meta-Selective Aromatic Borylation as Key Step in the Synthesis of Poipuol

Jens Cordes, Claas Wessel, Klaus Harms, Ulrich Koert*

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35043 Marburg, Germany
Fax +49(6421)2825677; E-mail: koert@chemie.uni-marburg.de

Received 2 May 2008

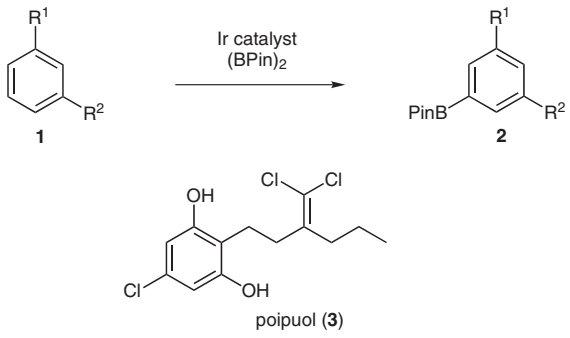
Dedicated to Prof. R. W. Hoffmann on the occasion of his 75th birthday

Abstract: A synthesis of the marine natural product poipuol is reported. The key reaction sequence consists of an iridium-catalyzed *meta*-selective CH-borylation followed by the conversion of the resulting arylboronic ester into an aryl chloride.

Key words: *meta*-selective aromatic substitution, boron, iridium, natural products, total synthesis

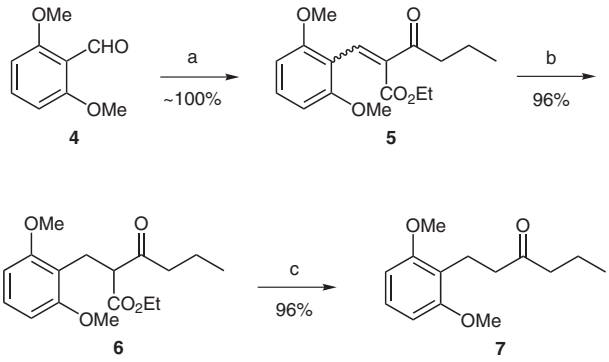
For a long time the direct *meta*-selective functionalization of benzene derivatives had been restricted to systems carrying electron-withdrawing groups and had been impossible for electron-rich systems. The situation changed with the discovery of iridium-catalyzed CH-borylation of arenes.[1] Miyaura et al. introduced the catalyst system $[Ir(cod)Cl]_2$ (cod = cyclooctadiene) in combination with 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) and bis(pinacolato)diboron [$(Bpin)_2$] as borylating reagent.[1a] The use of $[Ir(cod)(OMe)]_2$ allowed an aromatic CH-borylation at room temperature.[1b] The regioselectivity of the borylation is directed by steric factors, which lead in the case of a 1,3-disubstituted benzene derivative **1** to the predominant formation of the *meta*-substitution product **2** (Scheme 1). The synthetic potential of the CH-borylation of arenes was expanded by Maleczka and Smith with the introduction of a C–H activation/borylation/oxidation protocol to produce *meta*-substituted phenols.[1d]

To use this *meta*-selective aromatic borylation in the complex functional environment of a natural product synthesis, we were interested in the functional tolerance of this reaction. Here, we present first results addressing the point of functional tolerance in the context of a synthesis of the natural product poipuol (**3**) (Scheme 1). Poipuol (**3**) was isolated by Sitachitta et al. from the marine sponge *Hyrtios* sp., collected at a depth of 18 meters near Kauai Island, Hawaii.[2]



Scheme 1 *meta*-Selective arene borylation of 1,3-disubstituted benzene derivative **1** to produce 1,3,5-trisubstituted benzene **2**; structure of poipuol (**3**)

The starting point for the synthesis of the borylation precursor was the aromatic aldehyde **4** (Scheme 2). A Knoevenagel–Doebner reaction[3] of **4** with ethyl butyracetate led to condensation product **5** in nearly quantitative yield. The hydrogenation of **5** gave β-keto ester **6**. Treatment of the latter with potassium hydroxide in aqueous ethanol resulted in the formation of ketone **7** (Scheme 2).[4]

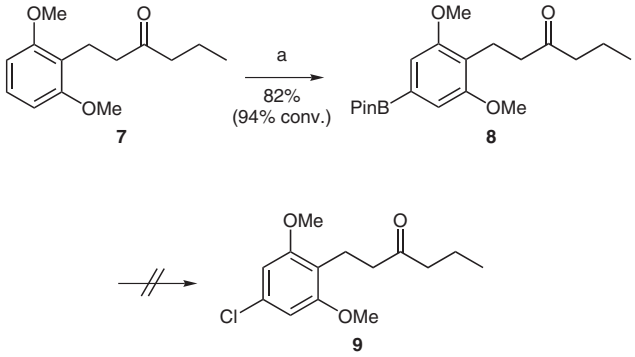


Scheme 2 *Reagents and conditions*: (a) $PrCOCH_2CO_2Et$, AcOH, piperidine, toluene, reflux; (b) NaOAc, $Pd(OH)_2/C$, H_2, EtOAc; (c) KOH, H_2O, EtOH, reflux.

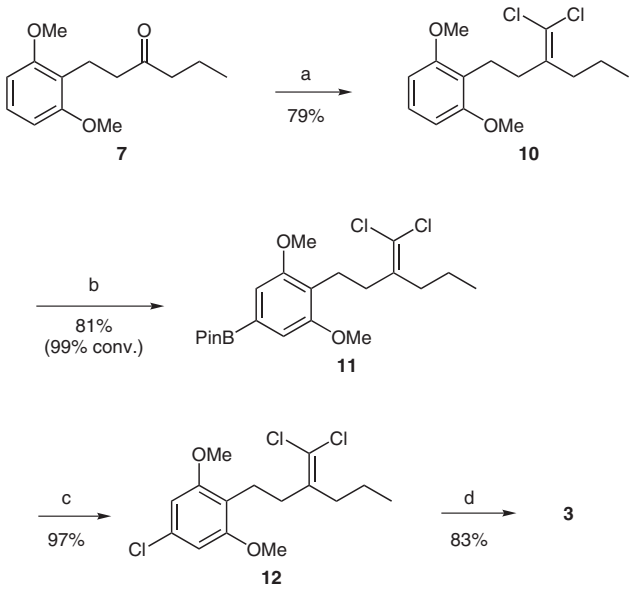
The CH-borylation of arene **7** in the presence of the catalyst system consisting of 0.75% $[Ir(cod)(OMe)]_2$/1.5% dtbpy/$(Bpin)_2$ (1 equiv) gave arylboronic ester **8** with complete *meta* selectivity and in very good yield (Scheme 3). In contrast to the low-temperature conditions reported by Miyaura,[1b] harsher conditions (microwave, 150 °C, 3 h) were necessary for the conversion of **7** into **8**. Notable is the compatibility of the ketone function with the borylation conditions.

The conversion of **8** into poipuol (**3**) would require the generation of aryl chloride **9** from the arylboronic ester (Scheme 3). Attempts to use copper(II) chloride[5] for this purpose failed due to side reactions with the ketone. An inseparable mixture of α-chloro ketones was obtained. Therefore, the transformation of ketone **7** into dichloroolefin **10** before the borylation–chlorination sequence was examined next (Scheme 4).

SYNTHESIS 2008, No. 14, pp 2217–2220
Advanced online publication: 11.06.2008
DOI: 10.1055/s-2008-1078449; Art ID: C01908SS



Scheme 3 *Reagents and conditions*: (a) $[Ir(cod)(OMe)]_2$, dtbpy, $(Bpin)_2$, hexane, microwave, 150 °C, 3 h.



Scheme 4 *Reagents and conditions*: (a) $(EtO)_2P(O)CCl_3$, *n*-BuLi, THF, Et_2O, –115 °C to reflux; (b) $[Ir(cod)(OMe)]_2$, dtbpy, $(Bpin)_2$, hexane, microwave, 150 °C; (c) $CuCl_2 \cdot 2H_2O$, H_2O, *i*-PrOH, microwave, 150 °C; (d) BBr_3, CH_2Cl_2.

The reaction of ketone **7** with diethyl (trichloromethyl)phosphonate and *n*-butyllithium delivered the desired dichloroolefin **10** (Scheme 4).[6] The following CH-borylation with catalyst system $[Ir(cod)(OMe)]_2$/dtbpy/$(Bpin)_2$ gave arylboronic ester **11** with complete *meta*-selectivity in very good yield (Scheme 4). An X-ray crystal structure of the product (Figure 1) allowed an unambiguous structural assignment of the borylation product.[7] Treatment of arylboronic ester **11** with ten equivalents copper(II) chloride dihydrate[5] in isopropyl alcohol–water at 150 °C (microwave) led to the formation of aryl chloride **12** in nearly quantitative yield. The synthesis of poipuol (**3**) was successfully completed by the final methyl ether cleavage of **12** mediated by boron tribromide (Scheme 4). The analytical data of synthetic poipuol (**3**) were identical to those previously reported.[2]

In conclusion, it was shown that ketone and dichloroolefin functionalities can tolerate iridium-mediated CH-borylation conditions. The reaction sequence of *meta*-selective CH-borylation and chlorination is an efficient way to prepare *meta*-disubstituted aryl chlorides. The marine natural product poipuol (**3**) was synthesized in seven steps in 58% overall yield when *meta*-selective CH-borylation–chlorination was applied as the key sequence. Other uses of iridium-mediated CH-borylation in a complex functional environment of a natural products synthesis are conceivable.

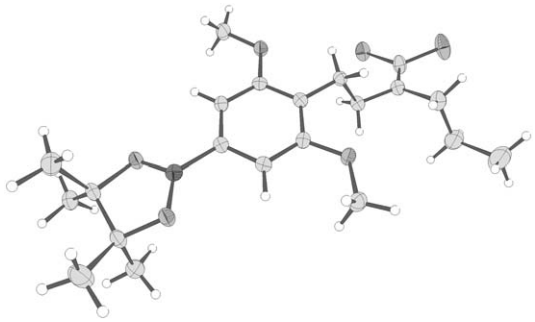


Figure 1 X-ray crystal structure of compound **11**[7]

All nonaqueous reactions were carried out in flame-dried glassware under argon atmosphere. All solvents were distilled by rotary evaporation. Solvents for nonaqueous reactions were dried as follows prior to use: THF was dried with KOH and subsequently distilled from sodium/benzophenone, and Et_2O from a K/Na (4:1) alloy. All commercially available reagents and reactants were used without purification unless otherwise noted. 2,6-Dimethoxybenzaldehyde (**4**) was prepared according to a literature procedure.[8] Reactions were monitored by TLC on Merck silica gel 60 F_{245} plates, which were visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with a $KMnO_4$ stain. Chromatographic purification of products was performed on Merck silica gel 60 (230–400 mesh) with a forced flow of eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure. Reactions under microwave conditions were performed with a CEM Discover LabMate. Yields refer to purified and spectroscopically pure products unless otherwise noted. IR spectra were recorded on a Bruker IFS 200 or a Nicolet Magna-IR 750 spectrometer. NMR spectra were recorded on a Bruker ARX300, DRX400, or DRX500 spectrometer at r.t. Chemical shifts are reported relative to the solvent resonance as internal standard. Mass spectra were recorded on a Finnigan MAT TSQ 700 or MAT 95S spectrometer.

Ethyl 2-(2,6-Dimethoxybenzylidene)-3-oxohexanoate (5)

2,6-Dimethoxybenzaldehyde (**4**; 10.0 g, 60.2 mmol) was dissolved in toluene (300 mL). Ethyl butyracetate (9.52 g, 60.2 mmol), glacial AcOH (1.5 mL), and piperidine (1.2 mL) were added and the mixture was heated in a Dean–Stark apparatus until the generation of H_2O ceased. After the mixture had cooled to r.t., EtOAc (250 mL) was added. The soln was washed with 1 M HCl (3 × 200 mL), brine (3 × 200 mL), sat. $NaHCO_3$ (3 × 200 mL), and H_2O (3 × 200 mL) and dried ($MgSO_4$). Removal of the solvents gave **5** as an *E*/*Z* mixture (1.0:1.5, according to NOESY).

Yield: 18.4 g (ca. 100%); yellow oil; $R_f = 0.30$ (hexane–MTBE, 1:1).

IR (film): 2964 (m), 2840 (w), 1721 (s), 1597 (s), 1474 (s), 1434 (m), 1377 (m), 1307 (w), 1260 (s), 1147 (w), 1114 (s), 1030 (m), 779 (m), 759 (w), 732 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*E*-isomer) = 7.80 (s, 1 H), 7.26 (t, *J* = 8.4 Hz, 1 H), 6.50 (d, *J* = 8.3 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.75 (s, 6 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 1.58 (pseudo sext, *J* = 7.4 Hz, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.87 (t, *J* = 7.5 Hz, 3 H); δ (*Z*-isomer) = 7.80 (s, 1 H), 7.27 (t, *J* = 8.4 Hz, 1 H), 6.50 (d, *J* = 8.3 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.77 (s, 6 H), 2.72 (t, *J* = 7.5 Hz, 2 H), 1.68 (pseudo sext, *J* = 7.3 Hz, 2 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*E*-isomer) = 198.2, 167.4, 158.6 (2 C), 135.5, 135.1, 131.7, 112.5, 103.5 (2 C), 60.6, 55.6 (2 C), 41.9, 17.7, 13.9, 13.8; δ (*Z*-isomer) = 202.4, 166.0, 158.2 (2 C), 134.5, 134.3, 131.7, 112.1, 103.7 (2 C), 61.2, 55.4 (2 C), 44.0, 17.1, 14.3, 13.8.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{22}O_5Na$ $[M + Na]^+$: 329.1359; found: 329.1358.

Ethyl 2-(2,6-Dimethoxybenzyl)-3-oxohexanoate (6)

Olefin **5** (18.4 g, 60.1 mmol) was dissolved in EtOAc (400 mL). NaOAc (7.94 g, 120 mmol) and $Pd(OH)_2$ (20% wet on C; 900 mg) were added and the mixture was stirred under a H_2 atmosphere at r.t. overnight. The suspension was filtered through Celite and the filtrate was washed with brine (150 mL). The organic layer was dried ($MgSO_4$) and concentrated.

Yield: 17.8 g (96%); yellow oil; R_f = 0.42 (hexane–MTBE, 1:1).

IR (film): 2962 (s), 2838 (m), 1713 (s), 1637 (m), 1596 (s), 1475 (s), 1368 (m), 1330 (m), 1258 (s), 1200 (s), 1113 (s), 1038 (m), 776 (m), 728 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 8.4 Hz, 1 H), 6.50 (d, *J* = 8.3 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.84–3.76 (m, 7 H), 3.21 (d, *J* = 8.4 Hz, 2 H), 2.49 (dt, *J* = 17.4, 7.2 Hz, 1 H), 2.29 (dt, *J* = 17.4, 7.2 Hz, 1 H), 1.53 (pseudo sext, *J* = 7.4 Hz, 2 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6, 170.2, 158.4 (2 C), 127.8, 114.7, 103.6 (2 C), 60.9, 57.9, 55.6 (2 C), 43.7, 22.1, 16.9, 14.0, 13.6.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{24}O_5Na$ $[M + Na]^+$: 331.1516; found: 331.1523.

1-(2,6-Dimethoxyphenyl)hexan-3-one (7)

Keto ester **6** (17.8 g, 57.7 mmol) was dissolved in EtOH (290 mL). H_2O (16 mL) and KOH (16.2 g, 289 mmol) were added and the soln was heated for 4 h under reflux. After the mixture had cooled to r.t., the EtOH was removed in vacuo. The residue was taken up in CH_2Cl_2 (300 mL), washed with H_2O (3 × 250 mL), and dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1).

Yield: 13.1 g (96%); colorless solid; R_f = 0.56 (hexane–MTBE, 1:1); mp 35 °C.

IR (KBr): 2960 (m), 2837 (w), 1711 (s), 1595 (s), 1474 (s), 1436 (m), 1367 (w), 1256 (s), 1189 (w), 1160 (m), 1115 (s), 1068 (w), 1040 (w), 777 (m), 727 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 8.3 Hz, 1 H), 6.52 (d, *J* = 8.3 Hz, 2 H), 3.79 (s, 6 H), 2.93–2.88 (m, 2 H), 2.58–2.53 (m, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 1.61 (pseudo sext, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.6, 158.2 (2 C), 127.8, 117.5, 103.6 (2 C), 55.6 (2 C), 44.5, 42.1, 17.8, 17.3, 13.8.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{21}O_3$ $[M + H]^+$: 237.1485; found: 237.1488.

1-[2,6-Dimethoxy-4-(pinacolatoboryl)phenyl]hexan-3-one (8)

In a glass tube, $(Bpin)_2$ (762 mg, 3.0 mmol), dtbpy (12.1 mg, 45.0 μmol), and $[Ir(cod)(OMe)]_2$ (14.9 mg, 22.5 μmol) were dissolved in hexane (6.0 mL). After the mixture had stirred at r.t. for 15 min, ketone **7** (709 mg, 3.0 mmol) was added. The tube was sealed with a Teflon cap and heated by microwave for 3 h to 150 °C. After cooling to r.t., the mixture was poured into MTBE (60 mL) and washed with H_2O (2 × 45 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1).

Yield: 887 mg (82%; or 94% on the basis of 92 mg recovered starting material **7**); colorless solid; R_f = 0.50 (hexane–MTBE, 1:1); mp 98 °C.

IR (KBr): 2982 (s), 2939 (m), 1708 (s), 1572 (s), 1451 (m), 1406 (s), 1365 (s), 1245 (w), 1164 (s), 1144 (m), 1124 (s), 967 (w), 852 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97 (s, 2 H), 3.84 (s, 6 H), 2.95–2.89 (m, 2 H), 2.57–2.51 (m, 2 H), 2.39 (t, *J* = 7.4 Hz, 2 H), 1.52 (pseudo sext, *J* = 7.4 Hz, 2 H), 1.34 (s, 12 H), 0.91 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.5, 157.9 (2 C), 127.8, 121.3, 109.6 (2 C), 83.9 (2 C), 55.9 (2 C), 44.6, 42.0, 25.0 (4 C), 18.1, 17.5, 13.9.

^{11}B NMR (160 MHz, $CDCl_3$): δ = 30.5.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{31}BO_5Na$ $[M + Na]^+$: 385.2157; found: 385.2147.

2-[3-(Dichloromethylene)hexyl]-1,3-dimethoxybenzene (10)

$(EtO)_2P(O)CCl_3$ (1.42 mL, 7.62 mmol) was dissolved in a mixture of THF (4.0 mL) and Et_2O (4.0 mL). The soln was cooled to –115 °C (EtOH/liquid N_2), and 2.5 M *n*-BuLi in hexane (3.1 mL, 7.6 mmol) was added dropwise. The mixture was stirred for 30 min, and then a soln of ketone **7** (600 mg, 2.54 mmol) in Et_2O (2.0 mL) was added. After stirring for 1 h at –115 °C, the soln was warmed to r.t. and then heated to reflux for 18 h. After the mixture had cooled to 0 °C, sat. aq NH_4Cl (15 mL) and Et_2O (15 mL) were added. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel, pentane–Et_2O, 19:1 to 9:1).

Yield: 607 mg (79%); colorless oil; R_f = 0.48 (hexane–MTBE, 9:1).

IR (film): 2960 (s), 2871 (m), 2835 (m), 1596 (s), 1474 (s), 1435 (m), 1280 (w), 1257 (s), 1188 (m), 1164 (m), 1117 (s), 1086 (m), 904 (m), 775 (m), 725 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 8.3 Hz, 1 H), 6.53 (d, *J* = 8.3 Hz, 2 H), 3.82 (s, 6 H), 2.82–2.76 (m, 2 H), 2.42–2.37 (m, 2 H), 2.31–2.26 (m, 2 H), 1.52 (pseudo sext, *J* = 7.5 Hz, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6 (2 C), 139.8, 127.2, 117.9, 115.0, 103.8 (2 C), 55.8 (2 C), 35.6, 32.8, 20.7, 20.6, 14.1.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{20}O_2$ $[M]^+$: 302.0840; found: 302.0851.

{4-[3-(Dichloromethylene)hexyl]-3,5-dimethoxyphenyl}(pinacolato)borane (11)

In a glass tube, $(Bpin)_2$ (254 mg, 1.0 mmol), dtbpy (4.0 mg, 15 μmol), and $[Ir(cod)(OMe)]_2$ (5.0 mg, 7.5 μmol) were dissolved in hexane (2.0 mL). After the mixture had stirred at r.t. for 15 min, dichloromethylene **10** (303 mg, 1.0 mmol) was added. The tube was sealed with a Teflon cap and heated by microwave for 3 h to 150 °C. After cooling to r.t., the mixture was poured into MTBE (20 mL) and washed with H_2O (2 × 15 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1).

Yield: 346 mg (81%; or 99% on the basis of 55 mg recovered starting material **10**); colorless solid; R_f = 0.20 (hexane–MTBE, 9:1); mp 81 °C.

IR (KBr): 2971 (s), 1575 (s), 1446 (m), 1404 (s), 1371 (s), 1305 (m), 1262 (w), 1238 (w), 1209 (w), 1178 (m), 1164 (s), 1145 (m), 1125 (s), 1087 (w), 693 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.97 (s, 2 H), 3.86 (s, 6 H), 2.82–2.78 (m, 2 H), 2.41–2.35 (m, 2 H), 2.30–2.24 (m, 2 H), 1.52 (pseudo sext, *J* = 7.5 Hz, 2 H), 1.35 (s, 12 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0 (2 C), 139.7, 127.8, 121.6, 115.0, 109.7 (2 C), 83.9 (2 C), 56.0 (2 C), 35.6, 32.7, 25.0 (4 C), 21.0, 20.6, 14.1.

^{11}B NMR (160 MHz, $CDCl_3$): δ = 31.5.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{31}BCl_2O_4Na$ $[M + Na]^+$: 451.1585; found: 451.1589.

5-Chloro-2-[3-(dichloromethylene)hexyl]-1,3-dimethoxybenzene (12)

In a glass tube, $CuCl_2 \cdot 2H_2O$ (1.0 g, 6.1 mmol) was suspended in a mixture of H_2O (0.5 mL) and *i*-PrOH (4.5 mL). Boronate **11** (260 mg, 0.61 mmol) was added and the tube was sealed with a Teflon cap and heated under microwave for 2 h to 150 °C. After cooling to r.t., the mixture was poured into MTBE (75 mL) and washed with H_2O (2 × 25 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1).

Yield: 199 mg (97%); colorless oil; R_f = 0.57 (hexane–MTBE, 9:1).

IR (KBr): 2961 (s), 1589 (s), 1453 (m), 1409 (m), 1229 (w), 1182 (w), 1167 (m), 1126 (s), 898 (w), 875 (w), 815 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.53 (s, 2 H), 3.80 (s, 6 H), 2.75–2.72 (m, 2 H), 2.38–2.35 (m, 2 H), 2.28–2.25 (m, 2 H), 1.52 (pseudo sext, *J* = 7.5 Hz, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8 (2 C), 139.4, 132.7, 116.3, 115.2, 104.7 (2 C), 56.0 (2 C), 35.6, 32.6, 20.6, 20.5, 14.1.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}Cl_3O_2$ $[M]^+$: 336.0451; found: 336.0457.

5-Chloro-2-[3-(dichloromethylene)hexyl]benzene-1,3-diol (Poipuol; 3)

Chlorobenzene **12** (70 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (4.0 mL). A 1 M soln of BBr_3 in CH_2Cl_2 (0.62 mL, 0.62 mmol) was added, and the resulting soln was stirred at r.t. for 3 d. After dilution of the mixture with CH_2Cl_2 (50 mL), H_2O (1 mL) was added and the mixture was stirred for 30 min. The soln was washed with H_2O (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica gel, pentane–Et_2O, 19:1 to 9:1).

Yield: 53 mg (83%); colorless solid; R_f = 0.35 (hexane–MTBE, 3:1); mp 54 °C.

IR (film): 3420 (br s), 2963 (s), 2934 (m), 2872 (w), 1611 (s), 1597 (s), 1510 (w), 1422 (s), 1340 (w), 1160 (s), 1096 (m), 1050 (s), 969 (w), 902 (s), 822 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.41 (s, 2 H), 4.99 (br s, 2 H), 2.76–2.71 (m, 2 H), 2.44–2.40 (m, 2 H), 2.30–2.25 (m, 2 H), 1.51 (pseudo sext, *J* = 7.6 Hz, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2 (2 C), 139.1, 132.2, 115.8, 113.0, 108.8 (2 C), 35.8, 32.6, 20.7, 20.6, 14.0.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{15}Cl_3O_2Na$ $[M + Na]^+$: 328.9873; found: 328.9868.

Acknowledgment

Generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References

(1) (a) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (c) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E. Jr.; Smith, M. R. III. *Science* **2002**, *295*, 305. (d) Maleczka, R. E. Jr.; Shi, F.; Homes, D.; Smith, M. R. III. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (e) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 489.

(2) Sata, N.; Galario, M. A.; Sitachitta, N.; Scheuer, P. J.; Kelly, M. *J. Nat. Prod.* **2005**, *68*, 262.

(3) Antonioletti, R.; Bovicelli, P.; Malancona, S. *Tetrahedron* **2002**, *58*, 589.

(4) Briese, R. R.; McElvain, S. M. *J. Am. Chem. Soc.* **1933**, 1697.

(5) Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547.

(6) Roedig, A.; Ganns, E. M.; Henrich, C.; Schnutenhaus, H. *Liebigs Ann. Chem.* **1981**, 1674.

(7) The crystal data of compound **11** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 686558. Crystal data: $C_{21}H_{31}BCl_2O_4$, *M* = 429.17, monoclinic, *C*2/*c*, *a* = 16.8261 (9) Å, *b* = 13.2384 (7) Å, *c* = 21.5067 (13) Å, β = 104.026 (4)°, *V* = 4647.8 (4) $Å^3$, *Z* = 8, D_{calcd} = 1.227 g/cm^3, 20619 collected reflections, 4102 independent (R_{int} = 0.0775), *R*1 = 0.0339, *wR*2 = 0.0709 (all data).

(8) Haight, A. R.; Bailey, A. E.; Baker, W. S.; Cain, M. H.; Copp, R. R.; DeMattei, J. A.; Ford, K. L.; Henry, R. F.; Oliver, P. A.; Parekh, S. I.; Patel, H. H.; Seif, L. S.; Staeger, M. A.; Wayne, G. S.; Wittenberger, S. J.; Zhang, W. *Org. Process Res. Dev.* **2004**, *8*, 897.