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Synthesis and SAR of 4-methyl-5-pentylbenzene-1,3-diol (MPBD), produced by *Dictyostelium discoideum*

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ABSTRACT

4-Methyl-5-pentylbenzene-1,3-diol (MPBD) is a secondary metabolite of SteelyA polyketide synthase, which controls cell aggregation and spore maturation of *Dictyostelium discoideum*. In this study, chemical synthesis of MPBD and its derivatives was achieved. Structure–activity relationship (SAR) studies for antimicrobial activities against *Escherichia coli* and *Bacillus subtilis* were also conducted.

The cellular slime mold *Dictyostelium discoideum* is an excellent model organism for the study of cell and developmental systems because it shows a unique two-stage life cycle.[1] Ordinarily, *D. discoideum* inhabit in the soil and predaceous bacteria as a unicellular amoeba. However, when starved, they aggregate and prompt a multicellular mound. The aggregation forms fruiting bodies consisting of spores and stalk at the end of its differentiation.

In recent years, *D. discoideum* has attracted increasing attention as the organisms which have the ability of the production as secondary metabolites for leading novel medical drugs. The *D. discoideum* genome contains more than 40 polyketide synthase genes, indicating that it has huge potential for polyketide production.[2,3] Various biologically active compounds from *D. discoideum* are thus reported.[4–7] For example, differentiation-inducing factor-1 (DIF-1) and its analogs produced by SteelyB are signal molecules that induce stalk cell formation.[8–10] They exhibit various bioactivities such as anti-tumor activity,[11] sugar metabolism promoting activity,[12] interleukin-2 production inhibitor,[13] and amyloid-β production inhibitor.[14]

4-Methyl-5-pentylbenzene-1,3-diol (MPBD **1**, Figure 1), which is produced by SteelyA polyketide synthase,[15] is also a signal molecule that regulates cell aggregation in early stage development[16] and induces spore cell formation in the later stages.[17] However, the only known biological activities of MPBD **1** are chemotaxis regulation, spore maturation activity, and anti-tumor activity.[18] While the first total synthesis of **1** was reported,[17] development of a strategy that allowed for the easier synthesis of MPBD **1** derivatives for structure–activity relationship (SAR) studies was required. Herein, we report the synthesis of MPBD **1** and its derivatives, and their antimicrobial activities by means of SAR.

In our overall retrosynthesis of MPBD **1** and its derivatives, the target molecule **1** could be prepared via the Wittig reaction and halogen alkylation of compound **2** (Scheme 1).[19] Intermediate **2** could be obtained from commercially available 1,3-dihydroxybenzoic acid **3**.

The total synthesis of MPBD **1** is shown in Scheme 2. First, **3** was methylated by treatment with dimethyl sulfate ($(MeO)_2SO_2$) and potassium carbonate (K_2CO_3) in acetone under reflux conditions to give **4** in 92% yield. Reduction of the methyl ester group on **4** using lithium aluminum hydride ($LiAlH_4$) afforded benzyl alcohol **5** in 98% yield. Regioselective iodination of **5** using *N*-iodosuccinimide (NIS) afforded the desired product **6** in 94% yield,[20] which was subjected to Swern oxidation to obtain the common intermediate **2** in 96% yield. Wittig reaction between aldehyde **2** and nBuPPh$_3$Br$_3$ gave olefin **7** (E/Z = 1.3/1) in 87% yield. Lithiation of **7** using *n*-butyllithium (*n*BuLi), followed by treatment with iodomethane (MeI), gave **8** in 97% yield. Olefin **8** was then hydrogenated using hydrogen gas with Pd/C to give **9** in 88% yield. Removal of the methyl protecting groups of **9** using BBr_3 afforded the desired MPBD **1** in 93% yield. Thus, the total synthesis of **1** was accomplished in eight steps, in 56% overall yield.

As MPBD derivatives for SAR study, 4-ethyl-5-pentylbenzene-1,3-diol (EPBD) and 4-*n*-propyl-5-pentylbenzene-1,3-diol (PPBD)

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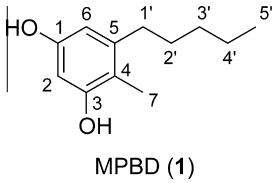
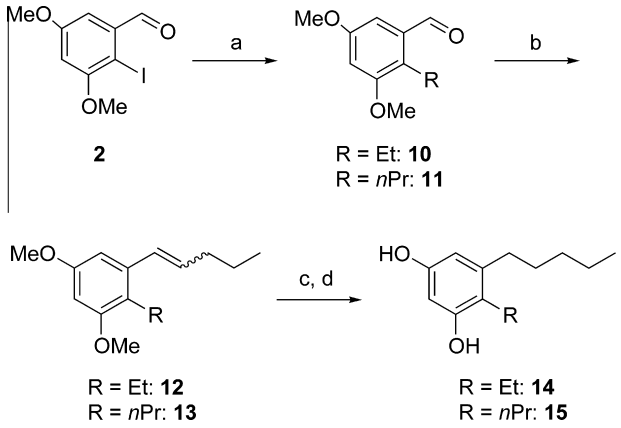


Figure 1. Structure of MPBD **1**. The carbon numbering of **1** was adapted from Ref. 17.

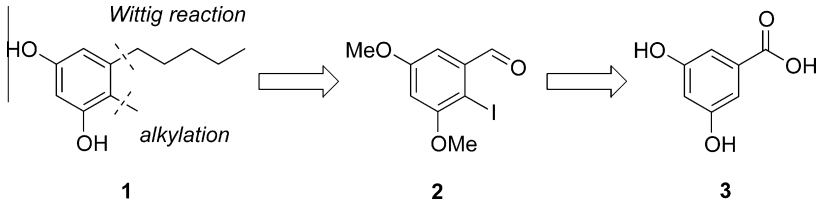
were designed and synthesized from compound **2** (Scheme 3). The lithiation–alkylation strategy using iodoethane or 1-iodopropane toward intermediate **7** did not afford the target products (data not shown), probably due to the steric repulsion resulting from the aryl anion in the S_N2 reaction. Ethyl and *n*-propyl substitutes were hence introduced by Negishi cross-coupling reactions of iodoethane and 1-iodopropane with zinc, respectively.[21] The reactions were carried out using 20 mol % pyridine-enhanced precatalyst preparation stabilization and initiation (PEPPSI)-IPr to give **10** and **11** in 77% and 69% yields, respectively. Wittig reaction of **10** and **11** with *n*BuPPh$_3$Br afforded olefins **12** (*E*/*Z* = 1/1.4) and **13** (*E*/*Z* = 1/1.3) in 73% yield. Interestingly, the *E*/*Z* ratios of **12** and **13** were the inverse of that observed in the MPBD synthesis, probably due to the change of steric environment. Thus, the desired products EPBD **14** and PPBD **15** were obtained via hydrogenation and deprotection in 84% and 82% yields, respectively, in two steps.

We also designed and synthesized a compound without a hydroxyl group at C3 for the SAR study (Scheme 4). Iodination of

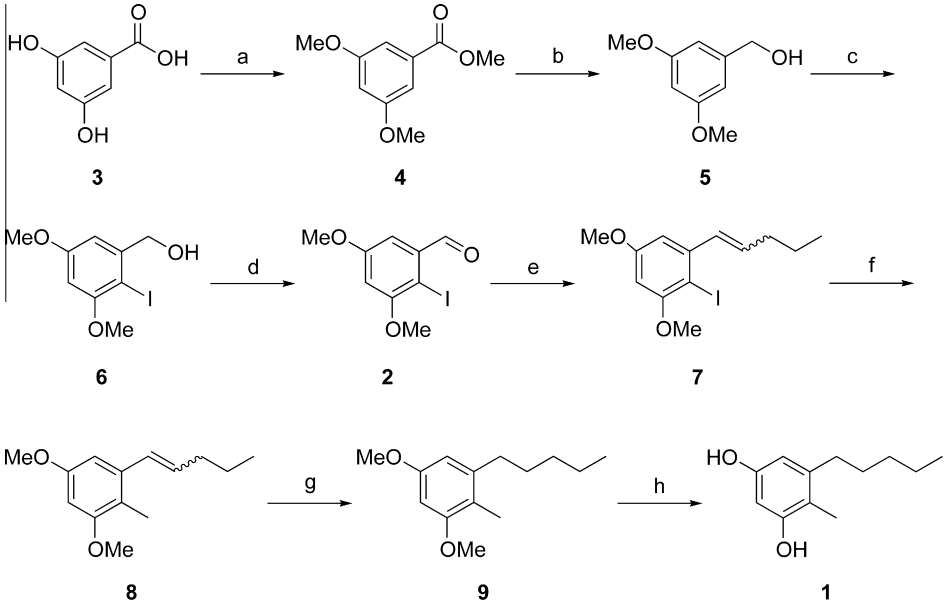


Scheme 3. Synthesis of EPBD **14** and PPBD **15**. Reagents and conditions: (a) Zn, TMSCl, iodoethane or 1-iodopropane, then, PEPPSI-IPr, DMF, rt, 2 h, 77% (**10**), 69% (**11**); (b) *n*BuLi, *n*BuPPh$_3$Br, THF, rt, 2 h, 73% (**12**), 73% (**13**); (c) H_2, Pd/C, THF, rt, 12 h; (d) BBr_3, CH_2Cl_2, −78 °C to rt, 21 h, 84%; (**14**), 82% (**15**) (two steps).

the starting material 4-amino-1-hydroxybensoic acid **16** was carried out by the Sandmeyer reaction to yield **17** in quantitatively.[22] Di-methylation of **17** with MeI gave **18** in 97% yield.[23] Negishi cross-coupling reaction of **18** with iodomethane and zinc was then carried out using PEPPSI-IPr to give **19** in 99% yield. After reduction of **19** using $LiAlH_4$, followed by Swern oxidation, Witting reaction of aldehyde **21** with *n*BuPPh$_3$Br was carried out to obtain olefin **22** (*E*/*Z* = 1/1.6) in 78% yield. Reduction of the olefin and removal



Scheme 1. Retrosynthetic analysis of MPBD (**1**).



Scheme 2. Total synthesis of MPBD **1**. Reagents and conditions: (a) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux, 4 h, 92%; (b) $LiAlH_4$, THF, 0 °C to rt, 2 h, 98%; (c) NIS, DMF, 40 °C, 4 h, 94%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 3 h, 96%; (e) *n*BuLi, *n*BuPPh$_3$Br, THF, 0 °C to rt, 30 min, 87%; (f) *n*BuLi, MeI, Et_2O, −78 °C to rt, 12 h, 97%; (g) H_2, Pd/C, EtOAc, rt, 24 h, 88%; (h) BBr_3, CH_2Cl_2, −78 °C to rt, 9 h, 93%.