Stereoselective Total Synthesis of (11β)-11-Methoxycurvularin

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A simple and highly efficient stereoselective total synthesis of (11β)-11-methoxycurvularin (**5**), a polyketide natural product, was achieved. The synthesis commenced with a Cu-mediated regioselective opening of (2*S*)-2-methyloxirane (**6**) and comprised a *Keck* asymmetric allylation and intramolecular *Friedel–Crafts* acylation as key steps (*Scheme 2*).

Introduction. – Fungal macrolides, such as curvularins, have recently attracted attention due to their interesting biological activities [1]. These secondary metabolites were found to be inhibitors of HSP90 [2], a promising target for anticancer drug discovery [3]. The curvularins, *e.g.*, compounds **1**–**5**, are octaketides composed of a 12-membered macrolide skeleton fused to a 1,3-dihydroxybenzene moiety (*Fig.*). The (11α)-11-methoxycurvularin[1]) (**4**) and (11β)-11-methoxycurvularin[1]) (**5**) are members of the curvularin family isolated from the mycelium of the hybrid strain ME 005 derived from *Penicillium citreoviride* 4692 and 6200 [4]. They were shown to have considerable cytotoxicity toward a panel of four human-cancer cell lines (NCI-H460, MCF-7, SF-268, MIA, and Pa Ca-2) [5]. Also, they were shown to inhibit sea urchin embryogenesis by acting on components of the mitotic apparatus [6]. The potential biological importance as well as the unique structural feature of these molecules prompted by *She*, *Pan*, and co-workers to synthesize and determine the absolute configuration of (11α)-11-methoxycurvularin (**4**) and (11β)-11-methoxycurvularin (**5**), by a stereoselective pathway [7].

In continuation of our work on the synthesis of biologically active natural products [8], we report herein an efficient straightforward and practical total synthesis of (11β)-11-methoxycurvularin (**5**) starting from commercially available starting materials. Our planned approach to **5** involved an intramolecular *Friedel–Crafts* acylation of **12** resulting in the macrolide-ring formation, a catalytic asymmetric allylation and a regioselective Cu-mediated opening of oxirane **6** as key steps (*Scheme 1*).

Results and Discussion. – The synthesis of (11β)-11-methoxycurvularin (**5**) initiated (*Scheme 2*) from commercially available oxirane **6**, which was subjected to a CuCN-mediated regioselective nucleophilic opening [9] with allylmagnesium chloride to provide an alcohol in 87% yield which was protected as its ^{t}BuMe$_2$Si ether by reaction with ^{t}BuMe$_2$SiCl (*tert*-butyldimethylsilyl chloride) to obtain **7** (*Scheme 2*). Protected **7**, on selective hydroboration with 9-BBN-H (= 9-borabicyclo[3.3.1]nonane) in THF,

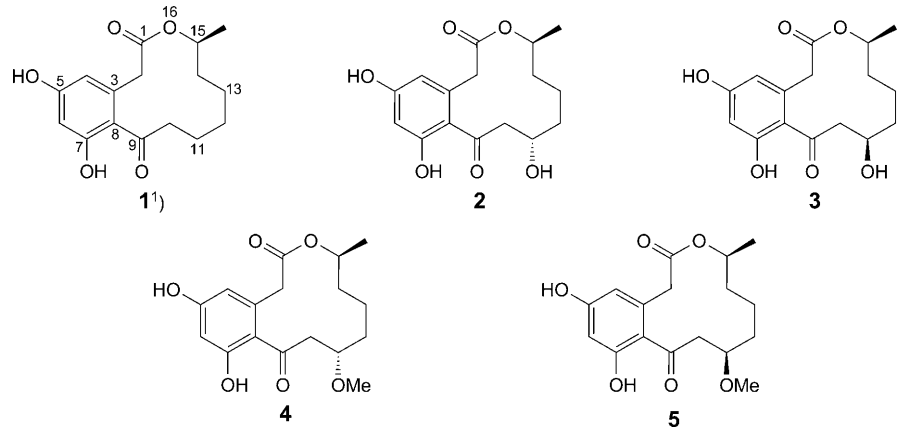
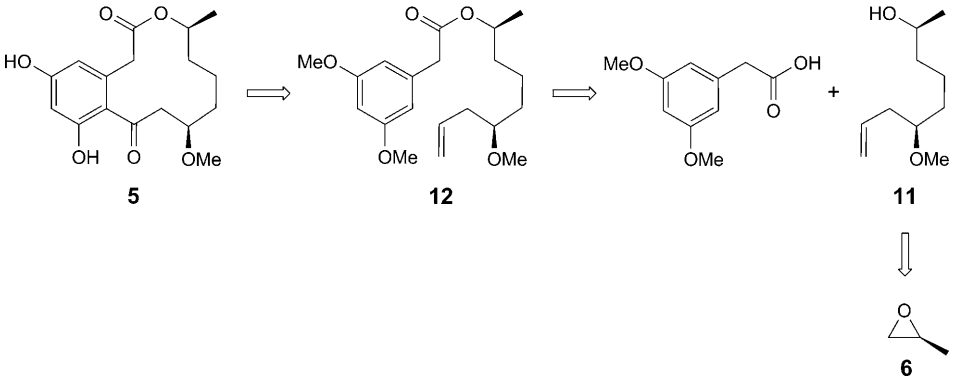


Figure. *Curvularin* (**1**), *(11α)-11-hydroxycurvularin* (**2**), *(11β)-11-hydroxycurvularin* (**3**), *(11α)-11-methoxycurvularin* (**4**), *and (1β)-11-methoxycurvularin* (**5**)[1])

Scheme 1. *Retrosynthetic Approach to (11β)-11-Methoxycurvularin* (**5**)

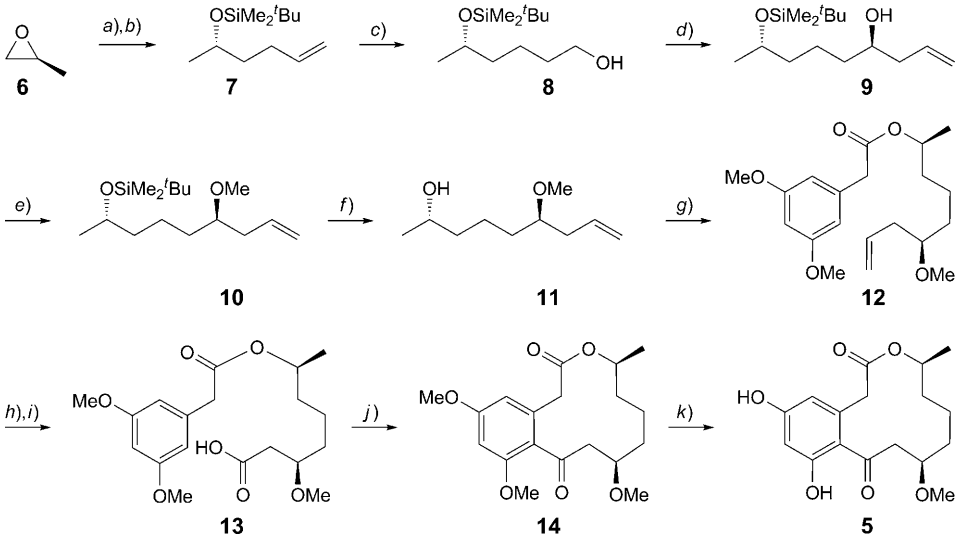


followed by treatment with NaOH and H_2O_2, gave alcohol **8** in 90% yield [10]. The primary-alcohol function in **8** was oxidized with IBX (2-iodoxybenzoic acid) in DMSO to afford the corresponding aldehyde which was subjected to catalytic asymmetric allylation with allyltributylstannane, a procedure developed by *Keck* and co-workers [11], to furnish the homoallylic alcohol **9** in 80% yield with an excellent diastereoselectivity of 95% de (as determined by ^{1}H-NMR analysis). The homoallylic alcohol **9**, on treatment with MeI/NaH, afforded methyl ether **10**. The ^{t}BuMe$_2$Si group in **10** was removed with 1M Bu_4NF in THF at room temperature to give **11** in 97% yield, which was esterified with 3,5-dimethoxybenzeneacetic acid in the presence of dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylpyridin-4-amine (DMAP) [12] to give ester **12** in 95% yield. Ozonolysis of the olefin moiety in **12** followed by further oxidation with $NaClO_2$ and NaH_2PO_4 gave the corresponding acid **13** in 90% yield. The desired

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

macrolide **14** was obtained in 41% yield by intramolecular *Friedel–Crafts* reaction of the carboxylic acid **13** with $CF_3COOH/(CF_3CO)_2O$ (at 25° for 8 h) [13]. Demethylation of **14** with freshly prepared AlI_3 at 10° for 45 min gave the target molecule **5** [14] in 96% yield.

Scheme 2



a) Allyl chloride, Mg, CuCN, THF, 0° to r.t., overnight. *b*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, CH_2Cl_2, 0°, 4 h; 98%. *c*) 9-BBN-H, THF, 40°, 4 h; NaOH, H_2O_2; 90%. *d*) 1. IBX, DMSO, CH_2Cl_2, 3 h; 90%; 2. (*R*)-BINOL (=(*R*)-[1,1′-binaphthalene]-2,2′-diol), 4-Å molecular sieves, Ti(O^{i}Pr)$_4$, allyltributylstannane, CH_2Cl_2, −78° to −20°; 80%. *e*) MeI, NaH, THF, r.t., 3 h; 85%. *f*) Bu_4NF, THF, r.t., 8 h; 97%. g) DCC, DMAP, Et_2O, r.t.; 95%. *h*) O_3, Ph_3P, CH_2Cl_2, −78°. *i*) $NaClO_2$, NaH_2PO_4; 90%. *j*) CF_3COOH, $(CF_3COO)_2O$, r.t., 8 h; 41%. *k*) AlI_3, Bu_4NI, benzene, 10°; 96%.

In conclusion, an efficient and straightforward total synthesis of (11β)-11-methoxycurvularin (**5**) was achieved by Cu-mediated regioselective oxirane opening, selective hydroboration, *Keck* asymmetric allylation, and *Friedel–Crafts* acylation as key reactions. The synthetic way of proceeding described here has a significant potential for the synthesis of a variety of other biologically important substituted 1,5-polyol-containing natural products.

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 used without further purification unless otherwise stated. The (2*S*)-2-methyloxirane (**6**) was purchased from *Aldrich*. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried (Na_2SO_4) and concentrated below 40°. Column chromatography (CC): silica gel (60–120 mesh; *Acme Synthetic Chemicals*). Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300*; at 25°. IR Spectra: *Perkin-Elmer-IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- (200 and 300 MHz) and ^{13}C-NMR (50 and 75 MHz) Spectra: *Varian-Gemini-*

FT-200 and *Bruker-Avance-300* instrument; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Agilent Technologies 1100* series instrument (*Agilent* ChemiStation software); in *m/z* (rel. %).

*(1,1-Dimethylethyl)dimethyl{[(1*S*)-1-methylpent-4-en-1-yl]oxy}silane* (**7**). To a suspension of Mg (0.74 g, 30.5 mmol) in dry THF (25 ml) at r.t. (condenser with cool-water circulation) allyl chloride (2.17 ml, 30.5 mmol) was added dropwise, followed by CuCN (68.5 mg, 0.76 mmol). The mixture was stirred for 0.5 h. Then, the mixture was cooled to 0°, optically pure (2*S*)-2-methyloxirane (**6**; 0.88 g, 15.2 mmol) in THF (3.3 ml) was added, and the mixture was warmed to r.t. and stirred overnight at r.t. The reaction was quenched with sat. NH_4Cl soln. (15 ml), the mixture extracted with AcOEt (3 × 10 ml), and the combined extract washed with brine (10 ml), dried (Na_2SO_4), and concentrated to yield the crude alcohol which was directly used for the next reaction without purification. To the crude alcohol in dry CH_2Cl_2, sequentially 1*H*-imidazole (2.258 g, 33.19 mmol) and ^{t}BuMe$_2$SiCl (2.27 g, 15.06 mmol) were added at r.t., and the mixture was stirred for 16 h. After completion of the reaction, the mixture was diluted with H_2O (5 ml) and extracted with CH_2Cl_2 (2 × 10 ml). The org. phase was washed with brine (1 × 5 ml), dried (Na_2SO_4), and concentrated and the crude product subjected to CC (AcOEt/hexane 1:9): **7** (2.74 g, 85% over the two steps). Clear liquid. $[\alpha]_D^{20} = +8.9$ ($c = 1.88$, $CHCl_3$). IR (neat): 2940*s*, 2860*m*, 1640*m*, 1254*m*, 1090*s*, 997*m*, 834*s*, 777*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.71–5.90 (*m*, 1 H); 4.90–5.07 (*m*, 2 H); 3.74–3.83 (*m*, 1 H); 2.05–2.20 (*m*, 2 H); 1.48–1.56 (*m*, 2 H); 1.1 (*d*, $J = 6.6$, 3 H); 0.8 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.4; 114.7; 71.24; 39.38; 30.6; 27.88; 25.86; 18.07; −4.41. LC-MS: 215 ($[M+1]^+$).

*(5*S*)-5-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}hexan-1-ol* (**8**). To a soln. of **7** (2.5 g, 11.68 mmol, 1 equiv.) in dry THF (100 ml) was added a soln. of 1M 9-BBN-H in THF (12.84 ml, 12.84 mmol, 1.1 equiv.), and the soln. was refluxed for 4 h. Then, the mixture was cooled to r.t., and 2M aq. NaOH (15 ml) was added, followed by 30% aq. H_2O_2 soln. (15 ml). The mixture was stirred for 12 h at r.t. After completion of the reaction, Et_2O (50 ml) was added, and the aq. layer further extracted with Et_2O (3 × 50 ml). The combined org. phase was dried (Na_2SO_4) and concentrated, and the crude material purified by CC (AcOEt/hexane 1:4): **8** (2.43 g, 90%). Colorless oil. $[\alpha]_D^{20} = +11.2$ ($c = 1.2$, $CHCl_3$). IR (neat): 3346*s*, 2933*s*, 2864*m*, 1465*m*, 1254*m*, 1102*m*, 837*m*, 775*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.72–3.8 (*m*, 1 H); 3.61 (*t*, 2 H); 1.99 (br. *s*, 1 H); 1.44–1.57 (*m*, 4 H); 1.25–1.41 (*m*, 2 H); 1.10 (*d*, $J = 6.8$, 3 H); 0.88 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 71.30; 63.1; 39.38; 31.6; 26.0; 25.86; 19.2; 18.07; −4.41. LC-MS: 233 ($[M+1]^+$).

*(4*R*,8*S*)-8-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}non-1-en-4-ol* (**9**). A soln. of IBX (4.43 g, 15.71 mmol) in dry DMSO was stirred for 30 min. Then, a soln. of **8** (2.43 g, 10.47 mmol) in CH_2Cl_2 (50 ml) was added at r.t., and the mixture was stirred for 5 h at r.t. After completion of the reaction, the mixture was filtered and the filtrate diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. phase was washed with brine (20 ml), dried (Na_2SO_4), and concentrated, and the crude aldehyde purified by CC (AcOEt/hexane 1:9) to give the aldehyde (2.2 g, 92%) as a colorless liquid which was directly used for the next reaction. A mixture of (*R*)-BINOL (0.27 g, 0.94 mmol) and Ti(O^{i}Pr)$_4$ (0.27 g, 0.95 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 (2.2 g, 9.56 mmol) in CH_2Cl_2 added, and the resulting mixture stirred for 10 min. The mixture was then cooled to −78°, allyltributylstannane (3.79 g, 11.45 mmol) was added, and the mixture was stirred for 36 h at −20°. After completion of the reaction, the reaction was quenched with sat. $NaHCO_3$ soln. (5 ml), and the mixture 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 (Na_2SO_4), and concentrated, and the residue purified by CC (AcOEt/hexane 2:8): **9** (2.08 g, 80%). Clear liquid. $[\alpha]_D^{20} = +2.3$ ($c = 1.88$, $CHCl_3$). IR (neat): 3440*s*, 2930*s*, 2857*m*, 1637*m*, 1463*m*, 1373*m*, 1252*m*, 1134*m*, 1042*m*, 999*m*, 912*w*, 834*m*, 772*s*, 661*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.81–5.71 (*m*, 1 H); 5.09–5.05 (*m*, 2 H); 3.78–3.70 (*m*, 1 H); 3.59–3.53 (*m*, 1 H); 2.26–2.20 (*m*, 1 H); 2.17–2.04 (*m*, 1 H); 1.49–1.12 (*m*, 6 H); 1.08 (*d*, $J = 6.59$, 3 H); 0.84 (*s*, 9 H); 0.08 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 134.83; 118.08; 70.53; 68.46; 41.9; 39.55; 36.76; 25.88; 23.72; 21.73; 18.13; −4.41. LC-MS: 273 ($[M+1]^+$).

*(1,1-Dimethylethyl){[(1*S*,5*R*)-5-methoxy-1-methyloct-7-en-1-yl]oxy}dimethylsilan* (**10**). To a stirred soln. of 60% NaH in oil suspension (0.55 g, 22.92 mmol) in dry THF (10 ml) was added slowly **9** (2.08 g, 7.64 mmol) in dry THF (20 ml), followed by MeI (1.19 g, 8.4 mmol). The mixture was stirred at r.t. for

4 h. After completion, the reaction was quenched with cold H_2O, and the mixture extracted with AcOEt (3×50 ml). The combined org. phase was washed with brine, dried (Na_2SO_4), and concentrated, and the crude material purified by CC (AcOEt/hexane 1:9): **10** (2.07 g, 95%). Colorless oil. $[\alpha]_D^{25} = +5.2$ ($c = 1.1$, $CHCl_3$). IR (neat): 2925*s*, 2856*s*, 1639*m*, 1461*m*, 1373*m*, 1252*m*, 1218*m*, 1099*m*, 911*w*, 834*m*, 772*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.88–5.74 (*m*, 1 H); 5.11–5.03 (*m*, 2 H); 3.8–3.74 (*m*, 1 H); 3.34 (*s*, 3 H); 3.24–3.16 (*m*, 1 H); 2.28–2.23 (*m*, 2 H); 1.5–1.25 (*m*, 6 H); 1.15 (*d*, $J = 6.59$, 3 H); 0.88 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 134.96; 116.86; 80.49; 68.52; 56.56; 39.94; 37.94; 33.61; 26.09; 23.96; 21.51; 18.26; −4.41. LC-MS: 287 ($[M+1]^+$).

(*2S,6R*)*-6-Methoxynon-8-en-2-ol* (**11**). To a cooled (0°) soln. of **10** (2.07 g, 7.23 mmol) in dry THF (8 ml), 1M Bu_4NF (7.23 mmol) in THF (7.2 ml), was added, and the mixture was stirred for 3 h at r.t. After completion, the reaction was quenched with H_2O (2 ml), and the mixture extracted with AcOEt ($2 \times$ 10 ml). The combined org. phase was dried (Na_2SO_4) and concentrated, and the crude material purified by CC (AcOEt/hexane 2:8): **11** (1.18 g, 95%). Viscous liquid. $[\alpha]_D^{20} = -0.2$ ($c = 1.88$, $CHCl_3$). IR (neat): 3445*s*, 2939*s*, 2840*m*, 1635*m*, 1463*m*, 1354*m*, 1243*m*, 1142*m*, 998*m*, 913*w*, 843*m*, 762*s*, 643*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.81–5.7 (*m*, 1 H); 5.06–5.0 (*m*, 2 H); 3.75–3.69 (*m*, 1 H); 3.31(*s*, 3 H); 3.2–3.14 (*m*, 1 H); 2.37 (br. *s*, 1 H); 2.29–2.17 (*m*, 2 H); 1.5–1.25 (*m*, 6 H); 1.15 (*d*, $J = 6.64$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 134.7; 116.82; 80.32; 67.82; 56.43; 39.21; 37.55; 33.19; 23.34; 21.35. LC-MS: 173 ($[M+1]^+$).

(1S,5R)-5-Methoxy-1-methyloct-7-en-1-yl 3,5-Dimethoxybenzeneacetate (**12**). To a stirred soln. of **11** (0.2 g, 1.16 mmol) in CH_2Cl_2 (10 ml) at 0° was added DCC (0.355 g, 1.74 mmol), followed by a cat. amount of DMAP. After 5 min, 3,5-dimethoxybenzeneacetic acid (0.25 g, 1.27 mmol) was added, and the mixture stirred for 17 h at r.t. H_2O (10 ml) was added, the mixture extracted with CH_2Cl_2 (20 ml), the org. layer washed successively with 10% aq. HCl soln., sat. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (AcOEt/hexane 1:10): **12** (0.386 g, 95%). $[\alpha]_D^{20} = -0.2$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2932*s*, 1729*s*, 1599*s*, 1462*m*, 1431*w*, 1293*w*, 1203*m*, 1154*s*, 1096*m*, 996*w*, 914*w*, 847*w*, 771*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.36 (*d*, $J = 2.54$, 2 H); 6.27 (*d*, $J = 2.54$, 1 H); 5.77–5.66 (*m*, 1 H); 5.02–4.98 (*m*, 2 H); 4.9–4.83 (*m*, 1 H); 3.73 (*s*, 6 H); 3.45 (*s*, 2 H); 3.26 (*s*, 3 H); 3.10–3.04 (*m*, 1 H); 2.2–2.0 (*m*, 2 H); 1.59–1.24 (*m*, 6 H); 1.19 (*d*, $J = 6.78$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.33; 160.73; 136.1; 134.74; 116.84; 107.05; 99.14; 80.12; 70.94; 56.39; 54.95; 42.01; 37.68; 35.96; 33.08; 21.0; 19.99. HR-ESI-MS: 373.1999 ($[M+Na]^+$, $C_{20}H_{30}NaO_5^+$; calc. 373.1990).

(1S,5R)-6-Carboxy-5-methoxy-1-methylhexyl 3,5-Dimethoxybenzeneacetate (**13**). Through a soln. of **12** (0.386 g, 1.1 mmol) in CH_2Cl_2 (2 ml) at −78°, ozone was bubbled. After completion of the reaction, the mixture was purged with N_2 to remove the excess of ozone and cooled to 0°. Then Ph_3P (0.57 g, 2.2 mmol) was added and the mixture stirred for 2 h. The mixture was concentrated. After adding hexane, the mixture was filtered through a *Celite* pad, the pad washed with hexane, and the filtrate concentrated to yield crude aldehyde which was subjected to the next step without further purification. To a stirred soln. of the crude aldehyde in *t*BuOH (1 ml) was added 2-methylbut-2-ene (0.5 ml) in *t*BuOH (0.5 ml). The mixture was cooled to 0° and treated with a soln. of $NaClO_2$ (0.086 g, 0.95 mmol) and NaH_2PO_4 (0.344 g, 2.87 mmol) in H_2O (1 ml). After 5 h, the mixture was diluted with brine (5 ml) and Et_2O (10 ml). The aq. phase was extracted with Et_2O, the combined org. phase washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (AcOEt/hexane 3:7): **13** (0.12 g, 90%). $[\alpha]_D^{20} = +14$ ($c = 0.8$, $CHCl_3$). IR (KBr): 2937*s*, 1729*s*, 1598*s*, 1461*m*, 1204*m*, 1205*s*, 1156*s*, 1065*w*, 835*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.43 (*s*, 2 H); 6.36 (*s*, 1 H); 4.91 (*dd*, $J = 12.3, 6.6$, 1 H); 3.77 (*s*, 6 H); 3.57 (*dd*, $J = 12.3, 5.7$, 1 H); 3.51 (*s*, 2 H); 3.33 (*s*, 3 H); 2.51 (*dd*, $J = 15.9, 6.9$, 1 H); 2.40 (*dd*, $J = 15.9, 4.8$, 1 H); 1.64–1.40 (*m*, 4 H); 1.35–1.25 (*m*, 2 H); 1.2 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 176.7; 171.0; 167.1; 160.7; 136.3; 107.2; 99.0; 77.4; 71.2; 56.8; 55.3; 42.0; 38.9; 35.7; 33.3; 20.8; 19.9. HR-ESI-MS: 391.1740 ($[M+Na]^+$, $C_{19}H_{28}NaO_7^+$; calc. 391.1732).

*(4S,8R)-4,5,6,7,8,9-Hexahydro-8,11,13-trimethoxy-4-methyl-2*H*-3-benzoxacyclododecin-2,10(1*H*)-dione* (**14**). Under N_2, **13** (80 mg, 0.22 mmol) was dissolved in CF_3COOH (6 ml) and $(CF_3CO)_2O$ (1 ml). The soln. was stirred overnight at r.t. and poured into an excess of $NaHCO_3$ soln. The mixture was extracted with Et_2O (3×5 ml), the extract dried (Na_2SO_4) and concentrated, and the residue purified by CC (hexanes/AcOEt 5:1): **14** (32 mg, 42%). Colorless oil. $[\alpha]_D^{20} = -9$ ($c = 0.7$, $CHCl_3$). IR (neat): 3385*w*, 2934*s*, 1724*s*, 1655*w*, 1603*s*, 1458*m*, 1313*m*, 1157*s*, 1084*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.49 (*s*, 1 H); 6.40

(*s*, 1 H); 6.25 (*d*, *J* = 15.6, 1 H); 4.88 (*t*, *J* = 6.3, 1 H); 3.83 (*s*, 2 H); 3.82 (*s*, 3 H); 3.73 (*s*, 3 H); 3.33 (*d*, *J* = 18.6, 3 H); 2.33 (*t*, *J* = 6.9, 1 H); 2.18 (*t*, *J* = 6.8, 1 H); 1.92 – 1.75 (*m*, 2 H); 1.53 – 1.38 (*m*, 4 H); 1.15 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 198.5; 170.5; 160.9; 157.5; 156.5; 133.2; 132.8; 122.5; 106.5; 97.8; 72.9; 55.8; 55.6; 55.4; 39.5; 34.2; 34.1; 24.4; 20.3. HR-MS-ESI: 373.1629 ($[M+Na]^+$, $C_{19}H_{26}NaO_6^+$; 373.1627).

*(4*S*,8*R*)-4,5,6,7,8,9-Hexahydro-11,13-dihydroxy-8-methoxy-4-methyl-2*H*-3-benzoxycyclododecin-2,10(1*H*)-dione* (**5**). To a soln. of I_2 (477 mg, 1.87 mmol) in dry benzene (4 ml) was added Al powder (67 mg, 2.51 mmol). The mixture was refluxed for 0.5 h and cooled to 10°. Then Bu_4NI (2 mg) and **14** (22 mg, 0.06 mmol) in dry benzene (2 ml) were added. The mixture was stirred for 15 min at 10° and quenched with 2M HCl at 0°. The mixture was then extracted with AcOEt (3 × 20 ml), the org. phase washed with $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 2 : 1): **5** (13.5 mg, 68%). Colorless oil. $[\alpha]_D^{20} = -6$ (*c* = 0.2 EtOH). IR (neat): 3402*s*, 2923*s*, 1959*m*, 1712*s*, 1655*w*, 1614*s*, 1461*m*, 1403*m*, 1270*m*, 1175*s*, 1083*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.98 (*s*, 1 H); 6.94 (*s*, 1 H); 6.34 (*d*, *J* = 2.4, 1 H); 5.97 (*d*, *J* = 2.4, 1 H); 5.13 (*t*, *J* = 6.0, 1 H); 3.95 (*d*, *J* = 15.9, 1 H); 3.78 (*d*, *J* = 14.1, 1 H); 3.59 (*d*, *J* = 16.5, 1 H); 3.33 (*d*, *J* = 5.2, 1 H); 3.25 (*s*, 3 H); 3.13 (*dd*, *J* = 14.1, 8.1, 1 H); 1.87 – 1.55 (*m*, 6 H); 1.25 (*d*, *J* = 5.2, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 204.3; 172.1; 159.6; 159.4; 135.6; 118.3; 113.2; 102.7; 75.7; 72.3; 54.2; 49.4; 40.2; 31.2; 30.5; 18.8; 17.9. HR-MS: 345.1312 ($[M+Na]^+$, $C_{17}H_{22}NaO_6^+$; calc. 345.1309).

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