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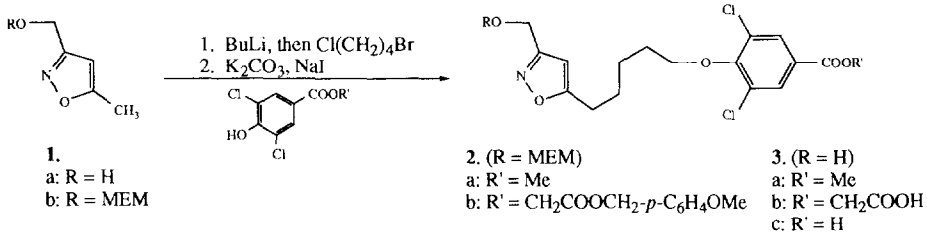
Cleavage of MEM Ethers by Tetrahalozincate Reagents

John M. Herbert*
Isotope Chemistry Laboratories, Department of Metabolism and Pharmnacokinetics
Sanofi Research Division, Willowburn Ave., Alnwick, Northumberland NE66 2JH, U.K.

Julian G. Knight and Brian Sexton
Department of Chemistry, University of Newcastle upon Tyne, NE1 7RU, U.K.

Abstract. A modification of the zinc halide-mediated removal of the MEM group is described. By the expedient of adding two molar equivalents of ethereal hydrogen chloride or of lithium halide, the method is extended to substrates which otherwise chelate the zinc reagent without undergoing deprotection. The compatibility of the resulting reagent systems with other functional groups is demonstrated, and examples are presented where deprotection of mono-MEM-protected 1,2- and 1,3-diols can be carried out, avoiding the cyclisation which occurs normally.

Since 2-methoxyethoxymethyl (MEM) was first described as a protecting group for the hydroxy function,[1] it has been used widely in organic synthesis. It is commonly removed by treatment with a Lewis acid,[1,2] although reports have appeared of its removal by acid[2] and, in one case, by lithium tetrafluoroborate.[3] In the course of the sequence illustrated in Scheme 1, several methods were tried in an effort to remove the MEM group from intermediates **2** without success. However, treatment with an excess of zinc bromide in the presence of two molar equivalents of ethereal hydrochloric acid gave reasonable yields of the desired alcohols. It is the investigation of this reagent system and some variations which is the subject of this report.



1.
a: R = H
b: R = MEM

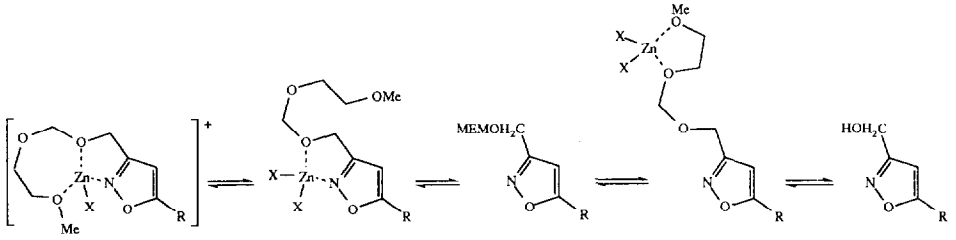
2. (R = MEM)
a: R' = Me
b: R' = CH_2COOCH_2-*p*-C_6H_4OMe

3. (R = H)
a: R' = Me
b: R' = CH_2COOH
c: R' = H

Scheme 1.

Results and Discussion

Since neither zinc bromide nor ethereal hydrogen chloride alone removed the MEM group from **2**, the means by which acid assisted the deprotection was of interest. The simplest inference is that zinc(II) is chelated by the substituted isoxazole in such a way that cleavage does not occur (Scheme 2),[1] and that acid does no more than break up this complex. Certainly, mixtures of **1b** or **2** with zinc bromide separated from dichloromethane as highly viscous oils which remained intractable even when dichloromethane was replaced by ether or tetrahydrofuran. If this was so, a lithium salt might have a similar effect, although the process should not proceed using a tetraalkylammonium halide. On this basis, trial reactions were carried out using **1b**, and varying the nature of the zinc salt and the additive (Table 1).



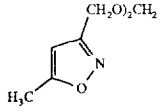
Scheme 2.

Neither acid nor a lithium salt alone deprotected **1b** effectively, although zinc bromide in dichloromethane did remove the MEM group slowly. As expected, mixtures of zinc halides with hydrogen chloride or a lithium halide were far more effective. However, the major factor influencing the efficiency of the reagent appeared to be the nucleophilicity of the halide; a proton was more effective than lithium as a counterion only where the halide was poorly nucleophilic, although there is some evidence for a decomplexation effect in that cleavage did not occur using tetraalkylammonium salts. The best yields of **1a** were achieved using zinc chloride-hydrogen chloride or zinc bromide-lithium bromide, suggesting that it is best to strike a balance between the strengths of the cation and the nucleophile. At one extreme, cleavage with zinc chloride-lithium chloride proceeded slowly and much of the product was isolated as the acetal **4**, possibly arising by attack of the alcohol upon the intermediate zinc complex; nevertheless, it is of interest that this reaction proceeds at all, since it was reported originally that zinc chloride did not cleave MEM ethers.[1] At the other extreme, the low yield obtained using zinc iodide-hydrogen chloride appeared to be due to degradation of the product. Better evidence for decomplexation of a zinc chelate by hydrogen or lithium halides is provided by the observation that the MEM ether **5b**, where the nitrogen of the isoxazole should not become involved in chelation, was deprotected to alcohol **5a** more effectively by zinc chloride alone than in the presence of an additive. Consequently, although decomplexation of a zinc chelate may be promoted by hydrogen or lithium halides, it appears that this is not the only effect being observed.

Table 1. Cleavage of Isoxazole MEM Ethers with Zinc(II) Halides and Inorganic Halides

Substrate	Zinc Salt	Additive	Solvent	Time	Alcohol	S.M.
1b	$ZnCl_2$ (8 eq.)	None	CH_2Cl_2	20 h	0	69%
	$ZnCl_2$ (8 eq.)	HCl	Et_2O	20 h	82%	9%
	$ZnCl_2$ (6 eq.)	LiCl	Et_2O-THF	72 h	0[a]	63%
	$ZnCl_2$ (8 eq.)	LiCl	Et_2O	72 h	45%[b]	0
	$ZnCl_2$ (8 eq.)	$BnN^+Me_3.Cl^-$	Et_2O	24 h	0	76%
	$ZnBr_2$ (5 eq.)	None	CH_2Cl_2	72 h	44%	44%
	$ZnBr_2$ (14 eq.)	None	CH_2Cl_2	48 h	44%	44%
	$ZnBr_2$ (3 eq.)	HCl	Et_2O-THF	90 min	12%	trace
	$ZnBr_2$ (6 eq.)	LiBr	THF	3 h	86%	0%
	$ZnBr_2$ (6 eq.)	$Bu_4N^+.Br^-$	Et_2O-THF	24 h	0	83%
	ZnI_2 (3 eq.)	HCl	Et_2O-THF	30 min	6%	8%
	ZnI_2 (6 eq.)	LiI	THF	4 h	72%	0
	None	HCl	Et_2O	72 h	0	44%
	None	LiBr	THF	72 h	0	90%
	None	LiI	THF	72 h	0	53%
	None	PPTS	MEK (reflux)[4]	72 h	53%	21%
2a	$ZnBr_2$ (4 eq.)	LiBr	THF	24 h	72%	0
	$ZnCl_2$ (2 eq.)	HCl	Et_2O	8 h	77%	0
	$ZnBr_2$ (3 eq.)	None	Et_2O/CH_2Cl_2	5 days	0	89%
	None	HCl	Et_2O	5 days	14%	68%
2b	$ZnBr_2$ (1 eq.)	HCl	Et_2O	1 h	6%[c]	0
5b	$ZnCl_2$ (8 eq.)	HCl	Et_2O-THF	24 h	35%	35%
	$ZnCl_2$ (8 eq.)	LiCl	Et_2O-THF	24 h	0[b]	88%
	$ZnBr_2$ (8 eq.)	None	Et_2O-THF	24 h	54%	37%

a. **4** (13%) was the only product. b. **4** (45%) was isolated also. c. Degraded to the acid **3c**.



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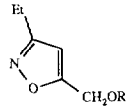
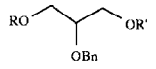


5.
a: R = H
b: R = MEM



6.
a: R, R' = H
b: R = H, R' = MEM
c: R, R' = MEM

Solutions of zinc(II) halides with ethereal hydrogen chloride or lithium halides were commonly homogeneous at concentrations where zinc halides alone were not and, when the mixtures were heterogeneous, the second phase was a liquid rather than a solid. Complete solution was usually achieved by addition of two molar equivalents of halide, suggesting that the species involved are tetrahalozincate complexes, probably in equilibrium with trihalozincates.[5]

Table 2. Deprotection using Zinc Halide/Hydrogen Chloride and Zinc Halide/Lithium Halide Systems.

Substrate	Reagent[a]	Solvent	Time	Yield
$Ph(CH_2)_3OMEM$	H_2ZnCl_4 (3 eq.)	Et_2O	90 min	43
	Li_2ZnCl_4 (6 eq.)	Et_2O-THF	20 h	24%
	$H_2ZnCl_2Br_2$ (3 eq.)	Et_2O	45 min	94%
	Li_2ZnBr_4 (6 eq.)	THF	4.5 h	67%
	$H_2ZnCl_2I_2$ (3 eq.)[b]	Et_2O	45 min	86%
	$H_2ZnCl_2I_2$ (3 eq.)	Et_2O-THF	1 h	62%
	Li_2ZnI_4 (6 eq.)	THF	45 min	89%
	Li_2ZnI_4 (1 eq.)	THF	24 h	0[c]
$BnOCH_2CH_2OMEM$	H_2ZnCl_4 (1.5 eq.)	Et_2O-THF	72 h	57%
	Li_2ZnCl_4 (6 eq.)	Et_2O-THF	72 h	0[b]
	$H_2ZnCl_2Br_2$ (3 eq.)	Et_2O-THF	6 h	74%
	Li_2ZnBr_4 (6 eq.)	THF	72 h	46%
	$H_2ZnCl_2I_2$ (3 eq.)	Et_2O-THF	72 h	0[d]
	Li_2ZnI_4 (6 eq.)	THF	72 h	0[d]
BnOMEM	H_2ZnCl_4 (6 eq.)	Et_2O-THF	1 h	90%
	Li_2ZnCl_4 (6 eq.)	THF	72 h	0[c]
Piperonyl-OMEM	$H_2ZnCl_2Br_2$ (3 eq.)	Et_2O-THF	72 h	24%[e]
	Li_2ZnBr_4 (6 eq.)	THF	48 h	0[e]
	Li_2ZnI_4 (6 eq.)	Et_2O-THF	2.5 h	0[e]
6c	Li_2ZnBr_4 (6 eq.)	THF	48 h	40%
	Li_2ZnI_4 (2 eq.)	THF	6 h	72%
	Li_2ZnI_4 (6 eq.)	THF	90 min	0[c]
7a	$H_2ZnCl_2Br_2$ (3 eq.)	THF	1 h	84%
	$ZnBr_2$ (10 eq.)	CH_2Cl_2	48 h	10%[f]
	Li_2ZnBr_4 (6 eq.)	THF	48 h	94%[g]
	Li_2ZnI_4 (6 eq.)	THF	24 h	63%

a. Reagents described as $H_2ZnCl_2Br_2$ and $H_2ZnCl_2I_2$ are mixtures of species. b. Heterogeneous

c. No apparent reaction. d. Benzyl Iodide was the major product. e. Extensive decomposition.

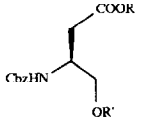
f. **7c** (17%) isolated also. g. Recovered **7b** $[\alpha]_D^{21}$ -8.03 (c 0.78 in ethanol; lit.[7] -8.71, c 1.1).

The optimum ratio of zinc salt to halide should therefore be 1:2 and this ratio was used throughout. Some improvement in efficacy, compared to zinc bromide in dichloromethane, may result from the homogeneity of the reagent system although, conversely, the formation of 3-phenyl-1-propanol from its MEM ether using zinc iodide-hydrogen chloride was more efficient when the mixture was heterogeneous (Table 2), which may be a reflection on the harshness of this reagent.

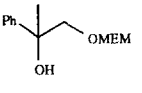
Assuming that the species in solution were, indeed, tetrahalozincates, it was of interest to carry out some optimisation and to examine compatibility with other functional groups. Variation of the ratio of reagent to substrate, using the MEM ether of amyl alcohol as a substrate,[6] suggested that complete deprotection was generally achieved using three molar equivalents of acid systems or six of a lithium tetrahalozincate. Although this may have been an excess, this ratio was used in the first instance in all subsequent experiments. Where the product was sensitive to the reagent, use of a smaller excess often gave a cleaner reaction.

When exposed to lithium tetrabromozincate, esters and aryl ethers were unaffected after 48 h, although the *tert*-butyldimethylsilyl group suffered approximately 5% degradation after the same period.[6,8] Not surprisingly, zinc bromide - hydrogen chloride cleaved the last in near-quantitative yield, and also caused a small amount of ester cleavage. Nevertheless, this system removed the MEM group in preference to the *tert*-butyl ester of **7a**, giving the alcohol **7b** without apparent loss of optical activity; surprisingly, zinc bromide alone gave **7b** in low yield accompanied by **7c**, where both the MEM and *tert*-butyl groups had been removed.

The effects of tetrahalozincates on a variety of substrates are summarised in Table 2. Benzyloxy groups withstood chloride and bromide complexes but not iodide complexes (benzyl iodide was invariably identified, but the identity of the other product of this cleavage was not established). Predictably, the methods do not tolerate double bonds: in no case was a significant quantity of the desired alcohol formed during attempts to deprotect the MEM ether of 2-methyl-2-propen-1-ol.[6] When this substrate was treated with H_2ZnCl_4, major products identified by GC-MS of the mixture were 2-chloro-2-methyl-1-propanol, 1,2-dichloro-2-methylpropane, and bis(2-chloro-2-methyl-1-propyl) ether. Despite the formation of **4**, noted already, formation of ethers from benzylic systems does not appear to be general. Deprotection of the MEM ethers of benzyl alcohol and piperonyl alcohol gave only the desired alcohol without any of the ether being detected, although piperonyl alcohol degraded under the reaction conditions. Although aryl ethers appear to be stable to tetrahalozincates, cleavage of tetrahydrofuran occurred on extended storage of reagent solutions. When solutions of bromide- or iodide- containing systems were left for any period in excess of a week, GC-MS of hydrolysed samples indicated the presence of 1,4-dibromobutane, 1,4-diiodobutane (and possibly also of 1,3-dibromobutane), 4-chloro-1-bromobutane, and of 4-chloro- and 4-bromo-1-butanols.



7.
a: R = *t*-Bu, R' = MEM
b: R = *t*-Bu, R' = H
c: R = H, R' = H



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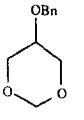
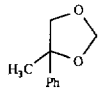


9.

Most procedures for the cleavage of MEM ethers suffer from the limitation that monoprotected 1,2-diols do not undergo deprotection in the normal fashion, but instead are converted into 1,3-dioxoles, although Corey and co-workers[9] solved this problem using isopropylthioboron reagents. It was therefore of interest to determine whether tetrahalozincates would facilitate removal of the MEM group from monoprotected diols without cyclisation. To this end, attempts were made to deprotect the ethers **6b** and **8** using bromo- and iodozincate reagents (Table 3). In both cases, the desired diols could be isolated depending upon the conditions. Although dioxane **9** was the major product from attempts to deprotect **6b** with bromozincate reagents, diol **6a** was isolated under acidic conditions. Using H_2ZnCl_4, **6a** became the sole product, again illustrating that conditions can be selected to suit the substrate. Deprotection of **8** was somewhat different: in the presence of acid, the yield of the desired diol was unsatisfactory (possibly a result of elimination to give the aldehyde), while lithium tetrabromozincate did not effect deprotection. Satisfactory results were, however, obtained using the more reactive lithium tetraiodozincate, and in no case was the dioxole **10** observed. The process was also applied successfully to the protected aminoalcohol **11**, in which case better results were obtained with lithium tetrabromozincate than with zinc bromide - hydrogen chloride; although deprotection was slow, this result parallels those obtained during deprotection of **1b**, where the best results were usually obtained with lithium as a counterion.



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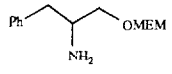

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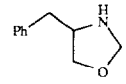


12.

Table 3. Deprotection of mono-MEM-protected diols with tetrahalozincates

Substrate	Reagent	Solvent	Time	Diol Yield	**9** Yield	**6b/8/11** Recovery
8	Li_2ZnBr_4 (6 eq.)	THF	72 h	0	-	35%
	$H_2ZnCl_2Br_2$ (3 eq.)	Et_2O-THF	5 h	15%	-	0
	Li_2ZnI_4 (6 eq.)	THF	72 h	56%	-	0
6b	H_2ZnCl_4 (3 eq.)	Et_2O-THF	75 min	73%	0	0
	$H_2ZnCl_2Br_2$ (2 eq.)	Et_2O-THF	75 min	14%	78%	0
	Li_2ZnBr_4 (3 eq.)	THF	75 min	10%	56%	0
11	$H_2ZnCl_2Br_2$ (3 eq.)	Et_2O-THF	72 h	5%	0	66%
	Li_2ZnBr_4 (6 eq.)	THF	72 h	54%	0	31%

In summary, it has been demonstrated that formation of tetrahalozincate complexes from zinc halides extends the utility of these reagents for the removal of MEM ethers. It is possible to select a system for any of the substrates tested which represents a balance between reactivity toward the MEM group and reactivity toward the remainder of the molecule, so that sensitive substrates can be deprotected. In addition, tetrahalozincate complexes can be used to remove the MEM group from monoprotected 1,2- and 1,3-diols without formation of the cyclic acetals observed with most other reagent systems.

Experimental

New compounds had satisfactory ^{1}H nmr and, with the exceptions of **2b** and **3b**, high-resolution mass spectra. Gas chromatography was performed using a Hewlett-Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5970MSD) on a capillary column (HP1, 30m x 0.25mm; 0.25μm layer); the injector temperature was 250°C and the oven temperature was increased, after an initial 2 minute delay, either from an initial 70°C to 200°C at 5°C per minute, or from an initial 100°C to 240°C at 10°C per minute. Additional low-resolution mass spectra were recorded using a Finnigan MAT TSQ700 triple quadrupole instrument or a VG Autospec magnetic sector instrument; high-resolution mass spectra were recorded using the latter instrument. ^{1}H nmr spectra were recorded using Jeol GSX-270 and Bruker AC80 instruments. Compounds **1a**, **2a** and **2b** were prepared using methodology described by Diana *et al.*,[10] and data for these compounds, and for the acetal **4** and the MEM ether **5b** are summarised in Table 4. Other MEM ethers were prepared from the corresponding alcohols by treatment with MEM chloride and diisopropylethylamine,[1] and their ^{1}H nmr and mass spectra are summarised in Table 5. Alcohols were available commercially with the exception of **5a**,[11] and **7c**,[7] which were prepared using published methods.

Typical Procedures

A. Using Zinc Halides and Ethereal Hydrogen Chloride

1M ethereal hydrogen chloride (3 ml) was added to a suspension of zinc halide (1.5 mmol) in THF or ether (3 ml), and the mixture was stirred until a solution was obtained [THF was added if the mixture remained heterogeneous], following which a solution of substrate (0.25 mmol) in THF or ether (1 ml) was added. The mixture was stirred or left to stand until the reaction either reached equilibrium or was complete (t.l.c. or GC-MS). The mixture was quenched by addition of 1M hydrochloric acid and extracted with ethyl acetate. The combined organic phases were dried and concentrated to give the crude product which was purified by chromatography if necessary.

B. Using Lithium Tetrahalozincates

A suspension of lithium halide (3 mmol) and zinc halide (1.5 mmol) in THF or ether (6 ml) was stirred until a solution was obtained [THF could be added to ethereal suspensions if the mixture remained heterogeneous], following which a solution of substrate (0.25 mmol) in THF or ether (1 ml) was added. The mixture was stirred or left to stand until the reaction either reached equilibrium or was complete (t.l.c. or GC-MS). The mixture was quenched by addition of excess aqueous sodium hydrogencarbonate (1M hydrochloric acid is an acceptable alternative) and filtered. The filter cake was washed though with ether or ethyl acetate, and the organic phase was separated. The aqueous phase was re-extracted with ethyl acetate and the combined organic phases were dried and concentrated to give the crude product which was purified by chromatography if necessary.

5-Benzyloxy-1,3-dioxane (**9**).

Following method B above using lithium bromide, zinc bromide, and **6b** (37.4 mg, 0.14 mmol), a mixture was obtained. Preparative t.l.c. gave 2-benzyloxy-1,3-propanediol (**6a**; 2.5 mg, 10%) and 5-benzyloxy-1,3-dioxane (**9**; 15.2 mg, 56%). $\delta_H(CDCl_3)$ 3.3-3.7 (5H, m), 4.55 (2H, s), 4.65 (1H, d), 4.82 (1H, d), 7.2-7.35 (5H, m); *m/z* (CI-NH_3) 212.1287 ($[MNH_4]^+$; *calc. for* $C_{11}H_{18}NO_3$ 212.1287), 181 (100%), 108, 91.

3(S)-(Benzyloxycarbonylamino)-4-hydroxybutanoic Acid (**7c**).

A suspension of zinc bromide (153.4 mg, 0.68 mmol) in dichloromethane (1 ml) containing **7a** (27.6 mg, 0.07 mmol) was stirred at room temperature for 24 h, diluted with additional dichloromethane, washed with aqueous ammonium chloride, and dried. After concentration under reduced pressure, preparative t.l.c. of the crude material in 1:1 ethyl acetate-hexane on silica gel gave *tert*-butyl 3(*S*)-(benzyloxycarbonylamino)-4-hydroxybutanoate (**7b**; 2.2 mg, 10%) and 3(*S*)-(benzyloxycarbonylamino)-4-hydroxybutanoic acid (**7c**; 3 mg, 17%), m.p. 105-109°C (lit.[12] m.p. 109-110°C). $\delta_H(CDCl_3)$ 2.49 (1H, dd), 2.70 (1H, br s), 2.88 (1H, dd), 3.75 (2H, br d), 4.08 (1H, m), 5.12 (2H, s), 5.53 (1H, br d), 7.3-7.4 (5H, m); *m/z* (EI) 235 ($M-H_2O$), 91 (100%).

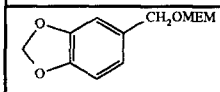
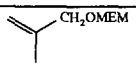
Table 4. Data for Isoxazole derivatives.

Compound	$\delta_H(CDCl_3)$	MS
1a[11]	2.40 (4H, s overlaying br s), 4.70 (2H, s), 6.02 (1H, s).	(EI) 113.0476 ($M^{+\cdot}$; calc. for $C_5H_7NO_2$: 113.0477), 83, 68 (100%), 43.
1b	2.20 (3H, s), 3.39 (3H, s), 3.55 (2H, t), 3.72 (2H, t), 4.63 (2H, s), 4.76 (2H, s), 6.02 (1H, s).	(CI-NH_3) 202.107536 (100%, $[MH]^+$; calc. for $C_9H_{16}NO_4$: 202.107933), 126, 114.
2a	1.4-2.0 (6H, m), 2.78 (2H, t), 3.39 (3H, s), 3.5-3.65 (2H, m), 3.65-3.8 (2H, m), 3.88 (3H, s), 4.06 (2H, t), 4.66 (2H, s), 4.79 (2H, s), 6.04 (1H, s), 7.98 (2H, s).	(CI-NH_3) 478, 476.1245 (100%, $[MH]^+$; calc. for $C_{21}H_{28}Cl_2NO_7$: 476.1243), 402, 400, 256, 180.
2b	1.2-2.1 (6H, m), 2.84 (2H, t), 3.42 (6H, s), 3.5-3.65 (2H, m), 3.65-3.85 (2H, m), 4.13 (2H, t), 4.65 (2H, s), 4.80 (2H, s), 4.88 (2H, s), 5.27 (2H, s), 6.08 (1H, s), 7.3-7.4 (4H, m), 8.03 (2H, s).	
3a[a]	1.4-2.0 (6H, m), 2.76 (2H, t), 2.95 (1H, br s), 3.87 (3H, s), 4.06 (2H, t), 4.66 (2H, s), 6.03 (1H, s), 7.91 (2H, s).	(CI-NH_3) 390, 388 (100%, $[MH]^+$), 358, 356 (388-MeOH), 314, 312 (388-HCOOMe), 191, 189, 138.
3b[b]	1.4-2.0 (6H, m), 2.79 (2H, t), 4.10 (2H, t), 4.68 (2H, s), 4.86 (2H, s, OCH_2COOH), 6.07 (1H, s), 7.98 (2H, s)	
4	2.41 (6H, s), 4.64 (4H, s), 4.80 (2H, s), 6.02 (2H, s)	(CI-NH_3) 239.1032 ($[MH]^+$; calc. for $C_{11}H_{15}N_2O_4$: 239.1032), 126 (100%) .

a. Additional data: m.p. 65-67°C. Found: C 52.6, H 4.9, N 3.6; $C_{17}H_{19}Cl_2NO_5$ requires C 52.6, H 4.9, N 3.6 %. ν_{max}(KBr) 3340 (O-H), 1730 (C=O); $\delta_C(CDCl_3)$ 25.4, 26.6, 27.2, 29.65, 52.6, 56.7, 73.6, 99.7, 127.0 (q), 121.6 (2Cq), 130.2 (2C), 155.4 (q), 164.6 (q), 173.7 (q).

b. **3b** degraded rapidly to **3c**: m.p. 114-116°C. Found: C 51.4, H 4.7, N 3.7; $C_{16}H_{17}Cl_2NO_5$ requires C 51.4, H 4.6, N 3.7 %. ν_{max}(KBr) 3600-2500 (O-H), 1717 (C=O); $\delta_H(CD_3SOCD_3)$ 1.4-2.0 (6H, m), 2.78 (2H, t), 4.07 (2H, t), 4.46 (2H, s), 6.23 (1H, s), 7.93 (2H, s); *m/z* (EI, 70eV) 375, 373 ($[M-H]^+$), 208, 206, 168, 138 (100%).

Table 5. Data for MEM ethers

Compound	$\delta_H(CDCl_3)$	MS
5b	1.29 (3H, t), 2.71 (2H, q), 3.41 (3H, s), 3.60 (2H, t), 3.76 (2H, t), 4.60 (2H, s), 4.82 (2H, s), 6.14 (1H, s)	(CI-NH_3) 216.1236 (100%, $[MH]^+$; calc. for $C_{10}H_{18}NO_4$: 216.1236), 142, 110, 89.
$Ph(CH_2)_3OMEM$	1.90 (2H, tt), 2.68 (2H, t), 3.39 (3H, s), 3.5-3.6 (4H, m), 3.69 (2H, t), 4.71 (2H, s), 7.18 (2H, d), 7.25-7.35 (3H, m).[13]	(CI-NH_3) 242.1759 (100%, $[MNH_4]^+$; calc. for $C_{13}H_{24}NO_3$: 242.1756), 225 ($[MH]^+$).
$BnOCH_2CH_2OMEM$	3.37 (3H, s), 3.5-3.8 (8H, m), 4.56 (2H, s), 4.75 (2H, s), 7.25-7.35 (5H, m).	(CI-NH_3) 258.1706 ($[MNH_4]^+$; calc. for $C_{13}H_{24}NO_4$: 258.1705), 242 ($[MH]^+$), 108, 91 (100%).
	3.40 (3H, s), 3.58 (2H, t), 3.72 (2H, t), 4.51 (2H, s), 4.72 (2H, s), 5.93 (2H, s), 6.7-6.9 (3H, m).[14]	(EI) 240.1002 (M^+·; calc. for $C_{12}H_{16}O_5$: 240.0998), 151, 135 (100%)
BnOMEM	3.40 (3H, s), 3.58 (2H, t), 3.74 (2H, t), 4.62 (2H, s), 4.80 (2H, s), 7.25-7.4 (5H, m).[3]	(EI) 165, 151, 120, 107, 91 (100%).
6b	2.4 (br s), 3.38 (3H, s), 3.52 (2H, t), 3.6-3.8 (7H, m), 4.661 (1H, d), 4.69 (1H, d), 4.71 (2H, s), 7.25-7.35 (5H, m)	(CI-NH_3) 288.1810 ($[MNH_4]^+$; calc. for $C_{14}H_{26}NO_5$: 288.1811), 91 (100%).
6c	3.37 (6H, s), 3.52 (4H, t), 3.6-3.8 (9H, m), 4.66 (2H, s), 4.71 (4H, s), 7.2-7.4 (5H, m).	(CI-NH_3) 376.2331 ($[MNH_4]^+$; calc. for $C_{18}H_{34}NO_7$: 376.2331), 193, 91, 89 (100%).
7a[a]	1.39 (9H, s), 2.74 (1H, dd), 2.96 (1H, dd), 3.34 (3H, s), 3.5-3.8 (6H, m), 4.60 (1H, m), 5.11 (2H, s), 5.38 (2H, s), 5.75 (1H, br d), 7.2-7.4 (5H, m).	(CI-NH_3) 398.2178 ($[MH]^+$; calc. for $C_{20}H_{32}NO_7$: 398.2179), 373, 297, 178, 91 (100%).
8	1.63 (3H, s), 3.50 (3H, s), 3.61 (2H, t), 3.72 (2H, t), 3.80 (1H, d), 3.96 (1H, d), 4.84 (2H, s), 7.36 (1H, t), 7.45 (2H, dd), 7.59 (2H, d).	(CI-NH_3) 258.1704 ($[MNH_4]^+$; calc. for $C_{13}H_{24}NO_4$: 258.1705), 242 ($[MH]^+$), 89 (100%).
11	1.55 (2H, br s), 2.54 (1H, dd), 2.78 (1H, dd), 3.22 (1H, m), 3.3-3.75 (6H, m), 3.26 (3H, s), 4.74 (2H, s), 7.19 (2H, d), 7.25-7.35 (3H, m).	(CI-NH_3) 240.1602 (100%, $[MH]^+$; calc. for $C_{13}H_{22}NO_3$: 240.1600).
n-$C_5H_{11}OMEM$	0.90 (3H, t), 1.25-1.4 (4H, m), 1.57 (2H, m), 3.39 (3H, s), 3.50-3.6 (4H, m), 3.70 (2H, t), 4.71 (2H, s).	(CI-NH_3) 194 ($[MNH_4]^+$), 177.1490 ($[MH]^+$; calc. for $C_9H_{21}O_3$: 177.1491), 89 (100%).
	1.73 (3H, s), 3.40 (3H, s), 3.56 (2H, t), 3.70 (2H, t), 3.99 (2H, s), 4.72 (2H, s), 4.88 (1H, s), 4.97 (1H, s).	(CI-NH_3) 178 ($[MNH_4]^+$), 161.1176 ($[MH]^+$; calc. for $C_8H_{17}O_3$: 161.1177), 89, 85 (100%).

a. $[\alpha]_D^{21}$ -11.4 (c 0.55 in ethanol). Deprotection gave **7b** with $[\alpha]_D^{21}$ -8.0 (c 0.78 in ethanol; lit.[7] -8.7, c 1.1).

References and Notes

1. Corey, E.J., Gras, J.L., and Ulrich, P., *Tetrahedron Lett.*, **1976**, 809.
2. Greene, T.W. and Wuts, P.G.M., "Protective Groups in Organic Synthesis", Second Edition (Wiley, 1991), pp. 27-29. s.a. Guindon, Y., Yoakim, C., and Morton, H.E., *J. Org. Chem.*, **1984**, *49*, 3912.
3. Marshall, J.A. and Luke, G.P., *J. Org. Chem.*, **1993**, 6231.
4. Monti, H.S., Léandri, G., Klos-Ringuet, M., and Corriol, C., *Synth. Comm.*, **1987**, *17*, 1749.
5. Prince, R.H., *in* King, R.B., *ed.*, "Encyclopaedia of Inorganic Chemistry" (Wiley, 1994), vol. 8, p. 4434, and references therein.
6. Products were not isolated, but merely identified from GC-MS of the crude mixture after work-up.
7. Herbert, J.M., Hewson, A., and Peace, J.E., Manuscript submitted for publication.
8. Methyl valerate, anisole, and 1-*tert*-butyldimethylsilyloxy-3-phenylpropane were used to test the stability of these functional groups. The acidic system was prepared in ether, while lithium bromide-zinc bromide was prepared in 1:1 ether-THF. The last of these was prepared as described previously (Hase, T.A., and Lahtinen, L., *Synth. Commun.*, **1978**, *8*, 573).
9. Corey, E.J., Hua, D.H., and Seitz, S.P., *Tetrahedron Lett.*, **1984**, *25*, 3.
10. Diana, G.D., Treasurywala, A.D., Bailey, T.R., Oglesby, R.C., Pevear, D.C., and Dutko, F.J., *J. Med. Chem.*, **1990**, *33*, 1306; c.f Diana, G.D., Cutcliffe, D., Oglesby, R.C., Otto, M.J., Mallamo, J.P., Akullian, V., and McKinlay, M.A., *J. Med. Chem.*, **1989**, *32*, 450.
11. Casnati, G. and Ricca, A., *Tetrahedron Lett.*, **1967**, 327.
12. Takahashi, Y., Yamashita, H., Kobayashi, S., and Ohno, M., *Chem. Pharm. Bull.*, **1986**, *34*, 2732. There was insufficient material for its optical rotation to be measured.
13. Gross, R.S. and Watt, D.S., *Synth. Comm.*, **1987**, *17*, 1749.
14. Rigby, J.H. and Wilson, J.A.Z., *Tetrahedron Lett.*, **1984**, *25*, 1429.

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