A Convergent Approach to Dibenzodioxocinones: Synthesis of Racemic Penicillide

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A convergent approach to dibenzodioxocinones was explored, thereby racemic penicillide ((±)-**1a**) could be obtained in 13 steps in 4.2% overall yield, based on 5-amino-2-methylphenol (**5**) (*Schemes 2–4*).

Introduction. – Penicillide (=11-hydroxy-3-[(1*S*)-1-hydroxy-3-methylbutyl]-4-methoxy-9-methyl-5*H*,7*H*-dibenzo[*b*,*g*][1,5]dioxocin-5-one; **1a**; *Fig.*) is a metabolite produced by a filamentous fungus (*Penicillium* sp.), which was isolated and identified by *Sassa*, *Udagawa*, and co-workers [1][2]. Since then, a number of its derivatives, *i.e.*, **1**–**3** (see *Fig.*), have been isolated and demonstrated to possess versatile biological activities such as ACTC inhibitory activity, oxytocin antagonism, and antihypertensive potential [3–5]. Recently, the modified penicillide compound **4a** has been disclosed by a research group of *Bayer* company [6] as a potent inhibitor against cholesterol ester transfer protein (CETP), which is one potential target relative to coronary heart disease [7]. It is noteworthy that the drug discovery aiming at more potent CETP inhibitors mainly focused on derivatization of penicillide, which provided a preliminary structure–activity relationship (SAR). For example, the SAR of the alkyl side chain (R^1 in **4a**, *Fig.*) was rather steep, and only the neopentyl (=2,2-dimethylpropyl) group showed a slight improvement of activity. The derivatization of the phenolic OH group in the 'lower' aromatic ring (R^4 in **4a**) by etherification, esterification, or formation of a carbamate showed that an α-branched bicyclic aliphatic C=O residue was necessary to obtain an improved activity with a longer half-time; and the exploration of substitution at the 'lower' aromatic ring (R^2 and R^3 in **4a**) caused a substantial increase of the *in vitro* activity. Despite the above achievements, it remains desirable to get more extensive SARs of the penicillide skeleton. To this end, it is pre-required to explore a synthetic approach to the penicillide scaffold, particularly in a convergent manner. However, to the best of our knowledge, racemic or enantiomerically pure penicillide has not been synthesized so far. Herein, we report the first synthesis of racemic penicillide ((±)-**1a**) in the context of our preliminary program on CETP inhibitors.

Results and Discussion. – Our retrosynthetic route for (±)-penicillide ((±)-**1a**) is outlined in *Scheme 1*. According to the designed route, (±)-**1a** will be prepared from

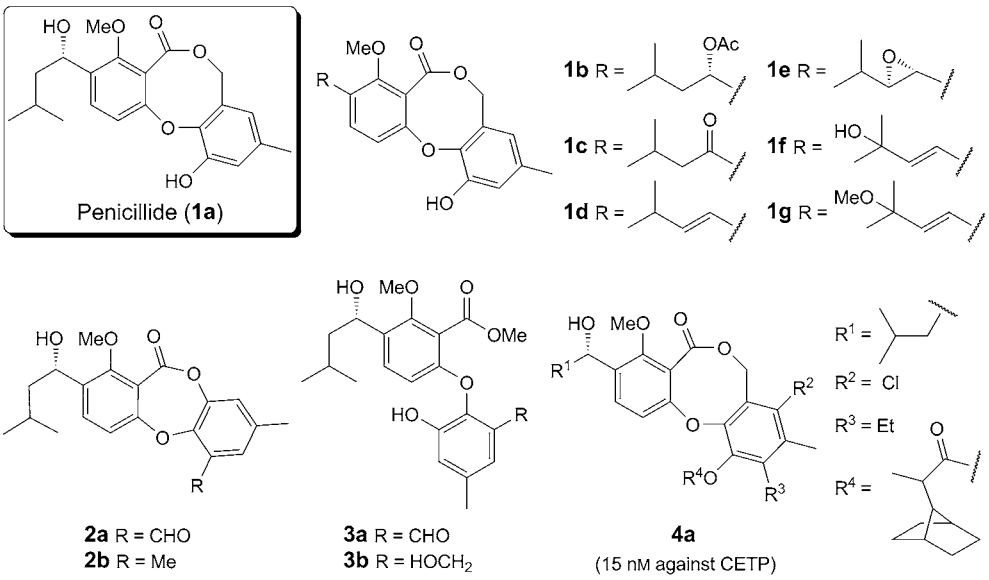
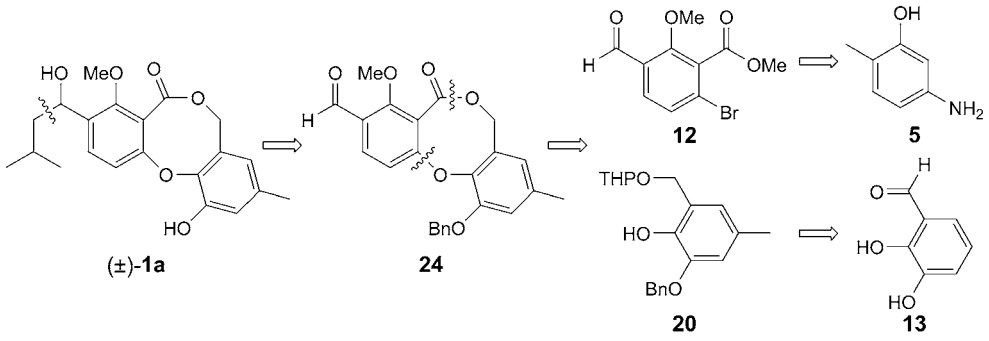


Figure. *Penicillide* (**1a**) *and natural products derived from* **1a**

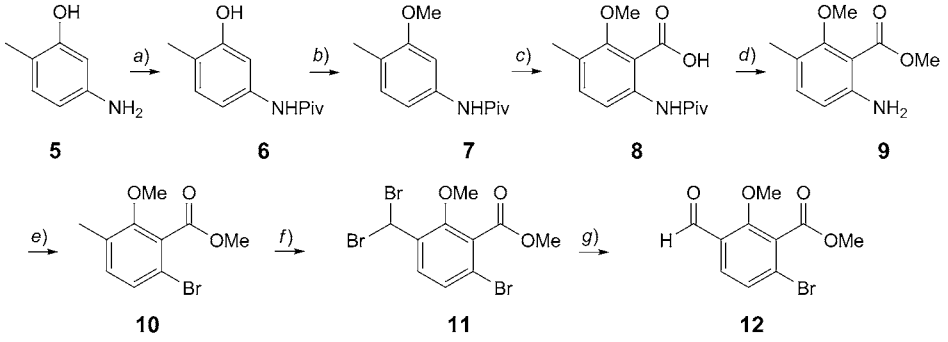
aldehyde **24** through nucleophilic addition of organometallics. Aldehyde **24** could be constructed from aryl bromide **12** and the corresponding phenol **20** in a convergent manner, which could be accomplished by an *Ullmann* coupling reaction and lactonization. In turn, **12** and **20** could be obtained from the commercially available starting materials **5** and **13**, respectively through multistep functional-group transformation. By this approach, not only (±)-penicillide ((±)-**1a**) might be obtained but also structural modifications of the parent (±)-penicillide might be conveniently achieved, thus allowing to perform subsequently structure–activity-relationship studies.

Scheme 1. *Restrosynthetic Route for (±)-Penicillide* ((±)-**1a**)



Thus, the commercially available 5-amino-2-methylphenol (**5**) was first selectively protected with the pivaloyl (=2,2-dimethylpropanyl) group (→**6**), followed by methylation of the phenolic OH group to give compound **7** in a two-step yield of 91% (*Scheme 2*). Then, **7** was regio-selectively lithiated with BuLi at −20°, and subsequently CO_2 gas was bubbled through the solution to give the carboxylic acid **8** in 90% yield. *Via* esterification and deprotection, compound **8** was converted into **9** in a one-pot reaction in 80% yield. By the *Sandmeyer* reaction, the NH_2 group of **9** was successfully replaced by a Br-atom (→**10**, 79% yield), and subsquent treatment with *N*-bromosuccinimide (NBS) (→**11**) followed by hydrolysis with H_2SO_4 provided the target intermediate **12** in a yield of 86%.

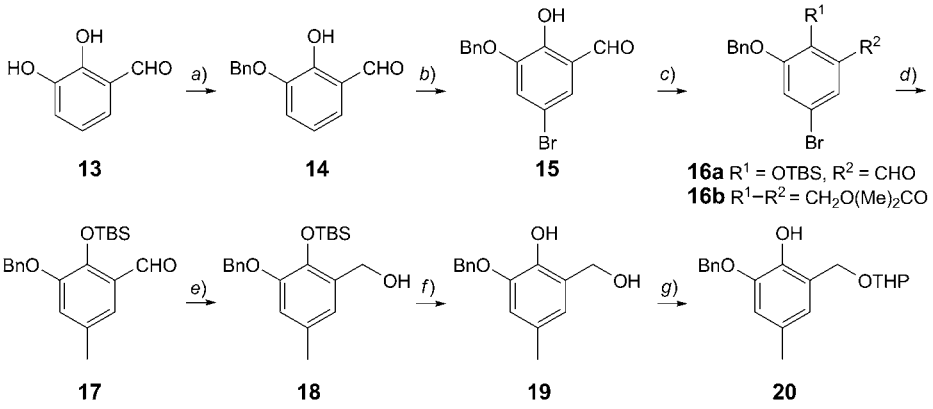
Scheme 2. *Preparation of Intermediate* **12** (Piv = Me_3CCO)



a) 2,2-Dimethylpropanoyl chloride (PivCl), $NaHCO_3$, AcOEt/H_2O, r.t., 1 h; 97%. *b*) MeI, K_2CO_3, DMF, r.t., 4 h; 94%. *c*) BuLi, THF, −20°, 2 h; CO_2 (gas), 2 h; 90%. *d*) $(MeO)_3CH$, H_2SO_4 (conc.), MeOH, reflux, 3 d; 80%. *e*) $NaNO_2$, aq. HBr soln., −20°, 1 h; CuBr, aq. HBr soln., r.t., until no gas evolved; 80°, overnight; 79%. *f*) *N*-Bromosuccinimide (NBS), 2,2′-azobis[2-propanenitrile] (AIBN; cat.), CCl_4, reflux, 12 h; 94%. *g*) H_2SO_4 (aq.), r.t., 1 h; 92%.

On the other hand, starting from commercially available 2,3-dihydroxybenzaldehyde (**13**), the OH group at C(3) was at first selectively benzylated with benzyl bromide in the presence of NaH (2.0 equiv.) to obtain compound **14** in 73% yield according to the known method [8] (*Scheme 3*). Subsequent bromination with NBS in the presence of $AcONH_4$ in MeCN at room temperature for 4 h, according to the method of *Das* and co-workers [9], gave the bromo derivative **15** in 85% yield. Then, the OH group of **15** was protected with the ^{t}BuMe$_2$Si group to afford compound **16a** in 95% yield. Treatment of **16a** with Me_2Zn in the presence of [Pd(dppf)Cl_2] (dppf = [1,1′-bis(diphenylphosphino-κ*P*)ferrocene] in refluxing anhydrous dioxane for 1 h afforded the coupling product **17** in 82% yield *via Negishi* reaction [10]. Notably, under the same coupling conditions, the corresponding Me coupling product could not be obtained in reasonable yields from either **15** or **16b** (**16b** was derived from **15** in two steps). Then, aldehyde **17** was reduced to the benzyl alcohol **18** in 91% yield with $NaBH_4$ in MeOH at room temperature for 4 h. After removal of the ^{t}BuMe$_2$Si group of **18** with $Bu_4NF \cdot x$ H_2O in THF (→**19**) and protection of the benzylic OH group with 3,4-dihydro-2*H*-pyran in the presence of TsOH, the target intermediate **20** was obtained in 79% yield over two steps.

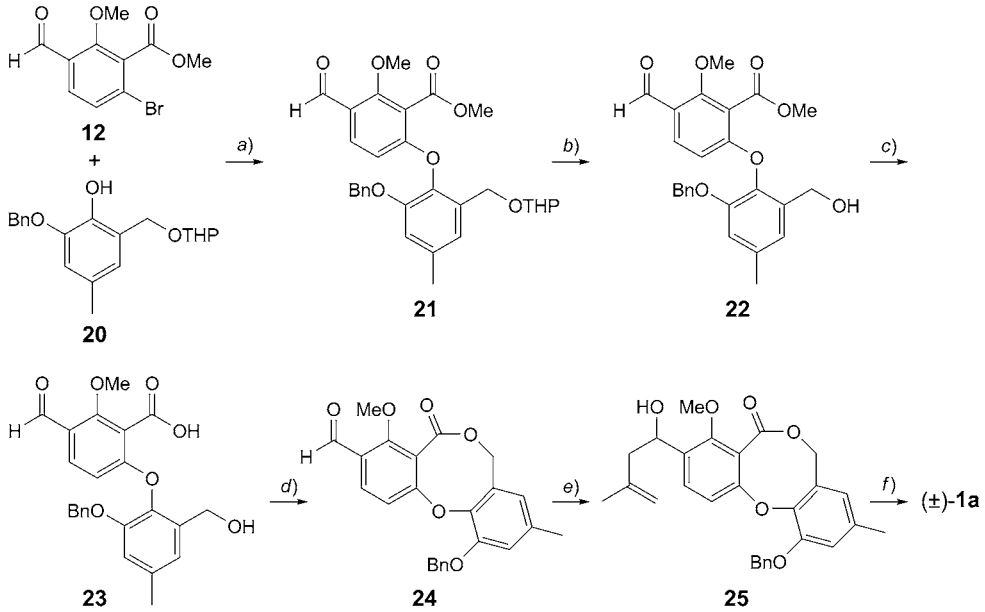
Scheme 3. *Preparation for Intermediate* **20**



a) NaH (2.0 equiv.), r.t., 1 h; BnBr/THF, r.t., 4 h; 73%. *b*) NBS, $AcONH_4$, MeCN, r.t., 4 h, 85%. *c*) $^tBuMe_2 \cdot SiCl$, $(^iPr)_2NEt$, DMF, r.t., 1 h; 95%. *d*) Me_2Zn, [1,1′-bis(diphenylphosphino-κP)ferrocene]dichloropalladium ([Pd(dppf)Cl_2]; cat.), 1,4-dioxane, reflux, 1 h; 82%. *e*) $NaBH_4$, MeOH, r.t., 4 h; 91%. *f*) $Bu_4NF \cdot x\ H_2O$, THF, r.t., 30 min; 94%. *g*) 3,4-Dihydro-2*H*-pyran, $TsOH \cdot H_2O$ (cat.), CH_2Cl_2, 0°, 1 h; 84%.

With **12** and **20** in hand, we performed the *Ullmann* coupling reaction (*Scheme 4*). After having tested several typical coupling conditions including Cu_2O/Pyridine [11], CuI/Me_2CHCO_2H/Cs_2CO_3/DMF [12], and CuBr/$^tBuCOCH_2CO^tBu$/Cs_2CO_3/1-methylpyrrolidin-2-one (NMP) [13], we could not get satisfying results. Fortunately, the coupling product **21** could be obtained in 60% yield in the presence of activated Cu powder and copper oxide black in refluxing MeCN after 12 h [14]. Then, removal of the terahydro-2*H*-pyran-2-yl (THP) group in **21** under acidic conditions led to **22** in 93% yield. The formyl group of **22** was protected as its dimethyl acetal by treatment with MeOH in the presence of a catalytic amount of $TsOH \cdot H_2O$; then the ester group in the resulting dimethyl acetal was saponified with KOH in refluxing MeOH for 12 h, to give acid **23** in 98% overall yield. Tremendous efforts to achieve the lactonization of **23** failed to give **24** in acceptable yields, such as $TsOH \cdot H_2O$-catalyzed lactonization, intramolecular *Mitsunobu* reaction and *Yamagushi* reaction. Fortunately, the problem could be solved by treatment of **23** in the presence of Et_3N with *Mukaiyama*'s reagent [15] in refluxing MeCN for 12 h, affording the desired lactone **24** in a satisfactory yield of 51% based on **22**. Attempts to obtain (±)-**1a** from **24** by a direct nucleophilic addition of 2-methylpropyl *Grignard* reagent or (2-methylpropyl)lithium to the formyl group were unsuccessful, resulting mainly in the corresponding benzyl alcohol due to reduction of the formyl group. Therefore, an indirect approach was adopted instead, and nucleophilic addition of a 2-methylprop-2-en-1-yl *Grignard* reagent to the formyl group of **24** was performed in anhydrous THF at $-10°$ for 1 h, giving **25** in 82% yield. Finally, hydrogenation of **25** was carefully performed with H_2 gas in the presence of 10% Pd/C in AcOEt/MeOH at room temperature for 3 h which saturated the C=C bond and removed the protective benzyl group, resulting in (±)-**1a** with a yield of 65%.

Scheme 4. *Synthesis of* (±)-**1a**



a) Cu, CuO, *N*,*N*-dimethylpyridin-4-amine (DMAP), MeCN, reflux, 12 h; 60%. *b*) $TsOH \cdot H_2O$, ^{i}PrOH/H_2O, reflux, 12 h; 93%. *c*) $TsOH \cdot H_2O$, MeOH, 1 h; KOH, reflux, 12 h. *d*) Et_3N, 2-chloro-1-methylpyridinium iodide (*Mukaiyama*'s reagent), MeCN, reflux; 51% over two steps. *e*) (2-Methylprop-2-en-1-yl)magnesium chloride (0.5M in THF), THF, $-10°$, 1 h; 82%. *f*) 10% Pd/C, H_2 (1 atm), MeOH/AcOEt, r.t., 3 h; 65%.

Conclusions. – In summary, we have developed a convergent approach to dibenzodioxocinones, by which racemic penicillide ((±)-**1a**) was synthesized through 13 steps in 4.2% overall yield based on 5-amino-2-methylphenol (**5**). The asymmetric syntheses of penicillide and derivatives thereof are under way.

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Experimental Part

General. Solvents were distilled from the appropriate drying agents before use. All the reagents were purchased from *Acros*, *Alfa Aesar*, and *National Chemical Reagents Group Co., Ltd.*, P. R. China. Column chromatography (CC): commercial silica gel (SiO_2, 300–400 mesh; *Qingdao Haiyang Chemical Group Co.*). TLC: TLC plates GF_{254} (*Yantai Jiangyou Silica R&D Co., Ltd.*, P. R. China), detection under UV light or with I_2. ^{1}H- and ^{13}C-NMR Spectra: *Varian-Mercury-Plus* spectrometer; at 300 or 400 (^{1}H) and 100 MHz (^{13}C); δ in ppm, with residual $CHCl_3$ (δ(H) 7.26; δ(C) 77.0) as internal standard, *J* in Hz. EI-, ESI-, HR-APCI-, and HR-ESI-MS: *Finnigan-Mat-95* mass spectrometer(APCI = atmospheric-pressure chemical ionization); in *m*/*z*.

N-*(3-Hydroxy-4-methylphenyl)-2,2-dimethylpropanamide* (**6**). To a heterogeneous mixture of 5-amino-2-methylphenol (**5**; 1.00 g, 8.13 mmol), Na_2CO_3 (2.05 g, 24.4 mmol), AcOEt (28 ml), and H_2O

(33 ml) was added 2,2-dimethylpropanoyl chloride (1.05 ml, 8.54 mmol). The two-phased system was stirred for 1 h. Then the org. phase was washed with 1N HCl (30 ml), dried (Na_2SO_4), and concentrated. Crystallization of the residue afforded **6** (1.84 g, 97%). TLC (petroleum ether/AcOEt 2:1): R_f 0.75. ^{1}H-NMR ($CDCl_3$, 400 MHz): 8.57 (*s*, 1 H); 7.89 (*s*, 1 H); 7.38 (*s*, 1 H); 6.99 (*d*, $J = 7.8$, 1 H); 6.39 (*d*, $J = 7.8$, 1 H); 2.19 (*s*, 3 H); 1.32 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 177.6; 155.6; 136.0; 130.3; 121.0; 110.2; 107.4; 39.6; 27.5 (3 C); 15.6. ESI-MS: 208.0 ($[M+H]^+$). HR-APCI-MS: 208.1349 ($[M+H]^+$, $C_{12}H_{18}NO_2^+$; calc.208.1338).

N-*(3-Methoxy-4-methylphenyl)-2,2-dimethylpropanamide* (**7**). A stirred soln. of **6** (1.00g, 4.83 mmol) and K_2CO_3 (1.67 g, 12.1 mmol) in DMF (10 ml) was treated at r.t. with MeI (0.36 ml, 5.8 mmol) in small portions. The mixture was stirred at r.t. for 4 h, then dil. with H_2O (10 ml) and extracted with AcOEt (3×20 ml). The combined extracts was washed with H_2O (2×50 ml), dried ($MgSO_4$), and concentrated, and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 1:6): **7** (1.00 g, 94%). TLC (petroleum ether/AcOEt 4:1): R_f 0.69. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.49 (*s*, 1 H); 7.27 (br. *s*, 1 H); 7.03 (*d*, $J = 8.1$, 1 H); 6.71 (*dd*, $J = 1.5$, 7.8, 1 H); 3.84 (*s*, 3 H); 2.17 (*s*, 3 H); 1.32 (*s*, 9 H). ESI-MS: 222.2 ($[M+H]^+$).

6-[(2,2-Dimethyl-1-oxopropyl)amino]-2-methoxy-3-methylbenzoic Acid (**8**). To a soln. of **7** (0.50 g, 2.26 mmol) in dry THF (10 ml) at $-20°$ was added dropwise 1.6M Buli in hexane (4.5 ml, 7.24 mmol), and the mixture was stirred for 2 h. Then CO_2 was bubbled continuously through the mixture for an additional 2 h. To the resulting yellow soln. was added H_2O (30 ml). The mixture was extracted with AcOEt (20 ml) and the aq. phase acidified with HCl to pH 1. The aq. phase was extracted with AcOEt (4×30 ml) and the combined the org. extract washed with brine, dried (Na_2SO_4), and concentrated: crude **8** (0.54 g, 90%). Red oil which was used for the next step without further purification. TLC (petroleum ether/AcOEt 4:1): R_f 0.24. ^{1}H-NMR ($CDCl_3$, 300 MHz): 11.72 (*s*, 1 H); 8.63 (*d*, $J = 8.7$, 1 H); 7.40 (*d*, $J = 8.4$, 1 H); 3.92 (*s*, 3 H); 2.32 (*s*, 3 H); 1.34 (*s*, 9 H). EI-MS: 265 (M^+).

Methyl 6-Amino-2-methoxy-3-methylbenzoate (**9**). To a soln. of **8** (12.6 g, 47.6 mmol) in MeOH (50 ml), conc. H_2SO_4 soln. (5.7 ml), and trimethoxymethane (5.7 ml, 52.4 mmol) were added dropwise, and the mixture was refluxed for 3 d. Then the mixture was cooled and 1N HCl added. After dilution with CH_2Cl_2 (30 ml), the pH of the aq. phase was adjusted to pH 13 by adding 3N NaOH. Then the aq. phase was, extracted with CH_2Cl_2 (3×50 ml) and the combined extract dried ($MgSO_4$) and concentrated; crude **9** (7.41 g, 80%) which was used for the next step without further purification. TLC (petroleum ether/AcOEt 3:1): R_f 0.64. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.03 (*d*, $J = 8.4$, 1 H); 6.40 (*d*, $J = 8.7$, 1 H); 5.01 (br. *s*, 2 H); 3.93 (*s*, 3 H); 3.74 (*s*, 3 H); 2.16 (*s*, 3 H). ESI-MS: 196.1 ($[M+H]^+$).

Methyl 6-Bromo-2-methoxy-3-methylbenzoate (**10**) [16]. To a soln. of **9** (7.41 g, 38 mmol) in 80 ml H_2O, aq. HBr soln. (21 ml) was added. The resulting mixture was cooled to $-20°$ and a soln. of $NaNO_2$ (2.86 g, 41.4 mmol) in H_2O was added dropwise. The mixture was stirred for 1 h, and then a soln. of CuBr (7.77 g, 54.3 mmol) in aq. HBr soln. (10 ml), was added dropwise. The resulting mixture was stirred until no gas was generated. Then the mixture was stirred at 80° overnight. After cooling and extraction with CH_2Cl_2 (3×100 ml), the combined org. extract was washed with sat. Na_2CO_3 soln. and brine, dried (Na_2SO_4), and concentrated and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 1:100): **10** (7.76 g, 79%). Green oil which was used for the next step without further purification. TLC (petrolium ether/AcOEt 20:1): R_f 0.62. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.23 (*d*, $J = 8.4$, 1 H); 7.09 (*d*, $J = 8.1$, 1 H); 3.96 (*s*, 3 H); 3.79 (*s*, 3 H); 2.26 (*s*, 3 H). ESI-MS: 259.0, 261.1 ($[M+H]^+$).

Methyl 6-Bromo-3-(dibromomethyl)-2-methoxybenzoate (**11**). To a flame-dried flask was added NBS (0.50 g, 2.81 mmol), AIBN (0.028 g, 0.18 mmol), and a soln. of **10** (0.228 g, 0.88 mmol) in CCl_4 (10 ml), and the suspension was refluxed in the dark. After 12 h, the mixture was cooled to r.t. and concentrated. The residue was subjected to CC (SiO_2, AcOEt/petroleum ether 1:100): pure **11** (0.344 g, 94%). TLC (petroleum ether/AcOEt 50:1): R_f 0.38. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.82 (*d*, $J = 8.4$, 1 H); 7.45 (*d*, $J = 8.4$, 1 H); 6.97 (*s*, 1 H), 3.98 (*s*, 3 H); 3.92 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 165.9; 151.7; 135.1; 132.6; 130.2; 129.3; 121.3; 63.2; 53.0; 32.5. EI-MS: 415, 417 (M^+).

Methyl 6-Bromo-3-formyl-2-methoxybenzoate (**12**) [16]. To a flame-dried flask was added **11** (0.344 g, 0.83 mmol) and conc. H_2SO_4 soln. (5 ml). The mixture was stirred at r.t. for 1 h (TLC monitoring) and then poured into ice water with stirring. The mixture was extracted with AcOEt ($3 \times$ 10 ml), the extract washed with Na_2CO_3 soln. and H_2O, dried (Na_2SO_4), and concentrated, and the

residue subjected to CC (SiO_2/AcOEt/petroleum ether 1:40): **12** (208 mg, 92%). TLC (petroleum ether/AcOEt 50:1): R_f 0.17. ^{1}H-NMR ($CDCl_3$, 300 MHz): 10.30 (*s*, $J = 8.4$, 1 H); 7.76 (*d*, $J = 7.2$, 1 H); 7.47 (*d*, $J = 7.2$, 1 H); 3.99 (*s*, 3 H); 3.98 (*s*, 3 H); data well in accordance with those of [16]. ESI-MS: 272.9, 274.9 ($[M+H]^+$).

3-(Benzyloxy)-2-hydroxybenzaldehyde (**14**). To a suspension of 60% NaH (5.8 g, 144 mmol) in dry THF (150 ml), a soln. of **13** (10.0 g, 72 mmol) in dry THF was added in dropwise under stirring. The suspension was stirred at r.t. for 1 h. Then benzyl bromide (12.3 g, 72 mmol) was added dropwise at 25° and stirring continued for 24 h. After addition of H_2O (300 ml), the mixture was acidified with HCl until the pH of the aq. layer was 2 and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phase was washed with 1N HCl, dried ($MgSO_4$), and concentrated and the residue subjected to CC (short SiO_2 column, AcOEt/petroleum ether 1:20) to give the crude product, which was purified by recrystallization from EtOH: **14** (10.7g, 65%). TLC (petroleum ether/AcOEt 10:1): R_f 0.42. ^{1}H-NMR ($CDCl_3$, 300 MHz): 11.12 (*s*, 1 H); 9.92 (*s*, 1 H); 7.47–7.32 (*m*, 5 H); 7.20 (*dd*, $J = 7.8$, 1.4, 1 H); 7.13 (*dd*, $J = 7.8$, 1.4, 1 H); 6.90 (*t*, $J = 7.8$, 1 H); 5.20 (*s*, 2 H); data well in accordance with those of [8b]. ESI-MS: 229.1 ($[M+H]^+$)

3-(Benzyloxy)-5-bromo-2-hydroxybenzaldehyde (**15**). To a soln. of **14** (4.00 g, 17.5 mmol) in MeCN (90 ml), $AcONH_4$ (137 mg, 1.75 mmol) and NBS (3.28 g, 18.4 mmol) were added. The mixture was stirred for 4 h at r.t. and then concentrated. H_2O (100 ml) was added to the residue, the mixture extracted with AcOEt (3 × 30ml), the combined org. extract dried ($MgSO_4$) and concentrated, and the residue subjected to CC (SiO_2 AcOEt/petroleum ether 1:20): **15** (4.59 g, 85%). TLC (petroleum ether/CH_2Cl_2 2:1): R_f 0.35. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.96 (*s*, 1 H); 9.86 (*s*, 1 H); 7.46–7.35 (*m*, 5 H); 7.33 (*d*, $J = 2$, 1 H); 7.23 (*d*, $J = 2$, 1 H); 5.16 (*s*, 2 H); data well in accordance with those of [17]. ESI-MS: 329.0, 331.1 ($[M+Na]^+$).

*3-(Benzyloxy)-5-bromo-2-{[(*tert*-butyl)dimethylsilyl]oxy}benzaldehyde* (**16a**). To a soln. of **15** (307 mg, 1 mmol) in DMF (1 ml), *N*,*N*-diisopropylethylamine (0.35 ml, 2 mmol) was added and the mixture stirred for 10 min at r.t. Then ^{t}BuMe$_2$Si (301 mg, 2 mmol) was added and the mixture stirred for 1 h at r.t. The reaction was quenched with H_2O (50 ml), the mixture extracted with AcOEt (3 × 50 ml), the combined org. extract washed with H_2O and brine, dried ($MgSO_4$), and concentrated, and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 1:100): **16** (401 mg, 95%). TLC (petroleum ether/AcOEt 15:1): R_f 0.78. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.40 (*s*, 1 H); 7.52 (*d*, $J = 2.4$, 1 H); 7.42–7.41 (*m*, 5 H); 7.21 (*d*, $J = 2.4$, 1 H); 5.03 (*s*, 2 H); 0.92 (*s*, 9 H); 0.07 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 188.7; 151.3; 148.5; 135.0; 128.9; 128.7 (2 C); 128.4 (2 C); 121.9; 121.1; 113.7; 71.4; 25.7 (3 C); 18.7; −4.3 (2 C). ESI-MS: 421.1, 423.1($[M+H]^+$).

*3-(Benzyloxy)-2-{[(*tert*-butyl)dimethylsilyl]oxy}-5-methylbenzaldehyde* (**17**). To a flame-dried flask was added **16** (2.21 g, 5.24 mmol), [Pd(dppf)Cl_2] (58 mg, 0.08 mmol), 1.2M dimethylzinc in toluene (5.2 ml, 6.29 mmol) and dry 1,4-dioxane (15 ml), and the suspension was heated at 110° for 1 h. After cooling, the mixture was quenched with 1N HCl (50 ml) and extracted with AcOEt (2 × 50 ml), the extract washed with H_2O and brine, dried ($MgSO_4$), and concentrated, and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 1:40): **17** (1.53 g, 82%). TLC (petroleum ether/AcOEt 15:1): R_f 0.57. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.46 (*s*, 1 H); 7.44–7.35 (*m*, 5 H); 7.21 (*d*, 1 H); 6.94 (*d*, 1 H); 5.05 (*s*, 2 H); 2.28 (*s*, 3 H); 0.94 (*s*, 9 H); 0.08 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 190.5; 150.1; 147.2; 136.0; 130.9; 128.6 (2 C); 128.3; 128.2 (2 C); 127.7; 119.7; 119.2; 71.0; 25.8 (3 C); 21.0; 18.8; −4.3 (2 C). ESI-MS: 357.2 ($[M+H]^+$).

*(3-(Benzyloxy)-2-{[(*tert*-butyl)dimethylsilyl]oxy}-5-methylbenzene)methanol* (**18**). $NaBH_4$ (378 mg, 10.0 mmol) was added in portions to a stirred soln. of **17** (891 mg, 2.5 mmol) in MeOH (200 ml) at 0°. The resulting mixture was stirred for 4 h at r.t. and then concentrated. The residue was dissolved in 3N HCl (50ml), the soln. extracted with CH_2Cl_2 (3 × 20 ml), and the combined CH_2Cl_2 ectract washed with H_2O (3 × 50 ml), dried (Na_2SO_4), and concentrated: **18** (812 mg, 91%). TLC (petroleum ether/AcOEt 10:1): R_f 0.41. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.42–7.30 (*m*, 5 H); 6.75 (*s*, 1 H); 6.68 (*s*, 1 H); 5.02 (*s*, 2 H); 4.67 (*s*, 2 H); 2.26 (*s*, 3 H); 2.23 (*s*, 1 H); 0.94 (*s*, 9 H); 0.06 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 148.9; 140.1; 136.5; 132.0; 130.7; 128.4 (2 C); 128.2 (2 C); 128.0; 121.0; 113.1; 70.6; 61.7; 25.9 (3 C); 21.0; 18.6; −4.0 (2 C). ESI-MS: 381.2 ($[M+Na]^+$).

3-(Benzyloxy)-2-(hydroxy)-5-methylbenzenemethanol (**19**). To a cold (0°) soln. of **18** (323 mg, 0.90 mmol) in dry THF (9 ml), $Bu_4NF \cdot x\ H_2O$ (471 mg, 1.8 mmol) added, the mixture was stirred for 0.5 h at r.t. H_2O (20 ml) was added, the mixture was extracted with AcOEt (3 × 20 ml), the combined org. extract washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2, AcOEt/petroleum ether 1:4): **19** (206 mg, 94%). TLC (petroleum ether/AcOEt 3:1): R_f 0.26. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.43–7.37 (*m*, 5 H); 6.73 (*s*, 1 H); 6.70 (*s*, 1 H); 5.91 (*s*, 1 H); 5.09 (*s*, 2 H); 4.70 (*s*, 2 H); 2.36 (*s*, 1 H); 2.28 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 145.4; 141.5; 136.3; 129.2; 128.7 (2 C); 128.3; 127.8 (2 C); 126.3; 121.5; 112.6; 71.1; 61.8; 21.0. ESI-MS: 267.1 ($[M+Na]^+$).

*2-(Benzyloxy)-4-methyl-6-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenol* (**20**). To a cold (−20°) soln. of **19** (0.892 g, 3.66 mmol) in dry CH_2Cl_2 (20 ml), $TsOH \cdot H_2O$ (0.07g, 0.37 mmol) was added, and the mixture was stirred at −20° for 15 min. Then 3,4-dihydro-2*H*-pyran (0.35 ml, 3.84 mmol) was added dropwise and the soln. stirred for 1 h. The reaction was quenched with Et_3N (1 ml), the mixture washed with brine and dried ($MgSO_4$), the solvent evaporated, and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 1:20) **20** (1.01 g, 84%). TLC (petroleum ether/AcOEt 4:1): R_f 0.67. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.44–7.34 (*m*, 5 H); 6.74 (*s*, 1 H); 6.71 (*s*, 1 H); 6.23 (*s*, 1 H); 5.08 (*s*, 2 H); 4.82 (*d*, *J* = 12, 1 H); 4.75 (*t*, *J* = 3.3, 1 H); 4.58 (*d*, *J* = 12, 1 H); 3.97 (*m*, 1 H); 3.57 (*m*, 1 H); 2.26 (*s*, 3 H); 1.88–1.53 (*m*, 6 H). ESI-MS: 351.1 ($[M+Na]^+$).

*Methyl 6-[2-(Benzyloxy)-4-methyl-6-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenoxy}-3-formyl-2-methoxybenzoate* (**21**). To a flame-dried flask was added **12** (1.11 g, 4.08 mmol), **20** (1.61 g, 4.89 mmol), activated Cu powder (0.653 g, 10.2 mmol), CuO black (0.816 g, 10.2 mmol), DMAP (1.49 g, 12.2 mmol) and dry MeCN (30 ml), and the suspension was refluxed for 12 h. After cooling, the mixture was diluted with CH_2Cl_2 (20 ml) and filtered over a pad of *Celite*®, the filter cake washed with CH_2Cl_2 (3 × 10 ml), the filtrate was concentrated, and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 6:1): **21** (1.27 g, 60%). Light yellow oil. TLC (petroleum ether/AcOEt 10:1): R_f 0.1. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.22 (*s*, 1 H); 7.76 (*d*, *J* = 8.7, 1 H); 7.28–7.16 (*m*, 5 H); 6.94 (*s*, 1 H); 6.83 (*s*, 1 H); 6.46 (*d*, *J* = 9.1, 1 H); 5.00 (*s*, 2 H); 4.69 (*d*, *J* = 12, 1 H); 4.68 (*s*, 1 H); 4.43 (*d*, *J* = 12, 1 H); 3.99 (*s*, 3 H); 3.95 (*s*, 3 H); 3.79 (*m*, 1 H); 3.49 (*m*, 1 H); 2.36 (*s*, 3 H); 1.66–1.41 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 187.7; 165.3; 161.7; 161.5; 150.1; 138.3; 136.5; 136.4; 132;2; 131.0; 128.2 (2 C); 127.6; 126.7 (2 C); 122.9; 122.5; 117.8; 114.9; 110.3; 98.4; 70.4; 64.7; 64.3; 61.8; 52.6; 30.2; 25.3; 21.4; 19.0. ESI-MS: 543.4 ($[M+Na]^+$). HR-ESI-MS: 543.1968 ($[M+Na]^+$, $C_{30}H_{32}NaO_8^+$; calc. 543.1995).

Methyl 6-[2-(Benzyloxy)-6-(hydroxymethyl)-4-methylphenoxy]-3-formyl-2-methoxybenzoate (**22**). To a flame-dried flask was added **21** (1.23 g, 2.37 mmol), $TsOH \cdot H_2O$ (3 mg), ^{i}PrOH (10 ml), and H_2O (3 ml), and the soln. was refluxed overnight. After cooling, the mixture was extracted with AcOEt (3 × 30 ml), the extract washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the residue subjected to CC (SiO_2, AcOEt/petroleum ether 1:3): **22** (0.96 g, 93%). Colorless amorphous solid. TLC (petroleum ether/AcOEt 3:1): R_f 0.20. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.22 (*s*, 1 H); 7.74 (*d*, *J* = 9.0, 1 H); 7.26–7.16 (*m*, 5 H); 6.88 (*s*, 1 H); 6.83 (*s*, 1 H); 6.46 (*d*, *J* = 9.0, 1 H); 5.02 (*s*, 2 H); 4.56 (*s*, 2 H); 3.40 (*s*, 3 H); 3.96 (*s*, 3 H); 2.78 (br. *s*, 1 H); 2.35 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 187.7; 165.6; 161.9; 160.9; 150.2; 138.0; 136.8; 136.3; 134.6; 131.6; 128.3 (2 C); 127.7; 126.7 (2 C); 123.3; 121.9; 117.4; 114.7; 109.9; 70.5; 64.7; 60.7; 52.9; 21.4. ESI-MS: 459.3 ($[M+Na]^+$). HR-ESI-MS: 459.1409 ($[M+Na]^+$, $C_{25}H_{24}NaO_7^+$; calc. 459.1420).

6-[2-(Benzyloxy)-6-(hydroxymethyl)-4-methylphenoxy}-3-formyl-2-methoxybenzoic Acid (**23**). To a soln. of **22** (912 mg, 2.09 mmol) in MeOH (12 ml), $TsOH \cdot H_2O$ (80 mg, 0.42 mmol) was added, and the soln. was stirred for 1 h. Then NaOH tablets (0.94 g, 23.5 mmol) were added, and the mixture was refluxed overnight. After cooling, the MeOH was evaporated, and 3N HCl was added to the residue until pH 3 was reached. The mixture was extracted with AcOEt (4 × 30 ml) and the combined extract concentrated: crude **23** (837 mg, 98%), which was used for the next step without further purification. TLC (CH_2Cl_2/MeOH 5:1): R_f 0.4. ^{1}H-NMR (DMSO, 400 MHz): 10.11 (*s*, 1 H); 7.67 (*d*, *J* = 8.8, 1 H); 7.25–7.18 (*m*, 5 H); 7.03 (*s*, 1 H); 6.98 (*s*, 1 H); 6.38 (*d*, *J* = 8.8, 1 H); 5.08 (*s*, 2 H); 4.37 (*s*, 2 H); 3.97 (*s*, 3 H); 2.34 (*s*, 3 H). ESI-MS: 421.0 ($[M-H]^-$).

*11-(Benzyloxy)-4-methoxy-9-methyl-5-oxo-5*H*,7*H*-dibenzo[*b*,*g*][1,5]dioxocin-3-carboxaldehyde* (**24**). To a soln. of 2-chloro-1-methylpyridinium iodide (4.04 g, 16 mmol) in dry MeCN (300 ml), a soln. of crude **23** (1.67 g, 4 mmol) in dry MeCN (40 ml) and Et_3N (4.4 ml, 31.6 mmol) was added at 80° by a

syringe pump within 5 h, and the mixture was stirred for another 8 h. After cooling to r.t., the mixture was concentrated, the residue redissolved in CH_2Cl_2 (30 ml), the soln. filtered over a pad of SiO_2, the filter cake washed with CH_2Cl_2 (5×10 ml), the filterate washed with H_2O (3×30 ml), dried $MgSO_4$, and concentrated, and the residue subjected to CC (SiO_2, CH_2Cl_2): **24** (814 mg, 51% over two steps). TLC (petroleum ether/AcOEt 2:1): R_f 0.8. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.35 (*d*, $J = 0.6$, 1 H); 7.98 (*d*, $J = 8.6$, 1 H); 7.50–7.35 (*m*, 5 H); 7.03 (*dd*, $J = 0.6$, $J = 8.6$, 1 H); 6.89 (*d*, $J = 1.5$, 1 H); 6.48 (*d*, $J = 1.2$, 1 H); 5.20 (*s*, 2 H); 5.13 (*s*, 2 H); 4.12 (*s*, 3 H); 2.28 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 187.8; 166.1; 161.2; 158.0; 150.4; 143.2; 136.5; 135.3; 133.3; 128.7 (2 C); 128.1; 127.32; 127.27 (2 C); 127.0; 121.5; 120.6; 118.7; 116.6; 71.3; 69.0; 64.7; 21.2. ESI-MS: 427.0 ($[M + Na]^+$). HR-ESI-MS: 427.1133($[M + Na]^+$, $C_{24}H_{20}NaO_6^+$;calc. 427.1158).

*11-(Benzyloxy)-3-(1-hydroxy-3-methylbut-3-en-1-yl)-4-methoxy-9-methyl-5*H,7H-*dibenzo[*b,g*][1,5]dioxocin-5-one* (**25**). To a cold ($-10°$) soln. of **24** (404 mg, 0.25 mmol) in dry THF (15 ml), 0.5M 2-methylprop-2-en-1-ylmagnesium chloride in THF (5 ml, 2.5 mmol) was added, and the mixture was stirred at $-10°$ for 1 h. After cautious quenching with sat. aq. NH_4Cl soln., the mixture was extracted with AcOEt (3×30 ml), the extract washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2, AcOEt/petroleum ether 1:4): **25** (379 mg, 82%). White amorphous powder. TLC (petroleum ether/AcOEt 2:1): R_f 0.5. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.62 (*d*, $J = 8.6$, 1 H); 7.60–7.30 (*m*, 5 H); 6.86 (*s*, 1 H); 6.46 (*s*, 1 H); 5.19 (*s*, 2 H); 5.08–5.14 (*m*, 3 H); 4.93 (*s*, 1 H); 4.84 (*s*, 1 H); 3.98 (*s*, 3 H); 2.47 (*dd*, $J = 13.6$, 3.2, 1 H); 2.32 (*m*, 1 H); 2.26 (*s*, 3 H); 1.83 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 167.4; 154.5; 152.3; 150.2; 144.0; 142.3; 136.7; 135.0; 134.4; 130.9; 128.6 (2 C); 127.9; 127.3; 127.2 (2 C); 121.6; 119.3; 118.0; 116.5; 114.2; 71.3; 69.0; 65.5; 47.3; 29.6; 22.2; 21.0. ESI-MS: 443.0 ($[M - OH]^+$). HR-APCI-MS: 461.1979 ($[M + H]^+$, $C_{28}H_{29}O_6^+$; calc. 461.1964).

rac-*11-Hydroxy-3-(1-hydroxy-3-methylbutyl)-4-methoxy-9-methyl-5*H,7H-*dibenzo[*b,g*][1,5]dioxocin-5(7*H*)-one* (±)-(**1a**). To the soln. of **25** (202 mg, 0.44 mmol) in MeOH/ AcOEt 5:1) (6 ml) was added 10% Pd/C (20 mg), and the mixture was stirred under H_2 (balloon) at r.t. for *ca.* 3 h (TLC monitoring). After addition of CH_2Cl_2 (20 ml), the mixture was filtered over a pad of *Celite*®, the filter cake washed with AcOEt, the combined filterate concentrated, and the residue subjected to CC (SiO_2, AcOEt/ petroleum ether 5:2): (±)-**1a** (106 mg, 65%). Light yellow amorphous powder. TLC (petroleum ether/ AcOEt 1:2): R_f 0.46. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.52 (*d*, $J = 8.6$, 1 H); 6.84 (s, 1 H); 6.83 (*d*, $J = 8.6$, 1 H); 6.64 (br. *s*, 1 H); 6.35 (*s*, 1 H); 5.06 (*m*, 3 H); 3.96 (*s*, 3 H); 2.23 (*s*, 3 H); 1.78 (*m*, 1 H); 1.66 (*m*, 1 H); 1.45 (*m*, 1 H); 0.97 (*d*, $J = 6.8$, 3 H); 0.95 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 167.9; 154.3; 151.2; 147.5; 141.3; 136.9; 135.0; 131.1; 125.7; 120.7; 119.3; 117.8; 117.7; 69.2; 66.6; 62.7; 47.6; 24.9; 23.4; 21.8; 20.8. ESI-MS: 355.0 ($[M - OH]^+$). HR-APCI-MS: 373.1654 ($[M + H]^+$, $C_{21}H_{25}O_6^+$; calc. 373.1651).

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