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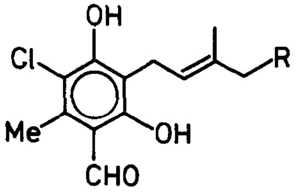
A GENERAL HIGHLY EFFICIENT ACCESS TO PRENYLATED PHENOLIC NATURAL PRODUCTS.
SYNTHESIS OF COLLETOCHLORINS B AND D

Hiroyuki Saimoto and Tamejiro Hiyama*

Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

A general approach is reported for the synthesis of phenolic natural products having terpenoid side chains: (1) construction of the requisite bromophenol ethers, (2) coupling the aromatic ring with a terpenoid chain through copper(I) ate complex, and (3) ether cleavage under neutral or basic conditions, and the feasibility of this strategy is demonstrated by efficient synthesis of colletochlorins B and D.

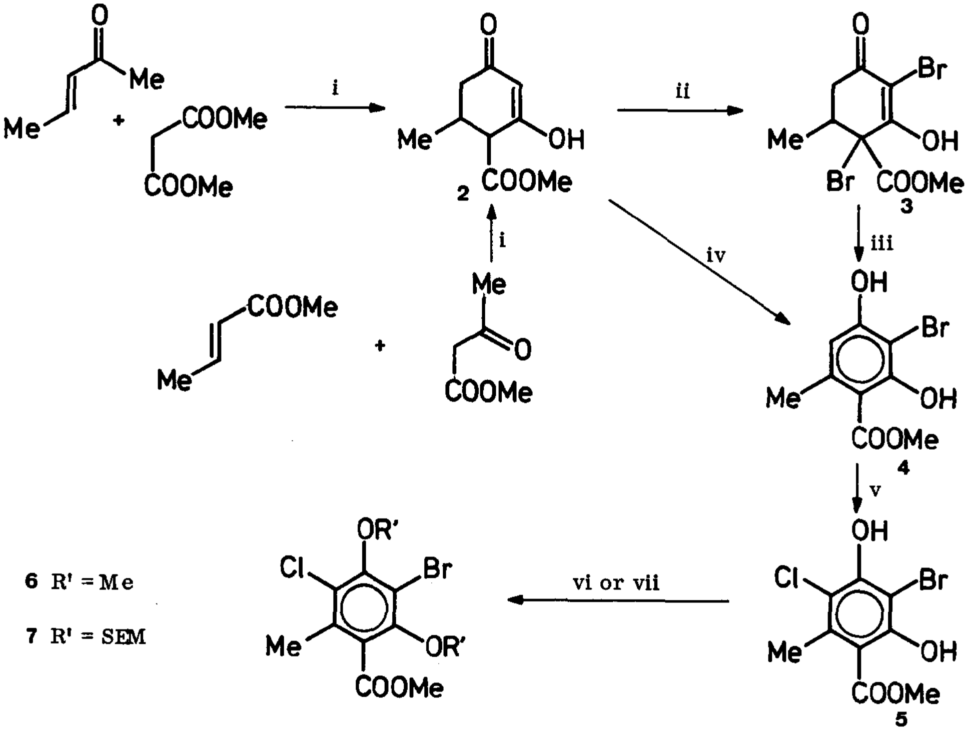
A group of natural products called "phenolic compounds" is characterized by multi-substituted (poly)hydroxylarenes which often involve a terpenoid side chain.[1] Particular examples are antibiotics ascofuranone,[2] ascochlorin,[3] and colletochlorins,[4] all of which possess a fully substituted resorcinol moiety in common and exhibit a variety of biological activity.[5] Efforts for synthesizing these natural products[6] have been made extensively but with little success. The major synthetic obstacle seems to be construction of the fully substituted benzene ring as well as connection of the aromatic moiety to the terpenoid side chain with or without phenolic protection.[7] We report herein the solutions for these problems as illustrated by efficient synthesis of colletochlorins B (**1a**) and D (**1b**).



1a R = $CH_2CH{=}CMe_2$ colletochlorin B

1b R = H colletochlorin D

The appropriately substituted bromoresorcinols **6** and **7** were synthesized from dimethyl malonate or methyl acetoacetate as shown in Scheme 1. Condensation of dimethyl malonate with 3-penten-2-one under basic conditions gave **2** (88% yield) which was treated with 2 mol of bromine in the presence of sodium hydride to afford **3** (71% yield). Dehydrobromination was carried out in hot acetic acid, and **4**[8]

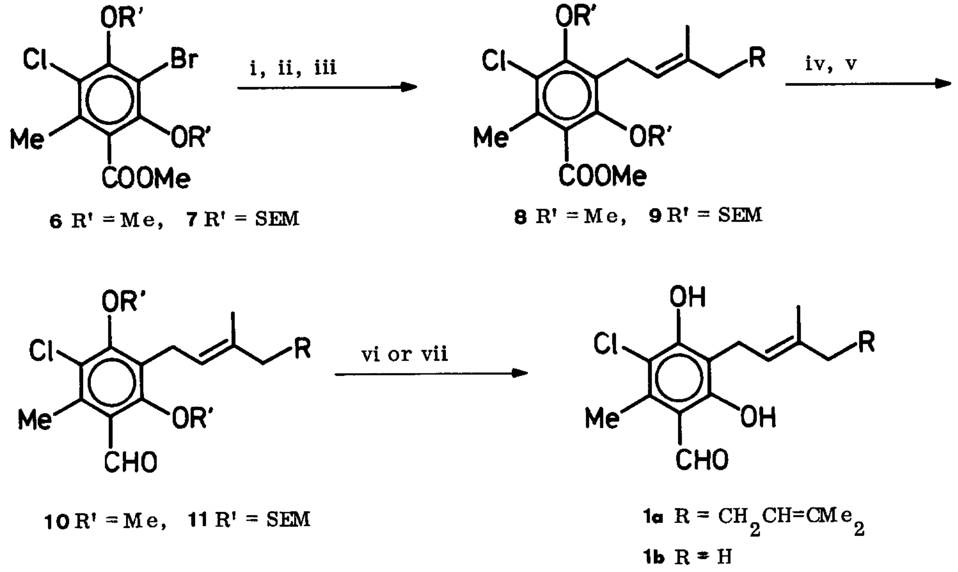


i) MeONa, MeOH, reflux; ii) NaH, Br_2, THF, r.t.; iii) AcOH, 100 °C; iv) Br_2, AcOH; v) SO_2Cl_2, CH_2Cl_2, r.t.; vi) Me_2SO_4, K_2CO_3, acetone; viii) SEM-Cl, iPr_2NEt, CH_2Cl_2

Scheme 1

was obtained in 42% yield. The resorcinol derivative was prepared alternatively from **2** (46%), which in turn was prepared from methyl acetoacetate and methyl crotonate (67%), by the reported procedure.[8] Chlorination of **4** with sulfuryl chloride gave **5**[9] (mp 108-109 °C). The phenolic hydroxyls of **5** were protected by methyl groups or 2-(trimethylsilyl)ethoxymethyl (SEM) groups to give **6**[9] (97% yield from **4**) or **7**[9] (97% yield from **4**), respectively.

Now the requisite bromobenzene in hand, we studied the connection of the aromatic moiety with a terpenoid side chain. The bromobenzene **6** was first converted by Br-Li exchange reaction into the corresponding lithium compound. Although this phenyllithium resisted to alkylation under various conditions, a mixed cuprate procedure was proved to be feasible. Thus, the bromobenzene **6** (0.88 g, 2.7 mmol) in THF (15 ml) was treated with a hexane solution of butyllithium (1.72 M, 1.79 ml, 3.08 mmol) at -78 °C for 30 min. To this reaction mixture was added $CuC\equiv CC(OMe)Me_2$ (3.0 mmol)[10] prepared in a mixture of hexamethylphosphoric triamide (HMPA) (0.95 ml), THF (6 ml), and hexane (1.7 ml). After 20 min, a THF (3 ml) solution of geranyl bromide (0.51 g, 2.2 mmol) was added at -78 °C. The whole was stirred for 7 h and allowed to warm to room temperature. Extractive workup



6 R' = Me, **7** R' = SEM

8 R' = Me, **9** R' = SEM

10 R' = Me, **11** R' = SEM

1a R = CH$_2$CH=CMe$_2$

1b R = H

i) nBuLi, THF, -78 °C; ii) CuC≡CC(OMe)Me$_2$, HMPA, THF; iii) geranyl bromide or BrCH$_2$CH=CMe$_2$; iv) LiAlH$_4$, Et$_2$O; v) PyHClCrO$_3$, CH$_2$Cl$_2$; vi) EtSNa-HMPA or EtSMgBr-DMF; vii) TBAF, THF

Scheme 2

followed by column chromatography (dichloromethane-hexane 5 : 1) gave the desired product **8a**[9] (0.58 g, 70% yield) (Scheme 2). Under the same conditions the SEM derivative **7** was transformed to **9a**[9] in 91% yield. When 1-bromo-3-methyl-2-butene was employed in place of geranyl bromide, the corresponding coupling product **8b**[9] was obtained in 92% yield. The methoxycarbonyl groups in **8a**, **8b**, and **9a** were transformed to the formyl groups by reduction-oxidation, and **10a**,[9] **10b**,[9] and **11a**[9] were obtained in 99%, 90%, and 91% yields respectively.

Removal of the ether protecting groups of the phenolic hydroxyls often encounters serious problems. For example, cleavage of the methyl ether bonds of **10b** takes place hardly as reported by Joullié:[6d] deprotection of one hydroxyl group only is achieved with Me$_3$SiI. Other demethylating reagents induce serious side reactions. Boron tribromide sometimes transforms the formyl group to a dibromomethyl appendage.[11] Strongly acidic conditions should be avoided, as chromane ring formation grows remarkable under these conditions.[12] We found basic or neutral procedures are indeed effective for the deprotection. The resorcinol dimethyl ether **10a** was treated with excess sodium ethanethiolate in HMPA at 100 °C for 2 h and at 120 °C for 1 h. Workup followed by preparative TLC gave colletochlorin B (**1a**) in 64% yield, mp 90-91 °C, lit.[6b] 90-91 °C. Bromomagnesium ethanethiolate in dimethylformamide (DMF) was found to be particularly suitable for **10b**, and colletochlorin D (**1b**) (mp 147-149 °C, lit.[4c, 6c] 140-142 or 142-144 °C) was produced in 53% yield. Removal of the SEM groups of **11a** was accomplished by using tetrabutylammonium fluoride (TBAF)[13] in HMPA at 70 °C for 2.5 h, and **1a** was produced in 70% yield.

In summary, by efficient synthesis of colletochlorins B and D, we have demonstrated the feasibility of a new rational strategy for the synthesis of naturally occurring "phenolic compounds" which involve multi-substituted (poly)hydroxylated carboaromatic ring and terpenoid side chain(s):[14] (1) protection of the hydroxyl group(s) by ether formation, (2) coupling the aromatic ring with terpenoid bromide with the aid of a mixed copper ate complex, and (3) deprotection under slightly basic or neutral conditions. Application of the principle to the synthesis of ascofuranone will be disclosed in due course.

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