued at −20° for 36 h. After completion of the reaction (TLC), it was quenched with sat. $NaHCO_3$ soln. (5 ml), stirred for an additional 30 min, and then extracted with CH_2Cl_2 (40 ml). The org. phase was washed with H_2O (15 ml), dried, and concentrated and the residue purified by CC (AcOEt/hexane 2:8): **2** (1.32 g, 80%). Clear liquid. $[\alpha]_D^{25} = +3.2$ ($c = 1$, $CHCl_3$); 95% ee by HPLC. IR (neat): 3445, 3072, 2930, 2861, 1612, 1513,1461, 1362, 1300, 1247, 1175, 1089, 1033. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.22 (*d*, *J* = 8.1, 2 H); 6.84 (*d*, *J* = 8.8, 2 H); 5.86–5.76 (*m*, 1 H); 5.1–5.06 (*m*, 2 H); 4.4 (*s*, 2 H); 3.9–3.85 (*m*, 1 H), 3.8 (*s*, 3 H); 3.68–3.63 (*m*, 1 H); 2.2 (*t*, *J* = 7.3, 2 H); 1.74–1.68 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 134.8; 130.1; 129.2; 117.4; 113.7; 72.8; 70.28; 68.48; 55.19; 41.8; 35.70. HR-ESI-MS: 259.1318 ($[M+Na]^+$, $C_{14}H_{20}NaO_3^+$; calc. 259.1310).

*(3*R*)*-tert-*Butyl 1-[(4-Methoxybenzyl)oxy]hex-5-en-3-yl Carbonate* (=*1,1-Dimethylethyl (1*R*)-1-{3-[(4-Methoxyphenyl)methoxy]propyl}but-3-en-1-yl Carbonate*; **3**). To a soln. of **2** (1.32 g, 5.5 mmol) in MeCN (40 ml) were added $(Boc)_2O$ (1.22 g, 5.5 mmol) and DMAP (0.26 g, 2.1 mmol) and stirred for 5 h. After completion of the reaction, the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (100 ml), the org. phase washed with 5% HCl soln. (3 × 50 ml), dried, and concentrated, and the crude product purified by CC (silica gel, petroleum ether/AcOEt 9:1): **3** (1.78 g, 95%). Colorless oil. $[\alpha]_D^{25} = +1.9$ ($c = 1$, $CHCl_3$). IR (neat.): 2978, 2929, 1756, 1613, 1368, 1275, 1251, 1058. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25 (*d*, *J* = 8.07, 2 H); 6.84 (*d*, *J* = 8.79, 2 H); 5.9–5.76 (*m*, 1 H); 5.1–5.06 (*m*, 2 H); 4.95–4.8 (*m*, 1 H), 4.45 (*s*, 2 H); 3.8 (*s*, 3 H); 3.58–3.43 (*m*, 2 H); 2.4 (*t*, *J* = 7.32, 2 H); 1.8–1.69 (*m*, 2 H); 1.5 (*s*, 9 H). LC/MS: 359 ($[M+Na]^+$).

*(4*S*,6*S*)-4-(Iodomethyl)-6-{2-[(4-methoxybenzyl)oxy]ethyl}-1,3-dioxan-2-one* (**4**). To a stirred soln. of **3** (1.5 g, 4.46 mmol) in dry MeCN (100 ml) was added I_2 (3.39 g, 13.3 mmol) at −40° for 10 h. After completion of the reaction (TLC), aq. $Na_2S_2O_3$ soln. (50 ml), followed by aq. $NaHCO_3$ soln. (50 ml) was added. The mixture was then extracted with AcOEt (3 × 50 ml), the extract washed with H_2O (15 ml), dried, and concentrated, and the residue purified by CC (AcOEt/hexane 3:7): pure **4** (1.45 g, 80%). Colorless oil. $[\alpha]_D^{25} = -4.6$ ($c = 1.2$, $CHCl_3$). IR (neat): 2924, 2856, 1746, 1611, 1512, 1389, 1245, 1183, 1096, 1030, 820, 761. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25 (*d*, *J* = 8.5, 2 H); 6.8 (*d*, *J* = 8.7, 2 H); 4.71–4.61 (*m*, 1 H); 4.45–4.36 (*m*, 3 H); 3.8 (*s*, 3 H); 3.7–3.54 (*m*, 2 H); 3.4–3.35 (*m*, 1 H); 3.28–3.22 (*m*, 1 H); 2.4–2.33 (*m*, 1 H); 2.0–1.91 (*m*, 2 H); 1.7–1.64 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3; 148.3; 129.9; 129.4; 113.8; 77.2; 75.8; 72.9; 64.5; 55.2; 35.3; 33.2; 5.4. HR-ESI-MS: 429.0155 ($[M+Na]^+$, $C_{15}H_{19}INaO_5^+$; calc. 429.0175).

*(2*S*)-4-[(4-Methoxybenzyl)oxy]-1-[(2*S*)-oxiran-2-yl]butan-2-ol* (**5**). To a stirred soln. of **4** (1.45 g, 3.5 mmol) in MeOH (20 ml) was added K_2CO_3 (2.46 g, 17.8 mmol) at 0°. The mixture was then warmed and stirred at 25°. After completion of the reaction (TLC), aq. $NaHCO_3$ soln. (50 ml) was added, and the mixture was extracted with AcOEt (3 × 50 ml). The combined org. phase was dried and concentrated and the residue purified by CC (AcOEt/hexane 4:6): **5** (0.783 g, 87%). Colorless oil. $[\alpha]_D^{25} = +4.8$ ($c = 1.3$, $CHCl_3$). IR (neat): 3430, 2928, 2866, 1611, 1512, 1389, 1345, 1189, 1096, 1030, 825, 781. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.24 (*d*, *J* = 8.7, 2 H); 6.87 (*d*, *J* = 8.5, 2 H); 4.45 (*s*, 2 H); 4.1–4.0 (*m*, 1 H); 3.79 (*s*, 3 H); 3.73–3.59 (*m*, 2 H); 3.12–3.06 (*m*, 1 H); 2.78–2.75 (*m*, 1 H); 2.51–2.48 (*m*, 1 H); 1.86–1.61 (*m*,

4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.2; 129.9; 129.2; 113.8; 72.9; 69.4; 68.5; 55.2; 49.9; 46.6; 39.8; 36.3. HR-ESI-MS: 275.1265 ($[M+Na]^+$, $C_{14}H_{20}NaO_4^+$; calc. 275.1259).

*(2*S*)-2-{(2*S*)-2-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]butyl}oxirane* (**6**). A soln. of **5** (0.7 g, 2.77 mmol) in anh. THF was slowly added to a 60% NaH suspension in oil (0.166 g, 6.92 mmol) followed by the addition of benzyl bromide (0.36 ml, 3 mmol). The mixture was stirred at r.t. for 4 h, quenched with cold H_2O, and extracted with AcOEt (3×50 ml). The org. phase was dried and concentrated and the residue purified by CC (AcOEt/hexane 2:8): **6** (0.9 g, 95%). Colorless oil. $[\alpha]_D^{25}=+5.2$ ($c=1.1$, $CHCl_3$). IR (neat): 2923, 2854, 1723, 1610, 1510, 1456, 1356, 1298, 1245, 1173, 1090, 840, 760, 697. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35 (*m*, 7 H); 6.86 (*d*, $J=8.7$, 2 H); 4.56–4.36 (*m*, 4 H); 3.81–3.79 (*m*, 1 H); 3.78 (*s*, 3 H); 3.63–3.5 (*m*, 2 H); 3.08–3.01 (*m*, 1 H); 2.74–2.71 (*m*, 1 H); 2.46–2.43 (*m*, 1 H); 1.95–1.76 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 138.5; 130.4; 129.3; 128.3; 127.7; 127.5; 113.7; 74.1; 72.6; 71.2; 66.2; 55.2; 49.4; 46.7; 37.0; 34.6. HR-ESI-MS: 365.1710 ($[M+Na]^+$, $C_{21}H_{26}NaO_4^+$; calc. 365.1729).

*(2*R*,4*S*)-4-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]hexan-2-ol* (**7**). A soln. of **6** (0.9 g, 2.63 mmol) in THF (20 ml) was added slowly to a stirred slurry of $LiAlH_4$ (0.2 g, 5.2 mmol) in THF. After being stirred for 6 h at 50°, the reaction was carefully quenched with H_2O. The mixture was extracted with AcOEt (3×50 ml), the org. phase dried (anh. Na_2SO_4) and concentrated, and the residue purified by CC (AcOEt/hexane 3:7): **7** (0.79 g, 88%). Colorless oil. $[\alpha]_D^{25}=+6.2$ ($c=1.2$, $CHCl_3$). IR (neat): 3430, 2925, 2855, 1735, 1611, 1512, 1456, 1246, 1174, 1090, 1033, 938, 819, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.21 (*m*, 7 H); 6.86 (*d*, $J=8.7$, 2 H); 4.65–4.38 (*m*, 4 H); 3.95–3.79 (*m*, 1 H); 3.78 (*s*, 3 H); 3.58–3.45 (*m*, 2 H); 2.68 (br. *s*, 1 H); 2.0–1.52 (*m*, 4 H); 1.12 (*d*, $J=6.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 137.8; 130.2; 129.3; 128.5; 128.4; 127.8; 127.7; 113.7; 77.1; 72.6; 70.9; 67.3; 66.0; 55.1; 43.0; 33.9; 23.5. HR-ESI-MS: 367.1866 ($[M+Na]^+$, $C_{21}H_{28}NaO_4^+$; calc. 367.1885).

*(2*R*,4*S*)-4-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]hexan-2-yl 2-(3,5-Dimethoxyphenyl)acetate* (=*(1*R*,3*S*)-5-[(4-Methoxyphenyl)methoxy]-1-methyl-3-(phenylmethoxy)pentyl 3,5-Dimethoxybenzeneacetate*; **8**). To a stirred soln. of **7** (0.2 g, 0.58 mmol) in CH_2Cl_2 (10 ml) was added DCC (0.179 g, 0.872 mmol) followed by a catalytic amount of DMAP at 0°. After 5 min, 2-(3,5-dimethoxyphenyl)acetic acid (0.136 g, 0.692 mmol) was added, and the mixture was stirred for 17 h at r.t. After completion of the reaction (TLC), H_2O (10 ml) was added, and the mixture was extracted with CH_2Cl_2 (20 ml). The org. layer was washed successively with 10% aq. HCl soln., sat. $NaHCO_3$ soln., and brine, dried, and concentrated and the residue purified by CC (AcOEt/hexane 1:10): **8** (0.29 g, 95%). $[\alpha]_D^{25}=+9.7$ ($c=1$, $CHCl_3$). IR (neat): 2923, 2853, 1731, 1601, 1512, 1461, 1294, 1250, 1204, 1155, 1101, 1066, 832. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.21 (*m*, 7 H); 6.85 (*d*, $J=8.7$, 2 H); 6.42–6.29 (*m*, 3 H); 5.1–5.02 (*m*, 1 H); 4.42–4.35 (*m*, 4 H); 3.78–3.72 (*m*, 10 H); 3.57–3.46 (*m*, 4 H); 2.0–1.59 (*m*, 4 H); 1.18 (*d*, $J=6.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.7; 160.7; 159.1; 138.5; 136.2; 130.5; 129.2; 128.3; 127.7; 127.5; 113.7; 107.2; 99.0; 73.3; 72.5; 70.8; 69.0; 66.3; 55.2; 42.0; 40.3; 34.1; 20.2. HR-ESI-MS: 545.2513 ($[M+Na]^+$, $C_{31}H_{38}NaO_7^+$; calc. 545.2515).

*(2*R*,4*S*)-4-(Benzyloxy)-6-hydroxyhexan-2-yl 2-(3,5-Dimethoxyphenyl)acetate* (=*(1*R*,3*S*)-5-Hydroxy-1-methyl-3-(phenylmethoxy)pentyl 3,5-Dimethoxybenzeneacetate*; **9**). To a soln. of **8** (290 mg, 0.55 mmol) in CH_2Cl_2/H_2O 19:1 (20 ml) at 0° was added DDQ (252 mg, 1.1 mmol), and the mixture was stirred at r.t. for 2 h. After completion of the reaction (TLC), it was quenched with sat. aq. $NaHCO_3$ soln. and the mixture, extracted with CH_2Cl_2 (3×20 ml). The org. phase was dried (anh. Na_2SO_4), the solvent removed under reduced pressure, and the residue purified by CC (AcOEt/hexane 2:8): **9** (208 mg, 90%). Colorless syrup. $[\alpha]_D^{25}=-5.2$ ($c=1$, $CHCl_3$). IR (neat): 3445, 2927, 2851, 1728, 1599, 1461, 1430, 1294, 1252, 1204, 1154, 1062, 837, 746. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.23 (*m*, 5 H); 6.44–6.32 (*m*, 3 H); 5.03–4.95 (*m*, 1 H); 4.49–4.29 (*m*, 2 H); 3.79–3.64 (*m*, 8 H); 3.53–3.45 (*m*, 3 H); 2.08–1.98 (*m*, 2 H); 1.8–1.74 (*m*, 1 H); 1.7–1.6 (*m*, 1 H); 1.24 (*d*, $J=6.0$, 3 H). ^{13}C-NMR (75, $CDCl_3$): 170.8; 160.8; 138.03; 136.2; 128.4; 128.4; 127.8; 107.3; 98.9; 75.4; 70.9; 68.6; 60.4; 55.3; 42.1; 39.9; 35.9; 20.5. ESI-MS: 425 ($[M+Na]^+$).

*(3*R*,5*R*)-3-(Benzyloxy)-5-{[2-(3,5-dimethoxyphenyl)acetyl]oxy}hexanoic Acid* (**10**). To a soln. of **9** (208 mg, 0.517 mmol) in acetone (50 ml) was added 1M *Jones* reagent (1.1 ml) at 0°, and the mixture was stirred at 0° for 15 min. After completion of the reaction ^{i}PrOH was added, and the resulting mixture was filtered through *Celite*, the filtrate concentrated, the residue dissolved in AcOEt (50 ml), and the soln.

washed with brine (3 × 15 ml), dried, and concentrated. The residue was purified by CC (silica gel, hexane/AcOEt 60:40): **10** (185 mg, 86%). Colorless oil. $[\alpha]_D^{25} = -3.8$ ($c = 1$, $CHCl_3$). IR (neat): 3350, 2950, 1726, 1600, 1449, 1429, 1259, 1154, 1062. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.23 (*m*, 5 H); 6.44–6.32 (*m*, 3 H); 5.03–4.95 (*m*, 1 H); 4.49–4.29 (*m*, 2 H); 3.79–3.64 (*m*, 6 H); 3.53–3.45 (*m*, 3 H); 2.48–2.23 (*m*, 2 H); 1.7–1.6 (*m*, 2 H); 1.24 (*d*, $J = 6.24$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.3; 172.3, 162.8; 138.23; 136.4; 128.5; 128.4; 127.9; 106.3; 99.3; 72.4; 71.3; 68.8; 60.7; 55.3, 46.3; 42.1; 40.2; 35.9; 20.5. LC/MS: 439 ($[M + Na]^+$).

*(4*R*,6*R*)-6-(Benzyloxy)-4,5,6,7-tetrahydro-9,11-dimethoxy-4-methyl-2*H*-3-benzoxecin-2,8(1*H*)-dione* (**11**). The acid **10** (185 mg, 0.44 mmol) was dissolved in $CF_3COOH/(CF_3CO)_2O$ 4:1 (5 ml), and the soln. was stirred for 8 h at r.t. After completion of the reaction (TLC), the mixture was poured into an excess of $NaHCO_3$ soln., and extracted with Et_2O (3 × 25 ml). The combined extract was washed with H_2O, the org. phase dried and concentrated, and the residue purified by CC (AcOEt/hexane 2:8): **11** (70 mg, 40%). Reddish oil. $[\alpha]_D^{25} = -6.2$ ($c = 1.1$, $CHCl_3$). IR (neat): 2925, 1730, 1634, 1610, 1459, 1336, 1239, 1157, 1089. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.17 (*m*, 5 H); 6.37 (*d*, $J = 1.5$, 1 H); 6.21 (*d*, $J = 1.5$, 1 H); 4.91–4.81 (*m*, 1 H); 4.57 (*m*, 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*, $J = 6.5$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 204.59; 168.75; 161.33; 159.02; 138.24; 134.4; 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. HR-ESI-MS: 421.1620 ($[M + Na]^+$, $C_{23}H_{26}NaO_6^+$; calc. 421.1627).

*(4*R*,6*R*)-4,5,6,7-Tetrahydro-6-hydroxy-9,11-dimethoxy-4-methyl-2*H*-3-benzoxecin-2,8(1*H*)-dione* (**12**). To a suspension of 5% (Pd/C 15 mg) in AcOEt (5 ml) was added a soln. of **11** (45 mg, 0.11 mmol) in AcOEt (3 ml). The mixture was stirred at r.t. for 12 h under 4 atm of H_2 pressure. After completion of the reaction, the mixture was filtered and concentrated. The residue was purified by CC (silica gel, petroleum ether/AcOEt 8:2): **12** (31 mg, 91%). Colorless liquid. $[\alpha]_D^{20} = +13.6$ ($c = 1$, $CHCl_3$). IR (neat): 3345, 2945, 1740, 1620, 1456, 1378, 1125. ^{1}H-NMR (300 MHz, $CDCl_3$): 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); 3.51–3.4 (*d*, $J = 13.5$, 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*, $J = 6.4$, 3 H). LC/MS: 331 ($[M + Na]^+$).

Xestodecalactone C (= *(4*R*,6*R*)-4,5,6,7-Tetrahydro-6,9,11-trihydroxy-4-methyl-2*H*-3-benzoxecin-2,8(1*H*)-dione*; **IIb**). A mixture of I_2 crystals (0.29 g, 1.16 mmol) and Al powder (0.042 g, 1.56 mmol) was taken up in dry benzene (10 ml), refluxed for 1 h, and then cooled to r.t. To this soln., a mixture of $(Bu_4N)I$ (0.0018 g, 0.0050 mmol) and **12** (0.012 g, 0.038 mmol) in dry benzene (5 ml) was added. The resulting mixture was stirred for 45 min at 10°. After completion of the reaction (TLC), it was quenched with AcOEt (3 × 10 ml). The org. phase was washed with brine, dried, and concentrated and the residue purified by CC (AcOEt/hexane 1:1): **IIb** (0.0010 mg, 96%). White solid. M.p. 166–168°. $[\alpha]_D^{20} = +29$ ($c = 0.7$, MeOH). IR (KBr): 3345, 2923, 1739, 1630, 1601, 1461, 1370, 1165. ^{1}H-NMR (400 MHz, (D_6)DMSO): 9.92 (*s*, 1 H); 9.71 (*s*, 1 H); 6.27 (*d*, $J = 1.7$, 1 H); 6.10 (*s*, 1 H); 4.75 (*d*, $J = 4.0$, 1 H); 4.72 (*dd*, $J = 11.2$, 5.6, 1 H); 3.96 (br. *s*, 1 H); 3.80 (*d*, $J = 19.0$, 1 H); 3.48 (*d*, $J = 19.0$, 1 H); 3.08 (*dd*, $J = 14.8$, 10.4, 1 H); 2.81 (*d*, $J = 14.5$, 1 H); 1.83 (*d*, $J = 13.0$, 1 H); 1.63 (*dd*, $J = 14.8$, 11.2, 1 H); 1.08 (*d*, $J = 6.5$, 3 H). ^{13}C-NMR (75 NHz, (D_6)DMSO): 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. HR-MS: 303.0843 ($[M + Na]^+$, $C_{14}H_{16}NaO_6^+$; calc. 303.0839).

REFERENCES

[1] J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2004**, *21*, 1; D. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1; J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2005**, *22*, 15.

[2] R. A. Edrada, M. Heubes, G. Brauers, V. Wray, A. Berg, U. Gräfe, M. Wohlfarth, J. Mühlbacher, K. Schaumann, S. G. Bringmann, P. Proksch, *J. Nat. Prod.* **2002**, *65*, 1598.

[3] K. Kinoshita, T. Sasaki, M. Awata, M. Takada, S. Yaginuma, *J. Antibiot.* **1997**, *50*, 961.

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

[5] V. S. Bernan, M. Greenstein, W. M Maiese, *Adv. Appl. Microbiol.* **1997**, *43*, 57; W. Fenical, P. R. Jensen, *Annu. Rev. Microbiol.* **1994**, *48*, 559–584.
[6] G. Bringmann, G. Lang, M. Michel, M. Heubes, *Tetrahedron Lett.* **2004**, *45*, 2829; T. Yoshino, F. Ng, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 14185.
[7] Q. Liang, J. Zhang, W. Quan, Y. Sun, X. She, X. Pan, *J. Org. Chem.* **2007**, *72*, 2694.
[8] J. S. Yadav, N. Thrimurthulu, K. Umagayathri, B. V. Subba Reddy, A. R. Prasad, *Tetrahedron Lett*. **2008**, *49*, 6617.
[9] V. Suresh, J. J. P. Selvam, K. Rajesh, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2008**, *19*, 1509; V. Suresh, K. Rajesh, J. J. P. Selvam, Y. Venkateswarlu, *Tetrahedron Lett*. **2008**, *49*, 7358.
[10] G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467; G. E. Keck, D. Krishnamurthy, M. C. Grier, *J. Org. Chem.* **1993**, *58*, 6543; N. Gogoi, J. Boruwa, N. C. Barua, *Eur. J. Org. Chem.* **2006**, 1722.
[11] L. F. Felpin, J. Lebreton, *J. Org. Chem*. **2002**, *67*, 9192.
[12] R. E. Taylor, M. Jin, *Org. Lett*. **2003**, *5*, 4959; J. J. W. Duan, A. B. Smith, *J. Org. Chem.* **1993**, *58*, 3703; P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, K. K. Jernstedt, *J. Org. Chem*. **1982**, *47*, 4013.
[13] H. Makabe, L. K. Kong, M. Hirota, *Org. Lett*. **2003**, *5*, 27.
[14] P. M. Baker, B. W. Bycroft, J. C. Roberts, *J. Chem. Soc. C* **1967**, 1913.
[15] J. G. Millar, A. C. Oehlschlager, J. W. Wong, *J. Org. Chem*. **1983**, *48*, 4404.
[16] F. Bracher, B. Schulte, *Liebigs Ann. Recl.* **1997**, 1979.
[17] A. T. Kreipl, C. Reid, W. Steglich, *Org. Lett.* **2002**, *4*, 3287.

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