Tetrahedron Letters, Vol 32, No 40, pp 5593-5596, 1991
Printed in Great Britain

0040-4039/91 $3.00 +
Pergamon Press plc

A Concise Synthesis Of (-)-Conduritol F From L-Quebrachitol Via $AlCl_3$-*n*-Bu_4NI Mediated Demethylation

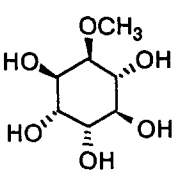
Takahiko AKIYAMA,* Hiroaki SHIMA, and Shoichiro OZAKI*

Department of Applied Chemistry, Faculty of Engineering,
Ehime University, Bunkyo-cho, Matsuyama 790, Japan

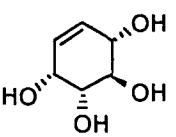
Keywords: (-)-conduritol F; (+)-conduritol B; L-quebrachitol; demethylation; $AlCl_3$

Abstract: *(-)-Conduritol F was prepared starting from naturally occurring cyclitol, L-quebrachitol, in 5 steps via $AlCl_3$-Bu_4NI mediated chemoselective demethylation of the methyl ether. A preparation of (+)-conduritol B was also described.*

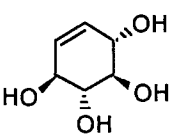
There is currently considerable interest in the synthesis of conduritols, cyclohex-5-ene-1,2,3,4-tetrol,[1] since these compounds are useful precursors in the preparation of cyclitols such as *myo*-inositol phosphates, and pseudo-sugars, and also because their derivatives present interesting biological activities.[2] Concise chiral syntheses of conduritols are hence desired. There are, however, few reports on the subject though chiral syntheses of conduritols via microbial oxidation of benzene have been recently reported.[3] As part of our continuing effort to explore the utility of L-quebrachitol (1L-2-*O*-methyl-*chiro*-inositol),[4,5,6] we wish to report a concise preparation of (-)-conduritol F,[7] the antipode of naturally occurring (+)-leucanthemitol, from L-quebrachitol via $AlCl_3$-*n*-Bu_4NI mediated chemoselective demethylation of the methyl ether, and also describe a first synthesis of (+)-conduritol B.



L-Quebrachitol

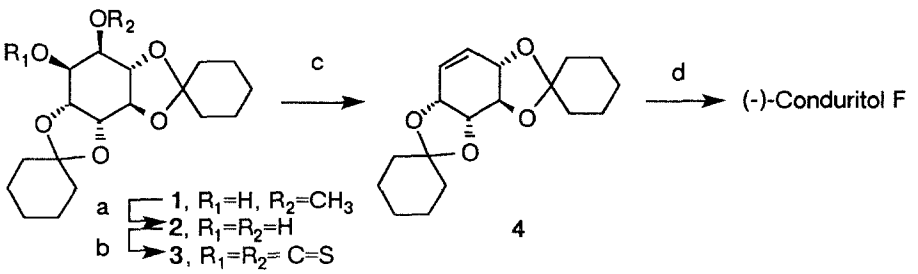


(-)-Conduritol F



(+)-Conduritol B

We reported, in a previous paper,[8] that a combined system of $AlCl_3$ and NaI[9] cleaved methyl ethers with vicinal OH group in preference to the *cis* cyclohexylidene moieties. Our strategy for the synthesis of (-)-



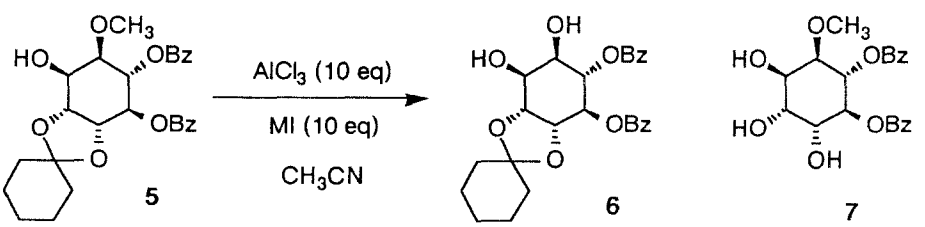
Scheme 1 a) See text, b)N,N'-thiocarbonyldiimidazole, acetone, reflux, 9 h, 90%, c) $P(OCH_3)_3$, reflux, 6 h, d) 80%trifluoroacetic acid in methanol, 90% from **3**.

Table 1 Demethylation of **1** by means of $AlCl_3$ and iodide ion.[a)]

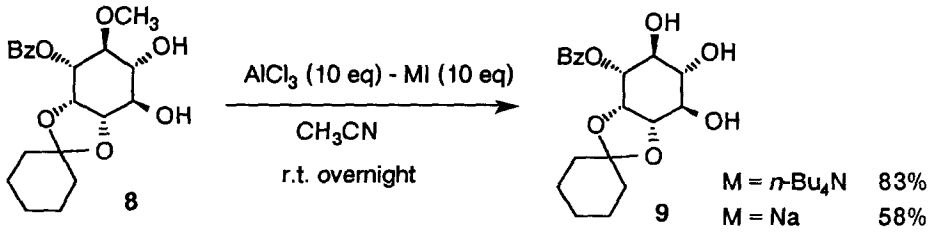
Run	Equiv. of $AlCl_3$	Metal Iodide (Equiv)	Time / h	Yield of **2** /%	Recovery of **1**/%
1	10	NaI (10)	20	57	13
2	20	KI (20)	34	41	37
3	10	LiI (10)	22	59	25
4	10	*n*-Bu_4NI (10)	26	78	12

a) Reactions were carried out in the presence of pyridine(10 eq) in CH_3CN at room temperature

conduritol F involves $AlCl_3$ mediated chemoselective demethylation as outlined in Scheme 1. Treatment of **1**, which was prepared in one step from L-quebrachitol, with $AlCl_3$ (10 equiv) and NaI (10 equiv) in the presence of pyridine (10 equiv) in CH_3CN gave **2** in 57% yield.[10] Concurrent cleavage of cyclohexylidene moieties took place in the system and chemoselective demethylation in preference to the *trans* cyclohexylidene group was difficult with the system. In order to overcome the difficulty, iodide source was examined and the results are shown in Table 1. Marked effect of the counter cations was observed and a use of tetrabutylammonium iodide instead of NaI[11] suppressed the cleavage of cyclohexylidene moiety and **2** was obtained in 78% yield.[12] Advantage of $AlCl_3$-*n*-Bu_4NI over $AlCl_3$-NaI is also demonstrated in the demethylation of **5** and **8**, in which case the presence of pyridine is not necessary. On treatment of **5** and **8** with $AlCl_3$-*n*-Bu_4NI in CH_3CN,

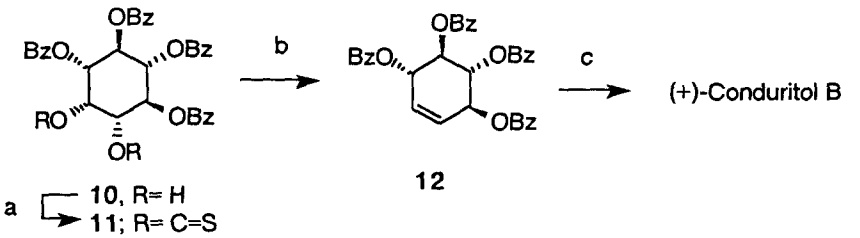


M = *n*-Bu_4N	0 °C, 2 h	88%	0%
M = Na	0 °C, 3 h	54%	17%



chemoselective demethylation took place without concurrent cleavage of the acetal groups, giving **6** and **9** in high yields respectively. $AlCl_3$-*n*-Bu_4NI was thus found to be much superior to $AlCl_3$-NaI for the chemoselective demethylation of the methyl ethers although both reagents system showed similar reaction rate.

Treatment of **2** with N,N'-thiocarbonyldiimidazole gave a cyclic thiocarbonate **3**, which was treated with trimethylphosphite to furnish **4**. Deprotection of the cyclohexylidene groups afforded (-)-conduritol F as crystals.[13] Thus, (-)-conduritol F was synthesized in 5 steps starting from L-quebrachitol. Although several reports appeared on the syntheses of it, our present method is the most straightforward and practical.



Scheme 2. a) N,N'-thiocarbonyldiimidazole, acetone, reflux, 5 h, 91%, b) $P(OCH_3)_3$, reflux, 5 h, 97%, c) NaOMe, MeOH, r.t. overnight.

Finally, we prepared (+)-conduritol B starting from a diol **10**, which was readily available from L-quebrachitol.[4] Although recemic and (-)-conduritol B have been already synthesized,[7] no preparation of (+)-conduritol B has been reported so far. Treatment of **10** with N,N'-thiocarbonyldiimidazole gave cyclic thiocarbonate **11**, which was treated with trimethylphosphite to give **12**. Deprotection of the benzoyl groups afforded (+)-conduritol B quantitatively.[14]

In conclusion, we found that a combined system of $AlCl_3$ and *n*-Bu_4NI selectively cleaved methyl ether in preference to the cyclohexylidene moieties and accomplished a short step synthesis of (-)-conduritol F from L-quebrachitol, and also a first synthesis of (+)-conduritol B. The present demethylation method will be a useful tool in manipulating naturally occurring cyclitols bearing methyl ethers such as L-quebrachitol and pinitol[11b] and will expand the utility of the cyclitols as chiral synthon in natural product syntheses.

Acknowledgment: The authors wish to express our gratitude to Yokohama Rubber Co. Ltd. (Tokyo Japan) for the kind gift of L-quebrachitol.

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11. Demethylation of methyl ethers employing BF_3OEt_2-*n*-Bu_4NI was already reported, but comparison of NaI and *n*-Bu_4NI was not studied: a) Mandal, A. K. N.; Soni, R.; Ratman, K. R. *Synthesis*, **1985**, 274-275. b) Ley, S. V.; Sternfeld, F. *Tetradedron*, **1989**, 45, 3463-3476.
12. A typical experiment procedure of the demethylation is as follows: To a solution of **1** (306 mg, 0.864 mmol), *n*-Bu_4NI (3.2 g, 8.6 mmol), and pyridine (0.69 ml, 8.6 mmol) in CH_3CN (9.0 ml) was added $AlCl_3$ (1.15 g, 8.6 mmol) at 0 °C. Stirring was continued for 26 h at room temperature. The reaction mixture was quenched by addition of water (30 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were successively washed with 10% Na_2SO_3 solution and brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The remaining residue was dissolved in small amount of CH_2Cl_2 and Et_2O was added. The precipitate thus formed was filtered off and the filtrate was concentrated and purified by preparative TLC ($CHCl_3$: Et_2O (v/v) = 3:1) to afford **2** (229 mg, 78%).
13. (-)-Conduritol F; $[\alpha]_D^{22}$ = -70.7° (c 0.75, CH_3OH), lit.[7c] $[\alpha]_D^{20}$ = -70.5° (c 0.75, CH_3OH), mp 131-132 °C, lit.[7f] [(+)-isomer] 129-130 °C.
14. (+)-Conduritol B; $[\alpha]_D^{22}$ = 191° (c 1.26, CH_3OH), lit.[7f](-)-isomer $[\alpha]_D^{20}$ = -179° (c 1.2, CH_3OH), mp 177-178 °C, lit.[7c][(-)-isomer] 179°C .

(Received in Japan 12 June 1991)