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Anchimerically Assisted Demethylation of Methyl Ethers in Inositol Derivatives with an $AlCl_3$-NaI System

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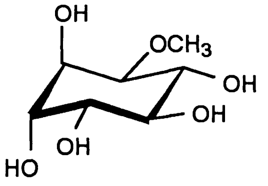
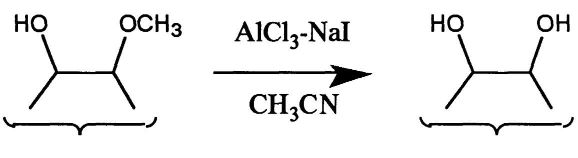
Investigated are $AlCl_3$ and NaI catalyzed chemoselective demethylation reactions of methyl ethers of partly protected inositol derivatives, reactions which are greatly promoted by vicinal OH group and proceed in preference to the cleavage of the *cis* cyclohexylidene moiety.

L-Quebrachitol (1L-(-)-2-*O*-methyl-*chiro*-inositol), a naturally occurring optically active inositol, has recently stimulated much attention as a chiral building block[1,2] and several optically active *myo*-inositol derivatives have been synthesized starting from it.[1] Demethylation of ring substituted *O*-methyl ether in cyclitol system is a crucial problem in manipulating it and traditionally drastic conditions such as HI,[2] and BCl_3,[1a] which cleave usual protecting groups altogether, have been used. Recently Ley[3] reported a $BF_3 \cdot OEt_2$-Bu_4NI catalyzed demethylation reaction of *O*-methyl-*O*-pentabenzoyl-*chiro*-inositol which proceeded in modest yield, but the demethylation reaction of cyclitol *O*-methyl ether which was achieved under mild conditions had not been appeared. In a previous paper,[1d] we reported that $AlCl_3$ and NaI system[4] selectively cleaved the methyl ether of inositol benzoate in preference to the *cis* cyclohexylidene group; this method was used in a chiral synthesis of D-*myo*-inositol 1-phosphate starting from L-quebrachitol. In this paper, we focussed attention on the demethylation reactions of methyl ethers in several inositols derived from L-quebrachitol with an $AlCl_3$-NaI system and found that the presence of OH group, vicinall to methyl ether, was essential in the cleavage reaction.

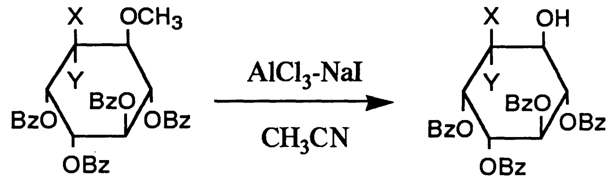


L-Quebrachitol



Scheme 1.

In the first place, we examined the demethylation reactions of inositol benzoates by the combined use of $AlCl_3$-NaI in CH_3CN and the results are shown in Table 1. Treatment of **1a** with a mixture of 10 equiv. of $AlCl_3$ and 10 equiv. of NaI in CH_3CN for 20 min gave an *O*-demethylated product **2a** in 95% yield. (Run 1) Demethylation of **1b** needed much longer time, but underwent smoothly to obtain **2b** in 92% yield. (Run 2) On the other hand, **1c** resisted demethylation under the same conditions and an *O*-demethylated product **2c** was



1a X=OH, Y=H
1b X=H, Y=OH
1c X=OBz, Y=H

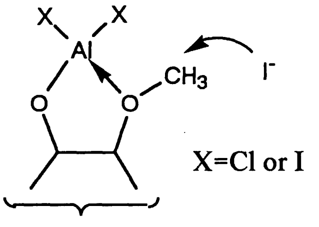
2a,b,c

Table 1. Demethylation of inositol benzoate 1

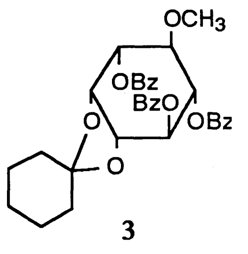
Run	Starting material	$AlCl_3$/equiv.	NaI/equiv.	Conditions	Yield of 2/%
1	**1a**	10	10	r.t. 20 min	95
2	**1b**	10	10	r.t. 15 h	91
3	**1c**	20	20	r.t. 7 d	27[a)]

a) 73% of the starting material was recovered.

obtained in a poor yield after 7 days with a large amount of the starting material recovered. Based on these results, we considered that vicinal OH group assisted the cleavage of methyl ether by forming the 5-membered ring by intramolecular coordination of aluminum to ether oxygen as shown in Scheme 2. The ease of demethylation of **1a**, bearing *cis* OH group to the methyl ether, in comparison to **1b**, with *trans* OH group, can be interpreted by considering the stability of the 5-membered rings formed. Pivotal role of vicinal OH group was also observed in the attempted ether cleavage reaction of **3**, in which case the *cis* cyclohexylidene moiety was cleaved preferentially and the methyl ether was partially cleaved under the forcing conditions (reflux 24 h) to give a demethylated compound in less than 25% yield with concomitant migration of the benzoyl group.



Scheme 2.



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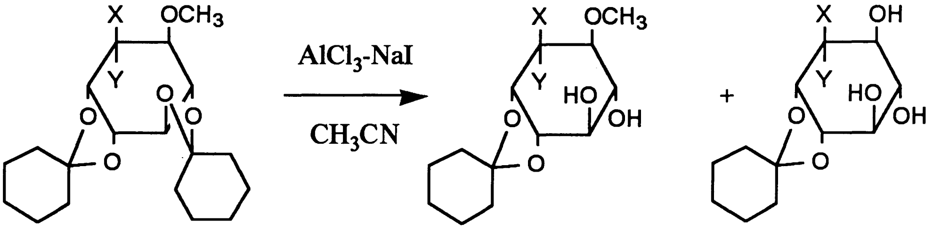
Next we investigated the vicinal OH group promoted demethylation reactions of cyclohexylidene protected inositol derivatives (Table 2). Treatment of a *myo*-inositol benzoate **4a** with $AlCl_3$-NaI in CH_3CN at room temperature gave a triol **6a** in 83% yield.(Run 1) When the reaction was carried out at 0 °C for 10 min, only *trans* cylclohexylidene moiety was cleaved and a diol **5a** was obtained exclusively (Run 2), indicating that the methyl ether was cleaved subsequent to the *trans* cyclohexylidene group and OH group, thus emerged, promoted the demethylation reaction. The demethylation reaction of **5a** actually proceeded similarly and **6a** was obtained.(Run 3) A *chiro*-Inositol benzoate **4b** also afforded the corresponding triol **6b**, accompanied by a diol **5b** at room temperature for 3 h (Run 4), though longer reaction time decreased the yield of **6b** by further



4a X= H, Y=OBz
4b X=OBz, Y=H
4c X=OTs, Y=H
4d X=OH, Y=H

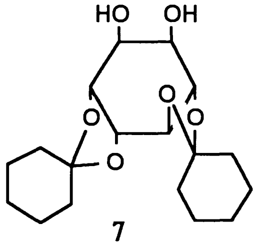
5a,b

6a,b,c

Table 2. Reaction of cyclohexylidene inositol derivatives

Run	Starting Material	$AlCl_3$/equiv.	NaI/equiv.	Conditions	Products / %	
1	**4a**	10	10	r.t. overnight	**6a**; 83[a]	
2	**4a**	5	5	0 °C, 10 min	**5a**; 77	
3	**5a**	10	10	r.t. overnight	**6a**; 58	
4	**4b**	10	10	r.t. 3 h	**5b**; 22	**6b**; 52
5	**4b**	5	5	0 °C, 1 h	**5b**; 89	
6	**4c**	10	10	r.t. overnight	**6c**; 75	
7	**4d**	4	4	r.t. 30 min	**8**; 49	
8	**4d**	10	10	r.t. 23 h[b]	**7**; 39	

a) Reported in Ref. 1d.
b) 10 equiv. of pyridine was added.



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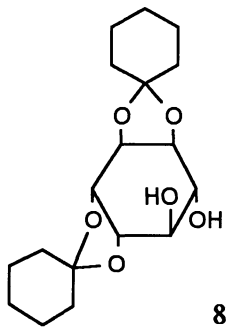

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cleavage of the *cis* cyclohexylidene moiety. The demethylation reaction of a tosylate **4c** also proceeded in a good yield. (Run 6) Finally, demethylation of **4d**, bearing *cis* OH group to the methyl ether, was studied. When **4d** was treated with $AlCl_3$ and NaI at room temperature, a sole product was not **7** but **8**, (Run 7) whose structure was identified with the authentic material synthesized from *chiro*-inositol by comparison with the 270 MHz NMR spectrum and TLC analysis. **7** was obtained exclusively by treatment of **4d** with $AlCl_3$ and NaI in the presence of 10 equiv. of pyridine. (Run 8) Although clear mechanism of the formation of **8** has not been clarified, **8** was considered to be produced by an acid catalyzed rearrangement of **7** in situ. This reaction is noteworthy in terms of the chemical selectivity; the methyl ether was cleaved faster than the labile *trans* cyclohexylidene moiety, and the strong accelerating effect caused by the vicinally *cis* substituted OH group was thus demonstrated.

Aluminum trichloride[5)] or boron trihalide[6)] catalyzed regioselective demethylation of aryl methyl ether promoted by the anchimerical assistance are reported. But similar demethylation of alkyl methyl ether usable in cyclitol system has not been studied.

In conclusion, we have demonstrated chemoselective demethylation promoted by vicinal OH group by the combined use of $AlCl_3$ and NaI, in which the accelerating effect of *cis* OH group is much stronger than that of *trans* OH group. Both benzoyl and *cis* cyclohexylidene moieties are compatible with this demethylation reaction and hence the present method will be a useful tool in manipulating naturally occurring cyclitols bearing methyl ether such as L-quebrachitol and pinitol.[1c)]

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7) A typical experiment procedure is as follows: To a solution of **1a** (110 mg, 0.180 mmol) in CH_3CN solution (2.5 ml) was added $AlCl_3$ (239 mg, 1.79 mmol) and NaI (270 mg, 1.80 mmol) at room temperature. Stirring was continued for 15 min. The reaction mixture was quenched by addition of water (10 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x 7 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 purified by preparative TLC (hexane:ethyl acetate (v/v) = 5:4) to afford **2a** (102 mg, 0.171 mmol, 95%).

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