

Alkylative Cleavage of the *Endo*-Cyclic C–O Bond in Lactol Ethers Employing Organometallic Reagents

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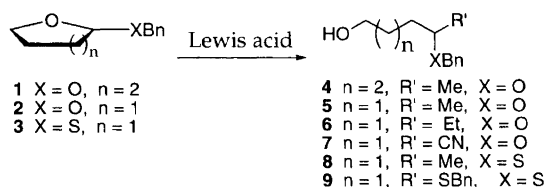
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Dedicated to Professor Lennart Ebersson on the occasion of his 65th birthday

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Simple lactol ethers undergo ring cleavage to give acyclic chain-extended products on treatment with organoaluminium and organotitanium reagents.

In the reactions of glycosides with Brönstedt or Lewis acids there are in principle two modes of bond breakage at the anomeric center, the *exo* and *endo* C–O bond cleavage. This has been debated previously^{1–3} and both routes have been shown to exist,^{4–6} although it seems that the *exo*-cleavage is the most general mode in aqueous or alcoholic solutions. Several years ago Guindon *et al.*^{7,8} found that glycosides were cleaved in the *endo*-mode by dimethylboron bromide to generate the corresponding 1-bromo-1-alkoxy derivatives. Independently, we found that benzyl pentopyranosides were cleaved in the *endo*-mode directly followed by stereoselective alkylation at C-1 on treatment with triorganyl aluminium reagents.^{9,10} Only a few other examples of alkylative *endo*-cleavage reactions have so far been reported.^{11–14} In these cases a two-component reagent mixture was used, consisting of a rather strong Lewis acid and a nucleophilic organometallic reagent. We here report on the *endo*-alkylative cleavage of simple tetrahydrofuran (THF) and tetrahydropyran (THP) ethers by organoaluminium and titanium reagents (Scheme 1).

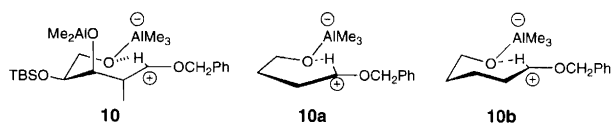


Scheme 1.

Thus, the lactol ethers were treated with the aluminium reagents in hexane to give the open chain derivatives as shown in Table 1. THP ether **1** reacted with AlMe₃ generating a good yield of **4** (entry 1). However, treatment of **1** with either AlEt₃ or Et₂AlCN gave no reaction

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(entries 2 and 3) and employing the stronger Lewis acid Me₂AlCl resulted only in *exo*-cleavage. Computations performed in order to clarify the origin of the diastereoselectivity in the Lewis acid induced alkylative *endo*-cleavage of other benzyl pentopyranosides implied that a seven-membered hydrogen-bonded ring intermediate **10** was formed prior to the methyl transfer.^{15,16} Guided by these computational data, we considered that since six-membered rings usually have less ring strain¹⁷ than seven-membered ones, a furanoside, expanding to a six-membered hydrogen-bonded intermediate **10a**, should be more favourable than a pyranoside expanding to a seven-membered intermediate **10b**. Recently, Corey *et al.* suggested a similar hydrogen-bonded intermediate for conformational restriction in complexes of formyl compounds with boron Lewis acids.^{18,19}



In line with this, treatment of THF ether **2** with AlMe₃ (entry 5) gave a faster reaction and a better yield than the corresponding reaction with THP ether **1** (entry 1). Moreover, THF ether **2** did also react with Et₃Al (entry 6) and Et₂AlCN (entry 7) giving acyclic products (**6** and **7**) in good yields. This is the first time that the *endo*-cyclic carbohydrate-like C–O bond has been directly substituted by other nucleophiles than methyl or alkynyl groups using alanes. Notably, the reaction with Me₂AlCl (entry 8) gave almost exclusively *exo*-cleavage. THF thioether **3** gave **8** on treatment with AlMe₃ (entry 9). To our knowledge no alkylative substitution of the *endo*-cyclic C–O bond in **3** or in related thio-glycosides has previously been reported, although related

Table 1. Lewis acid induced alkylative ring opening of THF and THP ethers.

Entry	Substrate	Lewis acid	Time/h	Temp./°C	Products	Yield (%)
1	1	AlMe ₃	60	Reflux	4	69
2	1	AlEt ₃	100	Reflux	No reaction	—
3	1	Et ₂ AlCN	100	Reflux	No reaction	—
4	1	Me ₂ AlCl	24	20	4/BnOH	0/87
5	2	AlMe ₃	12	Reflux	5	90
6	2	AlEt ₃	48	Reflux	6	79
7	2	Et ₂ AlCN	48	Reflux	7	73
8	2	Me ₂ AlCl	24	20	5/BnOH	1/86
9	3	AlMe ₃	12	Reflux	8	86
10	3	AlEt ₃	48	Reflux	No reaction	—
11	3	Et ₂ AlCN	48	Reflux	No reaction	—
12	3	Me ₂ AlCl	12	20	8/9/BnSH	8:9 1:1
13	1	Me ₂ TiCl ₂	6	-78	5/BnOH	60/12

reductive cleavages have been reported in which a C–H bond replaced the *endo* C–O bond.^{20–22} As seen in entries 10 and 11 no reaction was observed in the treatment of **3** with Et₃Al or Me₂AlCN. Application of the stronger Lewis acid Me₂AlCl resulted in both the *endo*-alkylative cleavage product **8** and a new compound **9**, which probably was formed by trapping of the intermediate cation similar to **10a** by benzylthiolate generated by *exo*-cleavage. In support of this, compound **9** was obtained in 92% yield on treatment of **3** with 3 equiv. of MeAlCl(SBn) generated by premixing Me₂AlCl and BnSH in hexane.

Chiral nonracemic complexes of aluminium and titanium were applied in order to explore the possibility of enantioselective substitution of the *endo*-cyclic C–O bond in **2**. Thus, a methyl group of AlMe₃ and Me₂AlCl was replaced by addition of one equivalent of (–)-menthol or (–)-8-phenylmenthol, respectively. However, no reaction of **2** was noticed on treatment with these reagents. Next, the titanium reagent was prepared as above via methyl replacement of Me₂TiCl₂,^{23,24} but all that could be detected in the reactions with **2** was benzylalcohol, besides unreacted starting material. Also the reagent formed by treating Me₂TiCl₂ with isopropanol gave the same result. The reactivity of THF ether **2** with Me₂TiCl₂ was verified since the open chain *endo*-cleavage product **5** was formed in a reasonable yield together with a small amount of benzylalcohol produced by *exo*-cleavage (entry 13). Chiral organotitanium reagents were previously used in enantioselective addition to carbonyl compounds.²⁵

In summary, benzyl THF ether **2** reacted with various alanes but the corresponding THP ether **1** only reacted with AlMe₃ to generate acyclic products, resulting from regioselective C-1 alkylative cleavage of the *endo*-cyclic C–O bond.

Experimental

Column chromatography separations were performed by using Merck SiO₂ 60A (0.035–0.070 mm) silica gel with ethyl acetate/heptane (E/H) mixtures as eluents. TLC

analyses were made on Merck SiO₂ 60 F254 precoated glass plates and the spots were visualized by charring with a solution of phosphomolybdic acid (25 g), Ce(SO₄)₂·4H₂O (10 g), conc. H₂SO₄ (60 mL) in H₂O (940 mL). NMR spectra were recorded in CDCl₃ at 21 °C (¹H) 400 MHz, CHCl₃ δ 7.27 and (¹³C) 100 MHz, CHCl₃ δ 77.2).

All reactions were carried out in oven-dried glassware equipped with rubber septa and under an argon atmosphere. The organometallic reagents were transferred by dried, argon-flushed syringes. Heptane was distilled from sodium and hexane was distilled from CaH₂ and stored over 4A molecular sieves. Ethyl acetate was distilled immediately before use. AlMe₃ (2.0 M in hexane; Aldrich), AlEt₃ (1.0 M in hexane; Merck), Et₂AlCN (1.0 M in hexane; Aldrich) and Me₂AlCl (1.0 M in hexane; Aldrich) were used as delivered. Substrates **1**, **2**²¹ and **3**²² were prepared according to the literature procedures.

General procedure for the Lewis acid treatment of 1–3. The Lewis acid (3.0 equiv.) was added to the substrate (0.2 M in hexane) at room temperature. The solution was stirred for the time and at the temperature indicated in Table 1. The progress of the reaction was monitored by TLC (E/H 1:3). The reaction mixtures were quenched by slow addition, with vigorous stirring, into cold aqueous ca. 2 M solution of NH₄Cl (adjusted to ca. pH 8 with 2 M NH₄OH). The solids were filtered off and thoroughly washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with water, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was column chromatographed (E/H 1:3) to give the products shown in Table 1. Spectral data are given below for new compounds.

4-Benzyloxy-1-hexanol (6). IR (Film): 3480 cm⁻¹. ¹H NMR (CDCl₃): δ 7.30 (m, 5 H), 4.57, 4.49 (AB q, each 1 H, J_{AB} = 11.6 Hz), 3.65 (m, 2 H), 3.40 (m, 1 H), 1.92 (m, 1 H), 1.72–1.65 (m, 6 H), 0.94 (t, 3 H, J = 7.4 Hz). ¹³C NMR (CDCl₃): δ 139, 128, 128, 127, 80, 71, 63, 30,

29, 26, 10. HRMS (CI-CH₄) Calc. for C₁₃H₂₁O₂ (M+H): 209.1541, found 209.1531.

2-Benzylloxy-5-hydroxypentanenitrile (7). IR (Film): 3480, 2240 cm⁻¹. ¹H NMR (CDCl₃): δ 7.30 (m, 5 H), 4.87, 4.55 (AB q, each 1 H, J_{AB}=11.6 Hz), 4.25 (t, 1 H, J=6.3 Hz), 3.66 (m, 2 H), 3.40 (m, 1 H), 1.99 (m, 2 H), 1.77 (m, 2 H). ¹³C NMR (CDCl₃): δ 136, 129, 129, 128, 118, 73, 68, 62, 30, 28. HRMS (CI-CH₄) Calc. for C₁₂H₁₆O₂N (M+H): 206.1181, found 206.1184.

4-(Benzylthio)-1-pentanol (8). IR (Film): 3490 cm⁻¹. ¹H NMR (CDCl₃): δ 7.30 (m, 5 H), 3.76 (s, 1 H), 3.74 (s, 1 H), 3.60 (m, 2 H), 2.67 (m, 1 H), 1.71–1.52 (m, 4 H), 1.29 (d, 3 H, J=6.8 Hz). ¹³C NMR (CDCl₃): δ 139, 129, 129, 127, 63, 39, 35, 33, 30, 21. HRMS (CI-CH₄) Calc. for C₁₂H₁₉OS (M+H): 211.1157, found 211.1156.

4,4-Bis(benzylthio)-1-butanol (9). A mixture of Me₂AlCl (1.53 mL, 1.53 mmol) and benzyl mercaptan (190 mg, 1.53 mmol) in hexane (5 mL) was stirred for 10 min at 20 °C followed by addition of compound **3** (100 mg, 0.51 mmol). The resulting mixture was then stirred at 20 °C for 5 h, quenched and worked up as above. The residue was column chromatographed (E H 1:3) to give **9** (151 mg, 92%) as a syrup: IR (Film): 3340 cm⁻¹. ¹H NMR (CDCl₃): δ 7.28 (m, 10 H), 4.57, 4.49 (AB q, each 2 H, J_{AB}=13.2 Hz), 3.54 (t, 1 H, J=6.9 Hz), 3.48 (t, 2 H, J=6.3 Hz), 1.84 (m, 2 H), 1.66 (m, 2 H), 1.28 (bs, 1 H). ¹³C NMR (CDCl₃): δ 138, 129, 129, 127, 62, 50, 35, 32, 30. HRMS (CI-CH₄) Calc. for C₁₈H₂₂OS₂ (M): 318.1113, found 318.1112.

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