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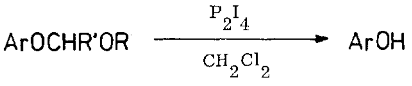
A MILD PROCEDURE FOR HYDROLYSIS OF ALKOXYMETHYL ARYL ETHERS TO GIVE HYDROXYARENES. A RATIONAL SYNTHESIS OF ASCOFURANONE

Hiroyuki Saimoto, Yukari Kusano, and Tamejiro Hiyama*
Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

A mild procedure is reported for cleavage of alkoxymethyl aryl ethers with P_2I_4 to afford hydroxyarenes, and this deprotection method was successfully applied to the synthesis of an antibiotic ascofuranone through a rational approach.

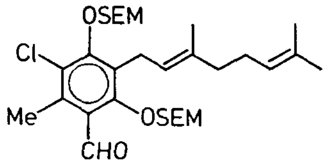
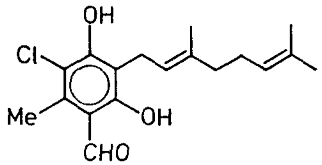
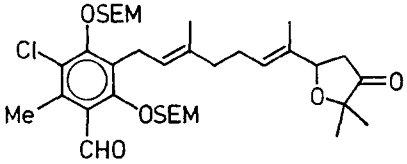
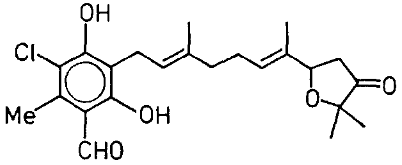
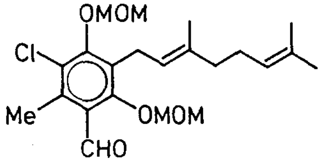
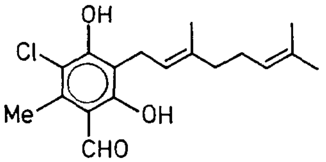
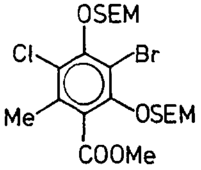
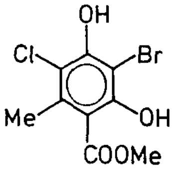
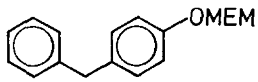
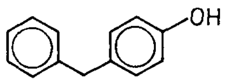
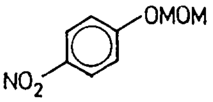
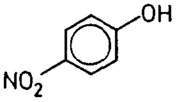
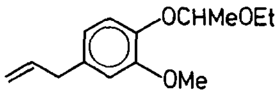
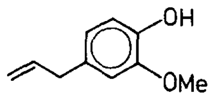
Natural products so called "phenolic compounds" or "phenolics" contain carboaromatic rings substituted by one or more hydroxyl groups as well as a terpenoid side chain.[1] Rational retro-synthetic analysis of these compounds leads to disconnection into the corresponding arenes and the terpenoid side chain.[2] Synthetic efforts thus far, however, have been hampered by a protection-deprotection problem of the phenolic hydroxyls. Particularly, deprotection under acidic conditions induces side reactions such as cyclization to a chromane structure, etc.[3] Basic conditions are not applicable to highly functionalized molecules such as ascofuranone.[4] We have found that alkoxymethyl ethers, which tolerate fairly wide range of C-C bond forming conditions,[5] are cleaved by diphosphorus tetraiodide[6,7] to regenerate the phenolic hydroxyl with the functionalized side chain intact.



$$\mathrm{ArOCHR'OR} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{P_2I_4}} \mathrm{ArOH}$$

A typical procedure is illustrated by the cleavage of (2-trimethylsilylethoxy)methyl (SEM) ether of colletochlorin B (**2**). Diphosphorus tetraiodide (15 mg, 0.027 mmol) was added to a dichloromethane (0.5 ml) solution of the bis-SEM ether **1** (21 mg, 0.036 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 25 min and at room temperature for 5 min. The reaction mixture was directly charged on the top of a short silica gel column (Wakogel C-100, 2.5 g) and eluted at 0 °C with ether to afford a crude product (11 mg) which was further purified by preparative TLC (silica gel, hexane-ethyl acetate 5 : 1) to give rise to colletochlorin B (10 mg, 86% yield). Other examples are shown in Table 1.

Table 1 Cleavage of Alkoxymethyl Aryl Ethers by P_2I_4

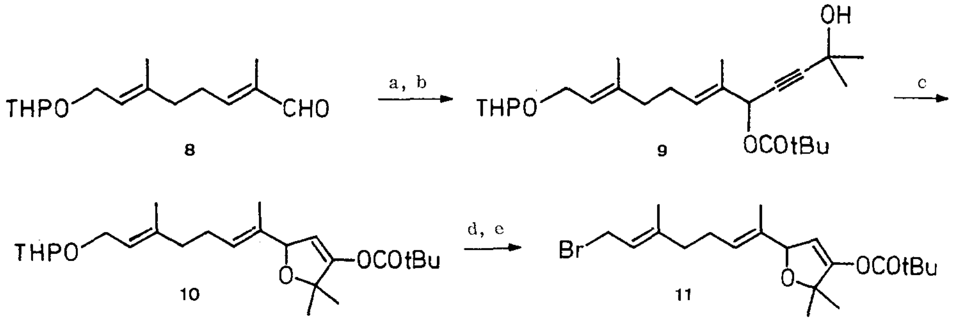
Run	Alkoxymethyl Aryl Ether	Hydroxyarene	Method and Yield (%)	
			P_2I_4	Reported
1	 1	 2	86	70^a 48^b
2	 3	 4	62	0^c
3	 5	 2	56	36^d
4	 6	 7	70	--
5			81	--
6			92	--
7			90	--

a) Tetrabutylammonium fluoride (TBAF) (10 eq) in HMPA (70 °C, 2.5 h). Cf. ref 8c.

b) Tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) (5 eq) in THF (r.t., 2.5 d).

c) TBAF or TASF (5 to 10 eq) in THF or HMPA failed to give **4**. BBr_3, $BBr_3 \cdot NEt_3$, $BBr_3 \cdot HN(SiMe_3)_2$, or MeSLi (Kelly, T. R.; Dali, H. M.; Tsang, W.-G. Tetrahedron Lett. 1977, 3859) gave complex mixture of products.

d) 6 M HCl-THF (1 : 1) (r.t., 4.5 h). Cf. ref 8a.



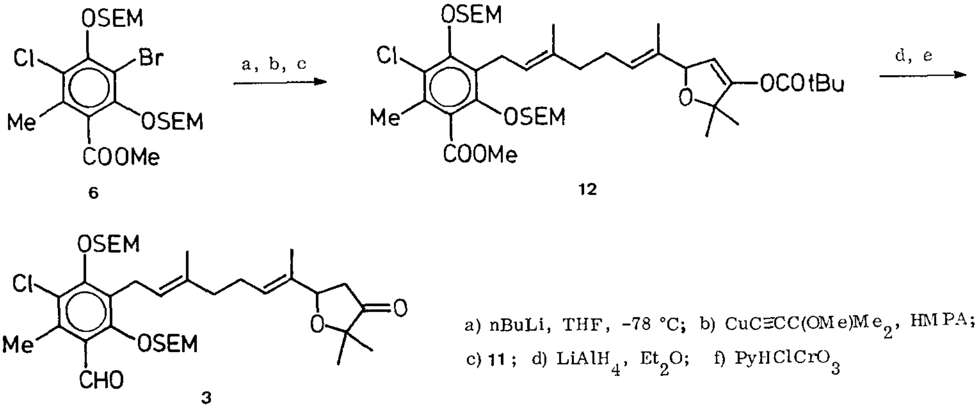
a) $LiC{\equiv}CC(OLi)Me_2$, THF; b) tBuCOCl, $4\text{-}Me_2N\text{-}C_5H_4N$, Py; c) $AgBF_4$ (0.1 eq), C_6H_6
d) PyHOTs, EtOH; e) CBr_4, $(octyl)_3P$, Et_2O

Scheme 1

In addition to the SEM ether, methoxymethyl (MOM) and methoxyethoxymethyl (MEM) ethers are cleaved by P_2I_4. Results by the conventional deprotection procedures also are listed in Table 1 which clearly shows the deprotection by P_2I_4 proceeds under extremely mild conditions. The new deprotection procedure allowed us to synthesize ascofuranone (**4**) (run 2), an antibiotic which exhibits antitumor, hypolipidemic, and antihypertensive as well as antitumor protective activities.[9]

The requisite precursor **3** was synthesized as shown in Schemes 1 and 2. The aldehyde **8**[10] was transformed to **9** (81%), whose Ag(I)-assisted rearrangement gave **10** (55% yield).[11] After removal of the tetrahydro-2-pyranyl (THP) protecting group (92% yield), the resulting alcohol was allowed to react with 2.3 eq of a brominating reagent, $CBr_4/(octyl)_3P$, in ether at 0 °C.[12] Concentration of the reaction mixture and purification of the residue by short column chromatography (neutral alumina, benzene elution) gave the unstable bromide **11** in 92% yield.

The aromatic segment **6**[2] was prepared from 2-bromo-4-methoxycarbonyl-5-methyl-1,3-benzenediol[13] by chlorination with SO_2Cl_2 followed by alkylation with SEM chloride/iPr_2NEt (97% overall yield). The bromobenzene **6** in THF was treated with butyllithium (1.2 eq) at -78 °C for 30 min and then



a) nBuLi, THF, -78 °C; b) $CuC{\equiv}CC(OMe)Me_2$, HMPA;
c) **11** ; d) $LiAlH_4$, Et_2O; f) $PyHClCrO_3$

Scheme 2

with $CuC{\equiv}CC(OMe)Me_2$ (1.1 eq) in a mixture of THF, hexamethylphosphoric triamide (HMPA) and hexane. The resulting mixed cuprate was allowed to react with the bromide **11** (0.9 eq) at -78 °C. Reaction at -78 °C for 3 h, warming to -40 °C, followed by workup and purification by preparative TLC, gave **12** (70% yield based on the bromide **11**). This was then converted into **3** in 95% yield by reduction and oxidation. Alkylation of **6** with geranyl bromide (91% yield) followed by the same functional group manipulation (91% yield) gave rise to **1**.[14]

In conclusion, a new deprotection procedure which involves cleavage of alkoxymethyl aryl ethers with P_2I_4 is proved to be expedient for the synthesis of naturally occurring "phenolics" as demonstrated by the synthesis of an antibiotic ascofuranone.[15] This new strategy will enable us to synthesize various kinds of prenylated phenolic natural products.[16]

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