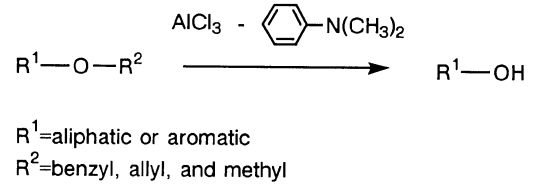
$AlCl_3$–*N, N*-Dimethylaniline: A Novel Benzyl and Allyl Ether Cleavage Reagent

Takahiko Akiyama,* Hajimu Hirofuji, and Shoichiro Ozaki*
Department of Applied Chemistry, Faculty of Engineering, Ehime University, Bunkyo-cho, Matsuyama 790
(Received December 16, 1991)

A combination system of $AlCl_3$–*N,N*-dimethylaniline was found to cleave benzyl ethers readily to give parent alcohols in excellent yields. The system also cleaved allyl as well as methyl ethers. Numerous functional groups such as benzoyloxy, phenylthio, and olefinic double bond were not affected. Comparisons of $AlCl_3$–*N,N*-dimethylaniline and $AlCl_3$–anisole were described.

A certain combination system of a Lewis acid and a soft nucleophile shows unique reactivity not exerted by a Lewis acid itself.[1] For the cleavage of carbon–oxygen bond, various combination systems have been reported.[2] A number of deprotecting methods have been developed for the cleavage of benzyl ether in addition to hydrogenolysis, such as TMSI (trimethylsilyl iodide),[3] TMSCl–NaI,[4] $SiCl_4$–NaI,[5] BBr_3,[6] BF_3–EtSH,[7] BF_3·OEt_2–Me_2S,[8] BF_3·OEt_2·–NaI,[9] and TMSCl–Ac_2O–cat. H_2SO_4.[10] These reagents, most of which are the combination of a hard Lewis acid and a soft nucleophile, have drawbacks such as instability and the stenches of the reagents, and long reaction time.

A reagent system of $AlCl_3$ and anisole is also a combination of a hard Lewis acid and a soft nucleophile, being successfully utilized in the deprotection of benzyl as well as benzhydryl esters, in particular, in the field of β-lactam chemistry.[11] We focused on the reagent system and found out that *p*-methoxybenzyl (PMB) group on the N^3-position of uridine was cleaved readily by use of $AlCl_3$–anisole without affecting N-glycosidic bond.[12] No application of the reagent system to the cleavage of the ether moiety, however, has been reported so far. We therefore examined the cleavage of benzyl ethers by use of $AlCl_3$–anisole. It was found that benzyl ether was

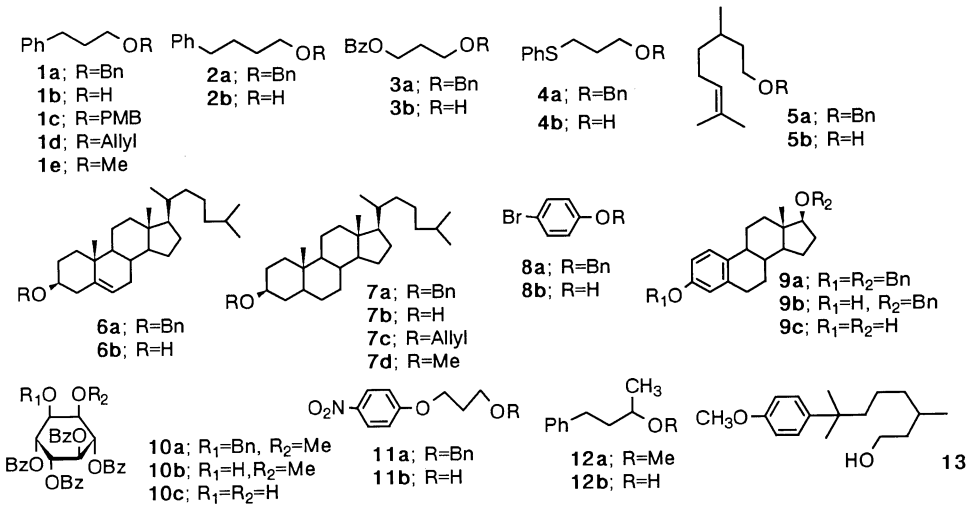


Scheme 1.

cleaved readily on treatment with $AlCl_3$–anisole to give parent alcohol in a good yield. During the study, we have found that $AlCl_3$–*N,N*-dimethylaniline is a stronger debenzylating reagent system than $AlCl_3$–anisole and is also effective for the cleavage of allyl as well methyl ethers.[13] In this paper we wish to describe the cleavage of benzyl, allyl, and methyl ethers with $AlCl_3$–*N,N*-dimethylaniline as well as $AlCl_3$–anisole. Comparisons of the two reagent systems are also described.

Results and Discussion

In the first place, benzyl 3-phenylpropyl ether (**1a**) was treated with $AlCl_3$ (3 equiv) and anisole (4 equiv) in CH_2Cl_2. The cleavage reaction proceeded smoothly at room temperature for 1 h to afford 3-phenyl-1-propanol



Scheme 2.

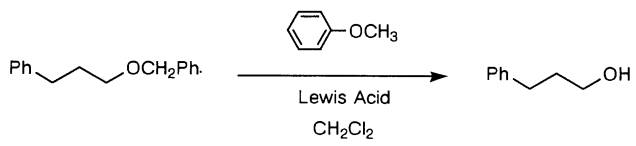


Table 1. Effects of Lewis Acids on the Debenzylation

Run	Lewis acid	Reaction time	Yield of alcohol	Recovery
		h	%	%
1	$AlCl_3$	1.0	91	0
2	$SnCl_4$	3	76	0
3	BF_3·Et_2O	5	15	74

3 Equiv of Lewis acid and 4 equiv of anisole were employed at room temperature.

(**1b**) in a high yield. When $AlCl_3$ (2 equiv) and anisole (3 equiv) were employed, the reaction was not completed. Effects of the Lewis acids on the debenzylation were examined and the results are shown in Table 1.

Strong Lewis acid was necessary for the cleavage of benzyl ether and other Lewis acids such as $SnCl_4$ or BF_3·OEt_2 were less satisfactory. Although this combined system of $AlCl_3$ and anisole proved to be effective for the cleavage of benzyl ether, tediousness in the removal of the remaining anisole in workup led us to screen other additives. We examined various kinds of soft nucleophiles, and the results are shown in Table 2.

Without an additive, messy products were obtained though the starting material disappeared readily. (Run 6) When triethylamine or pyridine was employed as a soft nucleophile, no reaction took place presumably due to the strong complex formation of the amine and $AlCl_3$.[14] (Runs 7 and 8) Electron-rich aromatic compounds such as *N,N*-dimethylaniline and phenol were found to be effective for the cleavage of benzyl ethers and *N,N*-dimethylaniline gave the best results among the compounds we examined. *N,N*-Dimethylaniline is also superior to anisole from the standpoint of practical use because it can be readily washed out from organic layer by aqueous acid treatment. Deprotection of a number of aliphatic and aromatic benzyl ethers were thus examined by use of $AlCl_3$ (3 equiv) and *N,N*-dimethylaniline (4 equiv) in CH_2Cl_2 at room temperature and the results are shown in Table 3. The cleavage reaction did not proceed at 0 °C, but was completed mostly in less than 1 h at room temperature to give parent alcohols in excellent yields. Functional groups such as benzoyloxy, phenylthio, and olefinic double bond were not affected under the present reaction conditons. For the cleavage of an aryl benzyl ether (**8a**), slightly larger amount of *N,N*-dimethylaniline (10 equiv) was necessary to obtain *p*-bromophenol (**8b**) in a high yield. (Run 11) The aryl benzyl ether moiety in estradiol-17β dibenzyl ether (**9a**) was cleaved selectively in preference to the aliphatic one affording **9b** in 80% yield.[15] (Run 12) Selective cleavage of PMB ether in preference to benzyl ether failed. In the case of **10a**, although the benzyl ether was cleaved to give the debenzylated alcohol (**10b**) in 50% yield, cleavage of the methyl ether took place concurrently to give **10c** in 28% yield. (Run 14) No reaction took place with **11a**, possessing a nitro moiety, and the starting material was recovered in 75% yield. (Run 16) *p*-Methoxybenzyl (PMB) ether (*1c*) was cleaved readily at 0 °C. (Run 18)

Although the combined system of $AlCl_3$–anisole also cleaved benzyl ethers smoothly to give parent alcohols in high yields, it occasionally gave different results from $AlCl_3$–*N,N*-dimethylaniline. In the case of **4a** possessing phenylthio group, which is expected to act as a soft nucleophile,[16] the desired alcohol (**4b**) was not obtained at all presumbly due to the competitive alkylation of the sulfide moiety. (Run 6) For the cleavage of **5a**, debenzylation did take place but anisole reacted with the olefinic double bond to give **13** in 63% yield. (Run 8) Cleavage of both aryl and alkyl benzyl ether moieties in **9a** underwent concurrently, affording **9c** in 73% yield. (Run 13) Methyl ether was not affected and **10b** was obtained in 93% yield form **10a**. (Run 15) Debenzylation of **11a**, bearing nitro group, took place readily to afford **11b** in 93% yield. (Run

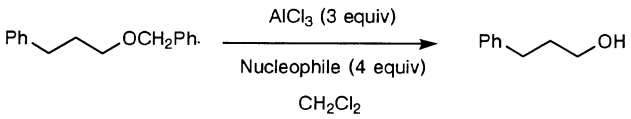


Table 2. Effects of Soft Nucleophile on the Debenzylation

Run	Nucleophile	Yield of alcohol	Recovery
		%	%
1	Anisole	91	0
2	*N,N*-Dimethylaniline	93	0
3	Phenol	87	0
4	*p*-Methoxy-*N,N*-dimethylaniline	71	0
5	*m*-Methoxy-*N,N*-dimethylaniline	67	0
6	None	0	0
7	Triethylamine	0	95
8	Pyridine	0	99

Table 3. Results of the Cleavage of Benzyl Ethers with $AlCl_3$ (3 equiv) and Additive in CH_2Cl_2 at Room Temperature

Run	Starting material	Additive (equiv)	Reaction time / h	Product	Yield / %
1	**1a**	$PhNMe_2$ (4.0)	0.5	**1b**	93
2	**1a**	PhOMe (4.0)	1.0	**1b**	91
3	**2a**	$PhNMe_2$ (4.0)	0.5	**2b**	86
4	**3a**	$PhNMe_2$ (4.0)	1.0	**3b**	88
5	**4a**	$PhNMe_2$ (4.0)	1.0	**4b**	96
6	**4a**	PhOMe (4.0)	3.0	**4b**	8
7	**5a**	$PhNMe_2$ (4.0)	1.5	**5b**	98
8	**5a**	PhOMe (4.0)	0.8	**5b**	0[a]
9	**6a**	$PhNMe_2$ (4.0)	1.0	**6b**	88
10	**7a**	$PhNMe_2$ (8.0)	2.5	**7b**	96
11	**8a**	$PhNMe_2$ (10.0)	0.5	**8b**	91
12	**9a**	$PhNMe_2$ (4.0)	1.0	**9b**	80
13	**9a**	PhOMe (8.0)	1.0	**9c**	73
14	**10a**	$PhNMe_2$ (8.0)	7.0	**10b**	50[b]
15	**10a**	PhOMe (5.0)	2.0	**10b**	93[c]
16	**11a**	$PhNMe_2$ (4.0)	1.0	**11b**	0[d]
17	**11a**	PhOMe (4.0)	3.0	**11b**	93
18	**1c**	$PhNMe_2$ (4.0)	0.75	**1b**	91[e]

a) **13** was obtained in 63% yield. b) $AlCl_3$ was used in 6.0 equiv and **10c** was obtained in 28% yield. c) $AlCl_3$ was used in 4.0 equiv. d) Staring material was recovered in 75% yield. d) The reaction was conducted at 0°C.

Table 4. Results of the Cleavage of Allyl Ethers with $AlCl_3$ and Additive in CH_2Cl_2

Run	Starting material	Equiv of $AlCl_3$	Additive (equiv)	Reaction conditions	Product	Yield / %
1	**1d**	3.0	$PhNMe_2$ (4.0)	r.t. 1 h	**1b**	83
2	**1d**	6.0	PhOMe (8.0)	Reflux 1 h	**1b**	65
3	**7c**	6.0	$PhNMe_2$ (8.0)	r.t. 2.5 h	**7b**	96

Table 5. Results of the Cleavage of Methyl Ethers with $AlCl_3$ and Additive in CH_2Cl_2

Run	Starting material	Equiv of $AlCl_3$	Additive (equiv)	Reaction conditions	Product	Yield / %
1	**1e**	3.0	$PhNMe_2$ (4.0)	r.t. 1 h	**1b**	61
2	**1e**	3.0	PhOMe (4.0)	r.t. 5 h	**1b**	0[a]
3	**7d**	6.0	$PhNMe_2$ (8.0)	Reflux 3.5 h	**7b**	96
4	**12a**	6.0	$PhNMe_2$ (8.0)	Reflux 5 h	**12b**	75

a) Starting material was recovered in 25% yield.

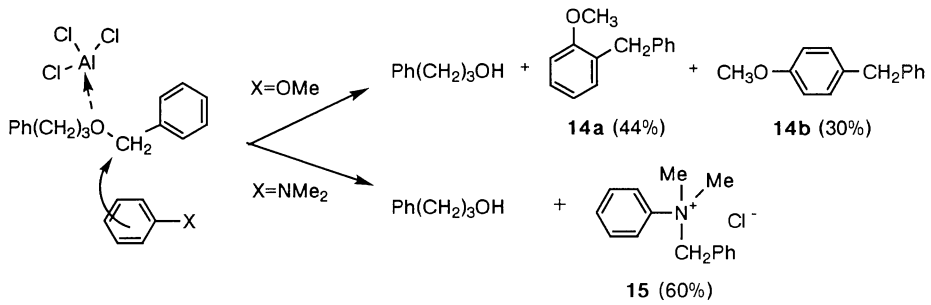
17)

Next we studied the cleavage reaction of allyl ethers[17] and the results are shown in Table 4. $AlCl_3$–*N,N*-dimethylaniline cleaved allyl ethers more smoothly than $AlCl_3$–anisole to afford parent alcohols in high yields.

Cleavage of methyl ethers[18] also took place with $AlCl_3$–*N,N*-dimethylaniline as shown in Table 5. Although the yields were moderate to high, *N,N*-dimethylaniline was found to be more effective reagent than anisole. Because $AlCl_3$–anisole does not cleave methyl ether, it is useful for the chemoselective cleavage of benzyl ether in the presence of methyl ether as demonstrated in Run 15 of Table 3.

The mechanism of the cleavage reaction is as shown in Scheme 3. The $AlCl_3$ coordinates with ether oxygen, then a soft nucleophile attacks soft benzylic carbon atom. When anisole was employed, Friedel–Crafts alkylation product, **14a** and **14b**, were obtained. With *N,N*-dimethylaniline, in contrast, the sole product obtained was an ammonium salt (**15**). The contrasting result of the cleavage of **4a** implies that the nucleophilicity of the soft nucleophile is in the following order; *N,N*-dimethylaniline>sulfide>anisole. The stronger nucleophilicity of *N,N*-dimethylaniline than anisole is in agreement with the reactivity order as Friedel–Crafts substrates.[19]

The $AlCl_3$–*N,N*-dimethylaniline system is an excellent reagent system for the cleavage of benzyl as well as allyl ethers. The features of the system are 1) short reaction time, 2) mild reaction conditions, 3) ease of handling of the reagent, and 4) compatibility of the functional groups



Scheme 3.

such as benzoyloxy, phenylthio, and olefinic double bond. The present method will be a new entry into the removal of benzyl as well as allyl ether protecting groups. When nitro group or methoxy group is present, this system did not work well, however, $AlCl_3$–anisole is effective in that case. It should be noted $AlCl_3$–*N,N*-dimethylaniline and $AlCl_3$–anisole work complementarily for the cleavage of benzyl ether.

Experimental

The melting points were recorded on a Yamato melting point apparatus and are uncorrected. MMR spectra were observed with a JEOL GSX-270 spectrometer or a Varian EM-390 with tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi EPI G-3 spectrometer. Specific rotations were recorded with a Union PM-101 digital polarimeter. Following alcohols (**1b**, **2b**, **5b**, **6b**, **7b**, and **8b**) used in this work were commercially available and were purified by distillation or recrystalliazation before use, as appropriate. $AlCl_3$ (anhydrous, purity >98%) was purchased from Wako Chemicals Industries Co., Ltd. and was ground into fine powder with being stored under N_2 atmosphere. *N,N*-Dimethylaniline and anisole were distilled over CaH_2 and stored over Molecular Sieves 4A. Purification of products were performed by column chromatography on silica gel (Wako gel C-300) or preparative TLC on silica del (Wako gel B-5F).

A typical procedure for the synthesis of benzyl ether is described for **1a**. Other benzyl ether except **3a**, **4a**, **10a**, **11a**, were prepared according to the similar method as **1a**, and purified either by distillation or column chromatogrphy.

Benzyl 3-Phenylpropyl Ether (1a). To a suspension of a 60% dispersion of NaH in mineral oil (761 mg, 19.0 mmol) in DMF (15 ml) was added dropwise 3-phenyl-1--propanol (2.07 g, 15.2 mmol) at 0 °C. Benzyl chloride (3.03 ml, 21.3 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 5 h. After excess sodium hydride was carefully destroyed with water, the reaction mixture was diluted with and ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to leave an oil, which was purified by distillation under reduced pressure to afford **1a** as an oil in 70% yield. Bp 145 °C (4 mmHg) (1 mmHg=133.322 Pa) (lit, bp 146—148 °C (6 mmHg));[20] ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.88 (2 H, tt, J=6.0, 7.5 Hz), 2.65 (2 H, t, J=7.5 Hz), 3.40 (2 H, t, J=7.5 Hz), 4.40 (2 H, s, OCH_2), and 6.85—7.38 (10 H, m, aromatic); IR (neat) 3000, 2900, 2800, 1590, 1470, 1430, 1350, 1080, 720, and 670 cm^{-1}.

***p*-Methoxyphenylmethyl 3-Phenylpropyl Ether (1c).** ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.71—1.99 (2H, m, $PhCH_2C\underline{H}_2$), 2.63 (2H, t, J=7.8 Hz, CH_2Ph), 3.31 (2H, t, J=6.0 Hz, CH_2O), 3.71 (3H, s, OCH_3), 4.31 (2H, s, OCH_2Ph), and 6.64—7.28 (5H, m, aromatic); IR (neat) 2900, 2800, 1600, 1480, 1430, 1280, 1220, 1160, 1080, 1020, 800, 730, and 680 cm^{-1}. Found: C, 79.67; H, 7.81%. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%

Allyl 3-Phenylpropyl Ether (1d). ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.68—2.10 (2H, m, CH_2), 2.60 (2H, dd, J=6, 8 Hz, CH_2Ph), 3.34 (2H, t, J=6 Hz, CH_2), 3.80—3.97 (2H, m, $C\underline{H}_2CH{=}CH_2$), 4.97—5.32 (2H, m, CH_2=) 5.60—6.10 (1H, m, $C\underline{H}{=}CH_2$), and 6.90—7.30 (5H, m, aromatic); IR (neat) 2900, 2800, 1470, 1430, 1080, 900, 720, and 660 cm^{-1}.

Methyl 3-Phenylpropyl Ether (1e).[21] ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.53—1.88 (2H, m), 2.51 (2H, t, J=7.5 Hz), 3.16 (3H, s, OCH_3), 3.16 (2H, t, J=7.5 Hz), and 6.70—7.09 (5H, m, aromatic); IR (neat) 2900, 2850, 1720, 1600, 1470, 1430, 1370, 1170, 1100, 1000, 730, and 680 cm^{-1}.

Benzyl 4-Phenylbutyl Ether (2a). ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.29—1.99 (4H, m, CH_2×2), 2.40—2.70 (2H, m, $PhCH_2$), 3.19—3.50 (2H, m, $C\underline{H}_2OCH_2OPh$), 4.30 (2H, s, OCH_2Ph), and 6.62—7.45 (10H, m, aromatic); IR (neat) 2900, 1600, 1490, 1440, 1360, 1100, 1020, 720, and 680 cm^{-1}.

3-(Benzyloxy)propyl Benzoate (3a). ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.95 (2H, quintet, J=6.0 Hz), 3.45 (2H, t, J=6.0 Hz), 4.28 (2H, t, J=6.0 Hz), 4.38 (2H, s, OCH_2), 6.90—7.43 (8H, m, aromatic), and 7.71—7.90 (2H, m, aromatic); IR (neat) 2950, 2850, 1710, 1420, 1250, and 1080 cm^{-1}. Found: C, 75.13; H, 6.84%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

3-Hydroxypropyl Benzoate (3b). To a solution of 3-(benzyloxy)-1-propanol (572 mg, 3.55 mmol) in pyridine (6 ml) were added a catalytic amount of 4-dimenhylaminopyridine (DMAP) and benzoyl chloride (592 mg, 4.23 mmol) at 0 °C. The reaction mixture was quenched by addition of 0.5 mol dm^{-3} HCl and the aqueous layer was extracted with Et_2O. The combined organic layer was washed wish brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give an oil, which was purified by column chromatography (SiO_2, hexane–ethyl acetate=8 : 1, v/v) to afford **3b** as an oil in 83% yield. ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.88 (2H, tt, J=6.0, 6.6 Hz), 3.15 (1H, s, OH), 3.59 (2 H, t, J=6.0 Hz), 4.29 (2H, t, J=6.6 Hz), 6.99—7.45 (3H, m, aromatic), and 7.67—7.97 (2H, m, aromatic); IR (neat) 3600, 3450, 3000, 1700, 1270, 1200, 1120, 740, and 660 cm^{-1}.

Benzyl 3-(Phenylthio)propyl Ether (4a).[9] To a suspension of a 60% dispersion of NaH in mineral oil (530 mg, 12.7 mmol) in DMF (8 ml) was added dropwise 3-chloro-1-propanol (0.88 ml, 10.6 mmol) at 0 °C. Benzyl chloride (1.81 ml, 12.7 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 1.5 h. After

excess sodium hydride was carefully destroyed with water, the reaction mixture was diluted with water and ethyl acetate. The organic layer was washed with wnter and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to leave an oil, which was purified by column chromatography (SiO_2, hexane–CH_2Cl_2=5 : 1, v/v) to afford benzyl 3-chloropropyl ether as an oil in 97% yield. To a solution of KOH (228 mg, 4.07 mmol) in methanol (10 ml) was added thiophenol (0.334 ml, 3.25 mmol) at room temperature. After 10 min, benzyl 3-chloropropyl ether (500 mg, 2.71 mmol) was added to the reaction mixture and the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of 0.5 mol dm^{-3} HCl and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed successively with water, sat. $NaHCO_3$ solution, and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave an oil, which was purified by column chromatography (SiO_2, hexane–ethyl acetate, 15 : 1, v/v) to afford **4a** as an oil in 81% yield. ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.90 (2H, tt, J=7.5, 8.4 Hz), 2.97 (2H, t, 8.4 Hz), 3.48 (2H, t, J=7.5 Hz), 4.38 (2H, s, OCH_2), and 6.99—7.22 (10H, m, aromatic); IR (neat) 3050, 1480, 1320, 1250, 1100, 1050, 840, and 740 cm^{-1}. Found: C, 74.47; H, 7.05%. Calcd for $C_{16}H_{18}O_2S$: C, 74.38; H, 7.02%.

3-Phenylthio-1-propanol (4b).[9] ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.77 (2H, tt, J=7.5, 8.4 Hz), 2.68 (1H, s, OH), 2.87 (2H, t, J=8.4 Hz), 3.55 (2H, t, J=7.5 Hz), and 6.82—7.19 (5H, m, aromatic); IR (neat) 3350, 2950, 1570, 1460, 1420, 1040, 1020, 890, 710, and 660 cm^{-1}. Found: C, 64.37; H, 7.21%. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19%.

Benzyl 3,7-Dimethyl-6-octenyl ether (5a).[22] ^{1}H NMR (90 MHz, $CDCl_3$) δ=0.88 (3H, d, J=6 Hz, CH_3), 1.1—2.25 (7H, m, CH_2×3, CH), 1.57 (3H, s, CH_3), 1.64 (3H, s, CH_3), 3.45 (2H, t, J=7 Hz, CH_2O), 4.40 (2H, s, CH_2Ph), 4.85—5.16 (1H, m, CH=), 7.1—7.4 (5H, m, aromatic); IR (neat) 2900, 2940, 1595, 1490, 1445, 1235, 1175, 1025, and 805 cm^{-1}.

Cholesteryl Benzyl Ether (6a). Mp 115—116.5 °C (acetone) (lit, 117 °C)[10] ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.68—2.40 (43H, m), 3.24—3.30 (1H, m, H-3), 4.56 (2H, s, CH_2), 5.37 (1H, d, J=5.5 Hz, H-6), and 7.26—7.35 (5H, m, aromatic); IR (nujol) 1090 and 1000 cm^{-1}.

5α-Cholestan-3β-yl Benzyl Ether (7a). Mp 103.5—104 °C (acetone) (lit, 104-105 °C);[7] ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.64—1.93 (47H, m), 3.33 (1H, m, H-3), 4.55 (2H, s, CH_2), and 7.26—7.34 (5H, m, aromatic); IR (nujol) 1090, 1010, and 720 cm^{-1}.

5α-Cholestan-3β-yl Allyl Ether (7c). Mp 67—68 °C (acetone) (lit, 68—69 °C);[23] ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.56—1.98 (46H, m), 3.99—4.02 (1H, m, H-3) 3.99—4.02 (2H, m, OCH_2), 5.11—5.30 (2H, m, CH_2=), and 5.85—6.00 (1H, m, =C<u>H</u>CH_2); IR (nujol) 1130, 1100, 1020, 990, and 920 cm^{-1}.

5α-Cholestan-3β-yl Methyl Ether (7d). MP 82.5—83.5 °C (acetone) (lit, 82—83 °C);[24] ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.63—2.00 (46H, m), 3.04—3.18 (1H, m, H-3), 3.32 (3H, s, OCH_3); IR (nujol) 1160, 1090, 920, and 910 cm^{-1}.

Benzyl 4-Bromophenyl Ether (8a). Mp 61—62.5 °C (lit, 59—60 °C);[7] ^{1}H NMR (90 MHz, $CDCl_3$) δ=4.91 (2H, s, CH_2), 6.68 (2H, d, J=8.4 Hz, aromatic), and 7.02—7.32 (7H, m, aromatic); IR (neat) 2900, 2800, 1470, 1440, 1360, 1220, and 980 cm^{-1}.

Estradiol-17β 3,17-Dibenzyl Ether (9a). Mp 79.5—81 °C (EtOH–acetone) (lit, 81—82 °C);[7] ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.87 (3H, s, CH_3), 1.15—2.29 (13H, m), 2.80—2.86 (2H, m), 3.49 (1H, t, J=8.2 Hz, H-17), 4.57 (2H, s, CH_2), 5.01 (2H, s, CH_2), 6.70 (1H, d, $J_{2,4}$=2.8 Hz, H-4), 6.77 (1H, dd, $J_{1,2}$=8.6 Hz, $J_{2,4}$=2.8 Hz, H-2), 7.10 (1H, d, $J_{1,2}$=8.6 Hz, H-1), and 7.22—7.44 (10H, m, aromatic); IR (nujol) 1600, 1220, 1140, and 1100 cm^{-1}.

Estradiol-17β 17-Benzyl Ether (9b). Mp 194—197 °C (EtOH–acetone) (lit, 195—196 °C);[7] ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.87 (3H, s, CH_3), 1.12—2.28 (11H, m), 2.58 (2H, s), 2.77—2.83 (2H, m), 3.51 (1H, t, J=8.2 Hz, H-17), 4.57 (2H, s, CH_2), 6.54 (1H, d, $J_{2,4}$=2.8 Hz, H-4), 6.61 (1H, dd, $J_{1,2}$=8.3 Hz, $J_{2,4}$=2.8 Hz, H-2), 7.12 (1H, d, $J_{1,2}$=8.2 Hz, H-1), and 7.26—7.35 (6H, m, aromatic, OH); IR (nujol) 3400, 1480, and 1080 cm^{-1}. Found: C, 82.48; H, 8.35%. Calcd for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34%.

1L-1,2,3,4-Tetra-*O*-benzoyl-6-*O*-benzyl-5-*O*-methyl-*chiro*-inositol (10a). This was prepared from 1L-1,2 : 3,4-di-*O*-cyclohexylidene-5-*O*-methyl-*chiro*-inositrol[25] by 6-*O*-benzylation followed by acidic hydrolysis of the cyclohexylidene moiety and per-*O*-benzoylation. Mp 138—139 °C (hexane : ethyl acetate=4 : 1, v/v); ^{1}H NMR (270 MHz, $CDCl_3$) δ=3.34 (3H, s, OCH_3), 3.87 (1H, dd, $J_{5,6}$=2.7 Hz, $J_{4,5}$=9.8 Hz, H-5), 4.27 (1H, dd, $J_{5,6}$=2.7 Hz, $J_{1,6}$=4.0 Hz, H-6), 4.95 (2H, s, OCH_2), 5.94 (2H, m, H-1,4), 6.12 (2H, m, H-2,3), 7.20—8.17 (25H, m, aromatic);IR (nujol) 2950 and 1720 cm^{-1}; $[\alpha]_D^{20}$ −75.8 ° (*c* 1.02, $CHCl_3$); Found: C, 71.69; H, 5.26%. Calcd for $C_{42}H_{36}O_{10}$: C, 71.99; H, 5.18%.

1L-1,2,3,4-Tetra-*O*-benzoly-5-*O*-methyl-*chiro*-inositol (10b).[26] ^{1}H NMR (270 MHz, $CDCl_3$) δ=3.00 (1H, s, OH), 3.46 (3H, s, OCH_3), 3.88 (1H, dd, $J_{5,6}$=3.1 Hz, $J_{4,5}$=8.9 Hz, H-5), 4.31 (1H, dd, $J_{5,6}$=3.1 Hz, $J_{1,6}$=7.3 Hz, H-6), 6.06 (4H, m, H-1,2,3,4), 7.20—8.20 (20H, m, aromatic); IR ($CHCl_3$) 3600, 3000, and 1700 cm^{-1}; $[\alpha]_D^{20}$ −86.6 ° (*c* 1.05, $CHCl_3$)

1L-1,2,3,4-Tetra-*O*-benzoyl-*chiro*-inositol (10c).[26] Mp 119—121 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ=3.40—3.55 (1H, m, H-5), 3.81 (1H, d, J=3.1 Hz, OH), 4.23—4.39 (1H, m, H-6), 4.44 (1H, d, J=3.0 Hz, OH), 5.89 (1H, t, J=9.8 Hz, H-3), 5.99 (1H, dd, J=3.4, 3.9 Hz), 6.01 (1H, dd, J=9.8, 3.4 Hz), 6.20 (1H, t, J=9.8 Hz), 7.20—8.10 (20H, m, aromatic); IR ($CHCl_3$) 3450, 1690, 1230, 1080, and 1060 cm^{-1}; $[\alpha]_D^{20}$ −127 ° (*c* 1.39, $CHCl_3$); Found: C, 67.33; H, 4.97%. Calcd for $C_{34}H_{28}O_{10}\cdot 0.5H_2O$; C, 67,43; H, 4.83%.

3-(Benzyloxy)propyl 4-Nitrophenyl Ether (11a). To a suspension of a 60% dispersion of NaH in mineral oil (163 mg, 6.51 mmol, prewashed with dry Et_2O) in DMF (15 ml) was added dropwise *p*-nitrophenol (1.06 g, 7.60 mmol) at 0 °C, and the mixture was stirred at room temperature for 0.5 h. Benzyl 3-chloropropyl ether (1.00 ml, 5.42 mmol) was added dropwise at room temperature and the resulting mixture was stirred at 140 °C for 3 h. After excess sodium hydride was carefully destroyed with water, the reaction mixture was diluted with water and ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to leave an oil, which was purified by column chromatography (SiO_2, hexane–ethyl acetate, 10 : 1, v/v) to afford **11a** as crystals in 74% yield. Mp 43.5—45.0 °C (hexane : CH_2Cl_2=3 : 1, v/v); ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.96 (2H, tt, J=5.4, 6.0 Hz), 3.42 (2H, t, J=6.0 Hz), 3.95 (2H, t, J=5.4 Hz), 4.25 (2H, s, OCH_2), 6.63 (2H, d, J=9.6 Hz, aromatic), 7.00—7.22 (5H, m, aromatic), and 7.86 (2H, d, J=9.6 Hz, aromatic); IR (neat) 3050, 2950, 2850, 1570, 1460, 1430, 1420, 1360, 1090, 1020, 700, and 650 cm^{-1}. Found: C,

66.49; H, 5.99; N, 4.72%. Calcd for $C_{16}H_{17}O_4N$: C, 66.89; H, 5.96; N. 4.88%.

3-(4-Nitrophenoxy)-1-propanol (11b). ^1H NMR (90 MHz, $CDCl_3$) δ=1.27 (1H, s, OH), 2.00 (2H, tt, J=6.0, 7.5 Hz), 3.74 (2H, t, J=7.5 Hz), 4.13 (2H, t, J=6.0 Hz), 6.80 (2H, d, J=9.3 Hz, aromatic), and 7.99 (2H, d, J=9.3 Hz, aromatic); IR (neat) 3350, 1590, 1480, 1320, 1250, 1100, 1050, 840, and 740 cm^{-1}. Found: C, 54.55; H, 5.78; N, 6.89%. Cacd for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.10%.

Methyl 3-Phenyl-1-methylpropyl Ether (12a). ^1H NMR (90 MHz, $CDCl_3$) δ=1.20 (3H, d, J=6.0 Hz, CH_3), 1.55—1.92 (2H, m), 2.63 (2H, q, J=6.0 Hz), 3.16—3.48 (1H, m, CH), 3.30 (3H, s, OCH_3), and 6.95—7.32 (5H, m, aromatic);IR (neat) 3030, 2950, 2900, 1720, 1580, 1480, 1440, 1370, 1140, 1080, and 740 cm^{-1}.

4-Phenyl-2-butanol (12b).[20] To a solution of 4-phenyl-2-butanone (2.02 ml, 13.5 mmol) in tetrahydrofuran (20 ml) was added a solution of NaBH4 (510.7 mg, 13.5 mmol) in water (5 ml) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and diluted with water and ether. The organic laver was washed with brine, dried over anhydrous Na_2SO_4, concentrated to leave an oil, wkich was purified by column chromatography (SiO_2, hexane–ethyl acetate, 4 : 1, v/v) to afford **12b** as an oil in 90% yield. ^1H NMR (90 MHz, $CDCl_3$) δ=1.15 (3H, d, J=6.0 Hz, CH_3), 1.36—1.86 (2H,m, CH_2, OH), 2.43—2.79 (2H, m, $PhCH_2$), 3.47—3.89 (1H, m, CH), and 6.80—7.18 (5H, m, aromatic); IR (neat) 3350, 3000, 2950, 1600, 1480, 1430, 1120, 1050, 730, and 680 cm^{-1}

A typical experimental procedure for the cleavage of benzyl ether with $AlCl_3$–*N,N*-dimethylaniline is as follows: To a solution of **1a** (100 mg, 0.443 mmol) and *N,N*-dimethylaniline (0.18 ml, 1.33 mmol) in CH_2Cl_2 (1.0 ml) was added powdered $AlCl_3$ (239 mg, 1.79 mmol) at room temperature. Stirring was continued for 30 min. The reaction mixture was quenched by addition of 1 mol dm^{-3} HCl (3 ml) and the aqueous layer was extracted with ethyl acetate (3×7 ml). The combined organic layer was successively washed with 5% $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The remaining residue was purified by short column chromatography (SiO_2, hexane : ethyl acetate=4 : 1, v/v) to afford **1b** (56.1 mg, 0.412 mmol, 93%). In order to isolate **15**, the aqueous layer was concentrated in vacuo to leave solid, which was washed with CH_2Cl_2. The organic layer was concentrated to leave an oil which was purified by column chromatography (SiO_2, CH_2Cl_2 : methanol=5 : 1, v/v) to afford **15** in 60% yield, which was recrystallized from Et_2O-methanol to give analytically pure **15** as mono hydrate in 39% yield.

A typical experimental procedure for the cleavage of benzyl ether with $AlCl_3$–anisole is as follows: To a solution of **1a** (70 mg, 0.31 mmol) and anisole (0.135 ml, 1.24 mmol) in CH_2Cl_2 (1.0 ml) was added powdered $AlCl_3$ (124 mg, 0.929 mmol) at room temperature. Stirring was continued for 30 min. The reaction mixture was quenched by addition of 1 mol dm^{-3} HCl (3 ml), and the aqueous layer was extracted with ethyl acetate (3×7 ml). The combined organic layer was successively washed with 5% $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The remaining residue was purified by short column chromatography (SiO_2, hexane : ethyl acetate (v/v)=4 : 1) to afford **1b** in 93%. The polar compounds were purified further by preparative TLC (SiO_2, hexane : CH_2Cl_2 (v/v)=30 : 1) to afford less polar isomer **14a** and plar isomer **14b** in 44 and 30% yield respectively.

3,7-Dimethyl-7-(4-methoxyphenyl)-1-octanol (13). To a solution of citronellol benzyl ether (383 mg,1.55 mmol) and anisole (0.68 ml, 6.26 mmol) in CH_2Cl_2 (5 ml) was added $AlCl_3$ (638 mg, 4.78 mmol) at 0°C. After stirring at room temperature for 0.8 h, the reaction mixture was quenched by addition of 10% HCl solution and the aqueous layer was extracted with ethyl acetate (3×8 ml). The combined organic layer was washed with 5% $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave an oil, which was separated by SiO_2 column chromatography to give **13** as an oil (260 mg, 0.984 mmol) in 63%. ^1H NMR (270 MHz, $CDCl_3$) δ=0.80 (3H, J=6.7 Hz, CH_3CH), 0.95—1.62 (10H, m, CH_2×4, CH, OH), 1.26 (6H, s, CH_3×2), 3.50—3.70 (2H, m, CH_2OH), 3.79 (3H, s, OCH_3), 6.83 (2H, d, J=9.0 Hz), 7.23 (2H, d, J=9.0 Hz);^{13}C NMR ($CDCl_3$) δ=19.45, 21.91, 29.02, 29.07, 29.19, 36.92, 37.70, 39.77, 44.75, 55.00, 60.82, 109.80, 113.17, 124.36, 125.51, 126.59, 128.03, 128.08, 141.67, 157.02; IR (neat) 3320, 2920, 1580, 1470, 1430, 1265, 1210, 1155, 1000, and 790 cm^{-1}. Found: C, 77.38; H, 10.49%. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%.

1-Benzyl-2-methoxybenzene (14a).[27] ^1H NMR (270 MHz, $CDCl_3$) δ=3.81 (3H, s, OCH_3), 3.97 (2H, s, CH_2), 6.83—6.90 (2H, m, aromatic), 7.03—7.08 (1H, m, aromtic), and 7.13—7.08 (6H, m, aromatic);^{13}C NMR ($CDCl_3$) δ=35.81, 55.25, 110.32, 120.41, 125.71, 127.35, 128.19, 128.90, 129.59, 130.26, 140.96, and 157.27.

1-Benzyl-4-methoxybenzene (14b).[27] ^1H NMR (270 MHz, $CDCl_3$) δ=3.78 (3H, s, OCH_3), 3.92 (2H, s, CH_2), 6.80—6.82 (2H, m, aromatic), and 7.06—7.32 (7H, m, aromatic);^{13}C NMR ($CDCl_3$) δ=40.95, 55.10, 113.79, 125.90, 128.31, 128.36, 128.73, 129.78, 141.51, and 157.90.

Benzyldimethylphenylammonium Chloride (15). Mp 168—169°C (Et_2O–methanol=2 : 1, v/v); ^1H NMR (270 MHz, $CDCl_3$) δ=1.82 (2H, s, OH), 4.01 (6H, s, CH_3×2), 5.71 (2H, s, CH_2) 7.07—7.20 (3H, m, aromatic), 7.27—7.34 (2H, m, aromatic), 7.53—7.60 (3H, m, aromatic), and 7.80—7.82 (2H, m, aromatic); IR (nujol) 3325 cm^{-1}. Found: C, 67.51; H, 7.63; N, 5.07%. Calcd for $C_{15}H_{18}NCl \cdot H_2O$: C, 67.78; H, 7.58; N, 5.27%.

References

1) K. Fuji and M. Node, *Yuki Gosei Kagaku Kyokai Shi,* **42**, 193 (1984).

2) T. W. Greene, "Protective Groups in Organic Systhesis," John Wiley & Sons, New York (1981), Chap. 1; M. V. Bhatt and S. U. Kulkarni, *Synthesis,* **1983**, 249.

3) M. E. Jung and M. A. Lyster, *J. Org. Chem.,* **42**, 3761 (1977).

4) G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Nalhotra, *J. Org. Chem.,* **44**, 1247 (1979).

5) M. V. Bhatt and S. S. El-Morey, *Synthesis,* **1982**, 1048.

6) J. P. Kutney, N. Abdurahman, P. L. Quesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.,* **88**, 3656 (1966).

7) K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.,* **44**, 1661 (1979).

8) K. Fuji, T. Kawabata, and E. Fujita, *Chem. Pharm. Bull.,* **28**, 3662 (1980).

9) Y. D. Vankar and C. T. Rao, *J. Chem. Res., Synop.,* **1985**, 232.

10) J. C. Sarma, M. Borbaruah, D. N. Sarma, N. C. Barua,

and R. P. Sharma, *Tetrahedron,* **42**, 3999 (1986).

11) T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.,* **1979**, 2793; M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, *J. Med. Chem.,* **22**, 757 (1979).

12) T. Akiyama, M. Kumegawa, Y. Takesue, H. Nishimoto, and S. Ozaki, *Chem. Lett.,* **1990**, 339; T. Akiyama, H. Nishimoto, and S. Ozaki, *Bull. Chem. Soc. Jpn.,* **63**, 3356 (1990); T. Akiyama, H. Nishimoto, and S. Ozaki, *Bull. Chem. Soc. Jpn.,* **64**, 2266 (1991).

13) Part of this work was published in a communication form; T. Akiyama, H. Hirofuji, and S. Ozaki, *Tetrahedron Lett.,* **32**, 1321 (1991).

14) Effects of the addition of tertiary amine in the $AlCl_3$-catalyzed cleavage of aromatic methyl ethers were already studied, where pyridine and triethylamine gave good results, indicative of a different mechanism from our study. see; R. G. Lange, *J. Org. Chem.,* **27**, 2037 (1962).

15) The reaction of **9a** with BF_3–EtSH showed low selectivity, whereas selective cleavage of the aromatic ether was effected by EtSNa in DMF.[7]

16) Y. Kiso, K. Ukawa, S. Nakamura, K. Ito, and T. Akita, *Chem. Pharm. Bull.,* **28**, 673 (1980); Y. Kiso, K. Ukawa, and T. Akita, *J. Chem. Soc., Chem. Commun.,* **1980**, 101.

17) SeO_2–AcOH: K. Kariyone and H. Yazawa, *Tetrahedron Lett.,* **1970**, 2885; Pd–C/TsOH: R. Boss and R. Scheffold, *Angew. Chem., Int. Ed. Engl.,* **15**, 558 (1976); Rh(I): E. J. Corey and J. W. Suggs, *J. Org. Chem.,* **38**, 3224 (1973).

18) $AlCl_3$–NaI: M. Node, K. Ohta, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, *Chem. Pharm. Bull.,* **31**, 4178 (1983); $AlCl_3$–EtSH: M. Node, K. Nishide, K. Fuji, and E. Fujita, *J. Org. Chem.,* **45**, 4275 (1980); BF_3·OEt_2–RSH: M. Node, H. Hori, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1,* **1980**, 2237; BF_3·–OEt_2–*n*-Bu_4N.I: A. K. Mandal, N. R. Soni, and K. R. Ratnam, *Synthesis,* **1985**, 274; AlI_3: M. V. Bhatt and J. R. Babu, *Tetrahedron Left.,* **25**, 3497 (1984).

19) P. Sykes, "A Guidebook to Mechanism in Organic Chemistry," 5th ed, Longman, New York (1981), p. 154.

20) Y. Kikugawa and Y. Ogawa, *Chem. Pharm. Bull.,* **27**, 2405 (1979).

21) H. Ishikawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.,* **51**, 2059 (1978).

22) M. Y. Kim, J. E. Starett, Jr., and S. M. Weinreb, *J. Org. Chem.,* **46**, 5383 (1981).

23) G. W. Gokel, J. C. Hernandez, A. W. Vicariello, K. A. Arnold, C. F. Campana, L. Echegoyen, F. R. Fronczek, R. D. Gandour, C. R. Morgan, J. E. Trafton, S. R. Miller, C. Minaganti, D. Eiband, R. A. Schultz, and M. Tamminen, *J. Org. Chem.,* **52**, 2963 (1987).

24) C. R. Narayanan and K. N. Iyer, *J. Org. Chem.,* **30**, 1734 (1965).

25) D. Mercier, J. E. G. Barnett, and S. D. Géro, *Tetrahedron,* **25**, 5681 (1969).

26) T. Akiyama, N. Takechi, H. Shima, and S. Ozaki, *Chem. Lett.,* **1990**, 1881.

27) Y. Nakai and F. Yamada, *Org. Magn. Reson.,* **11**, 607 (1978).