Chelation-controlled regioselective *endo* cleavage and stereoselective C-1 alkylation of pentofuranosides

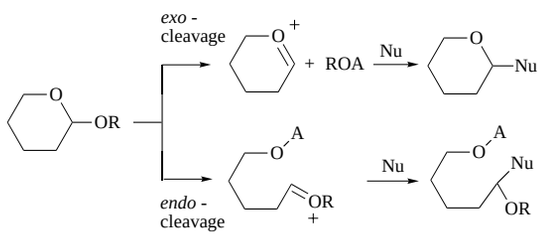
Roger Olsson, Pontus Rundström and Torbjörn Frejd *

Organic Chemistry 1, Department of Chemistry, Lund University, PO Box 124, S-221 00 Lund, Sweden

Combinations of Lewis acids and nucleophilic reagents trigger *endo*-opening of the furanoside ring of methyl furanosides 1, 10 and 13, resulting in the attachment of the nucleophilic group at C-1 of the carbohydrate. The stereoselectivity in the C–C bond-forming step is low for the 2-deoxyfuranosides but very high (dr 1:99) for the furanosides carrying a methoxy group in the 2-position when a combination of $TiCl_4$ and Me_2Zn is used. Different selectivities are obtained with Me_2Zn as compared with Me_3Al. Reagents based on several organometallic reagents of Al, Si, Ti and Zn in combination with $TiCl_4$ can be used.

Introduction

There is continuing interest in the regioselective cleavage of acetals and subsequent stereoselective substitution of one of the C–O bonds by means of Lewis acid–nucleophile systems.[1–10] Glycosides, constituting a large group of mixed acetals carrying several stereogenic centres, are recognized as potent starting materials for the synthesis of a wide variety of complicated natural products.[11,12] In most carbohydrate examples the exocyclic C–O bond has been substituted giving rise to new *O*-glycosides[13,14] or *C*-glycosides,[15] both with a high degree of stereocontrol (Scheme 1). A manifestation of the importance



A = Brønsted or Lewis acid

Scheme 1

of the *exo*-cleavage is clearly seen in the tremendous success of oligosaccharide synthesis in glycoscience.[16–19]

About 50 years ago Lindberg showed that glycosides, when treated with Lewis acids, underwent anomerization *via endo*-cleavage followed by ring closure.[20] The *endo*-cleavage mode has also been debated in relation to enzymic cleavage of carbohydrates.[21–24] The use of carbohydrates as stereochemically pure starting materials for organic synthesis would benefit from general methods taking advantage of the *endo*-cleavage mode. Cases of non-stereoselective *endo*-cleavage reactions have been reported using trimethylsilyl cyanide (TMSCN)/$SnCl_2$[25] or RCu[26,27] applied to simple tetrahydrofuran (THF) and tetrahydropyran (THP) ethers. More elaborate glycosides were cleaved by the use of Me_2BBr.[28–31]

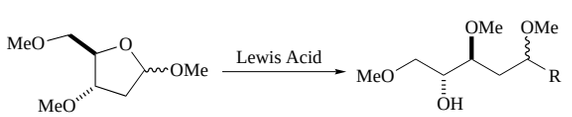
To our knowledge, the first example of alkylative *endo* cleavage was reported by Kawana *et al.*[32] who clearly pointed to the possibility of chelation of the reagent, in this case MeMgX, to the O-4/O-5 positions of methyl furanosides. The stereoselectivities were not always high but in one case a diastereoisomeric ratio (dr) of 87:13 was obtained. Stereoselective introduction of the cyano group was achieved *via endo*-cleavage by Hashimoto and Hayakawa on treating benzyl tri-*O*-benzyl-β-D-ribofuranoside with TMSCN and a catalytic amount of $BF_3{\cdot}OEt_2$.[33] Later, Martin *et al.* used the chelation control of pentofuranosides and hexopyranosides for the stereoselective allylation at C-1 by application of the Lewis acid–nucleophilic reagent combination $TiCl_4$/allyltrimethylsilane.[34] In several cases this allylative *endo* cleavage resulted in complete stereocontrol.

Previously, we reported stereoselective C-alkylations *via endo* C–O bond cleavage of benzyl pentopyranosides by reaction with $AlMe_3$ or organotitanium reagents.[35,36] This methodology was used in the synthesis of two γ-hydroxyisoleucine stereoisomers, (2*R*,3*R*,4*R*) and (2*S*,3*R*,4*R*), as well as their corresponding γ-lactones.[37] In these examples the organoaluminium or organotitanium reagents acted as both Lewis acids and nucleophile carriers. A limitation with these reagents was the difficulty in varying the nucleophilic part. Therefore the combination of a Lewis acid separate from the nucleophilic reagent would be advantageous. In particular, octahedral organotitanium chelates as intermediates were recently shown to influence strongly the stereoselectivity of addition to chiral α-alkoxy carbonyls.[38,39]

We here report on the use of various easily accessible organometallic reagents based on zinc,[40,41] aluminium,[42,43] silicon or titanium,[44–47] in combinations with $TiCl_4$ in the chelation-controlled regio- and stereo-selective C-alkylation of pentofuranosides. Since this methodology increases the number of transferable organyl groups to C-1, the general synthetic strategy of using readily available inexpensive carbohydrate derivatives[48] as building blocks in natural product synthesis is further expanded.

Results and discussion

The simple α/β-furanosides **1**, **10** and **13** were subjected to the *endo* C–O bond-cleavage reactions and the results are shown in Table 1. Addition of $AlMe_3$ to β-**1** (Scheme 2) resulted in a 2:1 dr of products of **2** and **3** in a low yield of 31% (Entry 1). While



α- or β-**1**

2/**3** R = Me
4/**5** R = Et
6/**7** R = Ph
8/**9** R = CN

Scheme 2

Table 1 Results of the reaction of glycosides **1**, **10** and **13** with $TiCl_4$ and various organometallic reagents

Entry	Substrate	Reagents (mol equiv.)[a]	Delay/min[a]	Reaction time/h	Temp./°C[b]	Products	dr/Isolated yield (%)[c]
1	β-**1**	$AlMe_3$ (3)		48	reflux	**2/3**	2:1/31
2	β-**1**	$MeTiCl_3$ (1)		33	25	**2/3**	/0
3	β-**1**	$MeTiCl_3$ (2)		22	25	**2/3**	3:1/52
4	β-**1**	$TiCl_4$ (1)/$ZnMe_2$ (3)	60	3	−72	**2/3**	1:1/49
5	β-**1**	$TiCl_4$ (1)/$AlMe_3$ (3)	60	2	−72	**2/3**	2:1/37
6	β-**1**	$TiCl_4$ (1)/$AlMe_3$ (3)	10	3	−72	**2/3**	2:1/47
7	β-**1**	$TiCl_4$ (1)/$ZnEt_2$ (3)	60	2	−72	**4/5**	3:2/27
8	β-**1**	$TiCl_4$ (1)/$ZnEt_2$ (3)	10	3	−72	**4/5**	3:2/55
9	β-**1**	$TiCl_4$ (1)/$ZnEt_2$ (3)	1	8	−72	**4/5**	3:2/12
10	β-**1**	$TiCl_3(OPr^i)$ (1)/$ZnEt_2$ (3)	10	33	25	**4/5**	3:2/9
11	β-**1**	$TiCl_4$ (1)/$AlEt_3$ (3)	10	12	−42	**4/5**	2:1/65
12	β-**1**	$MeTiCl_3$ (1)/$ZnEt_2$ (3)	10	12	−42	**4/5**	3:2/40
13	β-**1**	$TiCl_4$ (1)/$ZnPh_2$ (3)	30	12	−72	**6/7**	1:1/85
14	β-**1**	$TiCl_4$ (1)/Me_3SiCN (3)	10	12	−42	**8/9**	1:1/70
15	α-**1**	$TiCl_4$ (1)/$ZnEt_2$ (3)	30	12	−42	**4/5**	3:2/60
16	α/β-**10**	$TiCl_4$ (1)/$AlMe_3$ (3)	60	5	−42[d]	**11/12**	1:3/65
17	α/β-**10**	$TiCl_4$ (1)/$ZnMe_2$ (3)	60	5	−42[d]	**11/12**	1:99/61
18	α-**13**	$TiCl_4$ (1)/$AlMe_3$ (3)	45	12	−42	**14/15**	2:1/67
19	α-**13**	$TiCl_4$ (1)/$ZnMe_2$ (3)	35	7	−42	**14/15**	1:99/60
20	β-**13**	$TiCl_4$ (1)/$AlMe_3$ (3)	45	12	−42	**14/15**	2:1/71
21	β-**13**	$TiCl_4$ (1)/$ZnMe_2$ (3)	35	7	−42	**14/15**	1:99/56

[a] The Lewis acid to the left was added to the substrate, followed by a waiting period as indicated before addition of the reagent to the right. [b] All reactions were started at −72 °C and the temperature of the cooling bath was thereafter slowly raised to the indicated value (±3 °C). [c] The diastereomeric ratios (drs) were determined by GLC analyses. [d] The temperature of the solution was allowed to reach 5 °C before quenching.

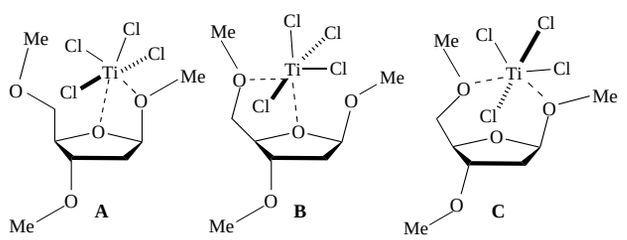


Fig. 1 *Ab initio*-calculated energies of the three most reasonable chelates between $TiCl_4$ and β-**1**. 1 cal = 4.184 J.

a stoichiometric amount of $MeTiCl_3$, accessible by Zn–Ti exchange by mixing $TiCl_4$ and $ZnMe_2$ in a 2:1 ratio,[45] gave no reaction at all with substrate β-**1** (Entry 2), use of two mole equivalents led to a 52% isolated yield of products **2** and **3** in a 3:1 dr (Entry 3). This indicated that the first mole equivalent of Lewis agent formed a chelate probably involving the ring oxygen (O-5), thereby activating the carbohydrate for alkyl donation at C-1 by the second mole equivalent of the Lewis acid serving only as an organyl donor. Different chelates may be formed due to the presence of four coordinating oxygens in the substrate. However, single-point *ab initio* calculations (3-21G)[49] on preoptimized geometries (PM3) of $TiCl_4$-chelates with substrate β-**1** suggested that the most favourable chelation was at O-4/O-5 (complex **B**, Fig. 1). The other two reasonable chelates (**A** and **C**) were of considerably higher energy. No chelating effect at all was found at O-3/O-4.

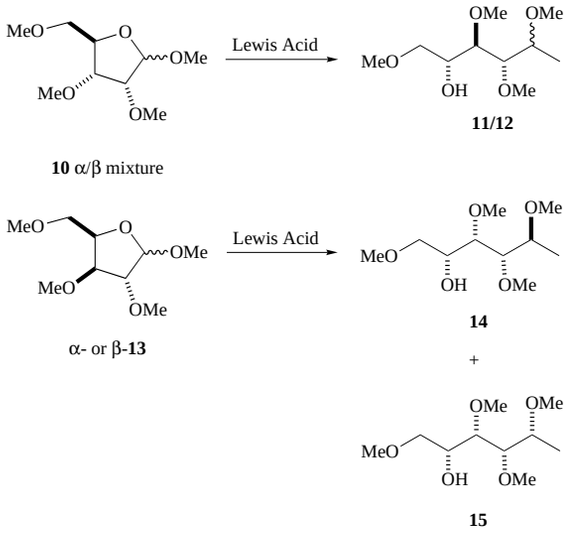
This reasoning led us to first let the carbohydrate and the chelating Lewis acid ($TiCl_4$) form the complex (such as **B**) before the nucleophile carrier was introduced. Thus, treating substrate β-**1** first with one mole equivalent of $TiCl_4$ at −72 °C, and then, after a 60 min complexation time, with the nucleophile carrier $ZnMe_2$ resulted in a 49% yield of products **2/3** but without any selectivity (Entry 4). No reaction occurred in the absence of $TiCl_4$. Changing the organyl donor from $ZnMe_2$ to $AlMe_3$ (Entry 5) gave the same selectivity (2:1) as when only $AlMe_3$ was used. The yields were only 31 and 37%, respectively, in these cases, but shortening the complexation time from 60 min to 10 min increased the yield to 47% (Entry 6).

It was now interesting to see whether it was possible to use reagents carrying other nucleophiles than the methyl group. Thus, $ZnEt_2$ turned out to work well as an ethyl donor although the diastereoselectivity of products **4/5** was quite low (3:2). The complexation time (1, 10 or 60 min) had no significant influence on the selectivity, but the highest yield (55%) was achieved with a 10 min delay (Entries 7–9). A slight increase in both yield and selectivity was noticed when $AlEt_3$ was used as the alkyl donor instead of $ZnEt_2$ (Entries 8 and 11). The weaker Lewis acid $TiCl_3(OPr^i)$ (a higher temperature was necessary) together with $ZnEt_2$ gave at best 9% yield of products **4/5** (Entry 10). The α-anomer of substrate **1** reacted with $TiCl_4/ZnEt_2$ to give the same ratio of products **4/5** as the β-anomer in a reasonable yield (Entry 15). For an interpretation see below.

The combination of $TiCl_4$ and ZnR_2 or AlR_3 resembles the Ziegler–Natta catalyst, which is formed by the couple $TiCl_4/AlEt_3$. Here the alkylated titanium species is the actual coordinating catalyst while $AlEt_3$ serves to initiate the reaction by alkyl transfer to titanium.[50] In order to find out whether a similar alkyl-group transfer between the organyl donor and Ti^{IV} precedes the substitution reaction of the *endo* C–O bond, compound β-**1** was first treated with one mole equivalent of $MeTiCl_3$ (instead of $TiCl_4$) before the addition of $ZnEt_2$. The product formed (**4/5**) originated exclusively from attack of an ethyl group, showing the same diastereoselectivity as the combination $TiCl_4/ZnEt_2$ (Entry 12). If a ligand exchange precedes the substitution reaction then both methyl and ethyl attack at C-1 would be expected. Since this is not the case, ligand exchange seems not to have any influence on this reaction. Once the titanium species has formed the chelate with the carbohydrate there may not be any possibility for alkyl transfer. The delay between the addition of Lewis acid and the organyl donor had an influence on the yields as seen in Entries 7–9.

Both a phenyl group and a cyano group could be introduced at C-1 of substrate β-**1** by $TiCl_4/ZnPh_2$ and $TiCl_4/Me_3SiCN$, respectively, in good yields, showing that the organyl part can be groups other than simple alkyls (Entries 13 and 14).

For compound β-**1** as a substrate a slight tendency of increased selectivity was noticed in the series $ZnMe_2 < ZnEt_2 < AlMe_3 = AlEt_3 < MeTiCl_3$ (see Entries 4, 8, 5, 11 and 3, in that order). Thus, the larger reagents gave the higher selectivities. An increase of the steric hindrance in the substrate, *e.g.* by introducing a substituent at C-2, would perhaps work in the same direction. Indeed, when the α/β-anomeric mixture of the permethylated ribofuranoside **10** was treated with $TiCl_4/AlMe_3$



Scheme 3

(Scheme 3), a higher diastereoselectivity (**11/12** 1:3) was reached (Entry 16) as compared with β-**1** (2:1, Entries 5 and 6). Surprisingly, changing the methyl donor to $ZnMe_2$ resulted in excellent selectivity, 1:99 (Entry 17). This is not what we expected since we expected the aluminium reagent to be larger than the zinc reagent. However, the 2-OMe group constitutes an extra Lewis-acid-coordination site, making it very difficult to draw any simple conclusions at present since there exists no investigation of the complexation situation of carbohydrates carrying multiple Lewis-acid-coordination sites. Also xylofuranoside **13** (Scheme 3) gave an excellent selectivity (**14/15** 1:99) with $ZnMe_2$, while application of $AlMe_3$ gave not only a lower selectivity but also the reversed diastereoselectivity (2:1 as compared to 1:99, Entries 20 and 21, respectively).

With a derivative similar to compound **13** Martin *et al.*[34] found that the β-anomer performed well in their reactions, while the α-anomer was essentially unreactive. Such a difference between the anomers was not observed in our reactions; in the case of compound **13** the α and β anomers gave the same main products and diastereomeric ratios with both $AlMe_3$ and $ZnMe_2$ (Entries 18–21). Also, reactions performed separately with the α and β anomers of substrate **1** resulted in the same product mixtures of compounds **4** and **5** (*cf.* Entries 8 and 11). Thus, the reaction with one anomer proceeds mainly by retention while the reaction with the other one gives inversion of the stereocenter at C-1, a pattern that also was observed in our earlier work with benzyl pentopyranosides.[35] This indicates that a common intermediate is formed before the transfer of the organic group to C-1.

Computations performed to clarify the origin of the selectivity in the reactions of pentopyranosides implied that a hydrogen-bonded, seven-membered-ring intermediate was formed prior to methyl transfer.[51,52] In the furanoside cases **1**, **10** and **13** such hydrogen-bonded structures will be six-membered (Fig. 2) and would orient the oxocarbenium unit in the average plane of the ring system. The nucleophile would then have to attack either from below or from above this plane depending on the nature of the nucleophilic reagent and the substituents on the substrate. Similar hydrogen bonding was recently postulated by Corey *et al.* to explain the enantioselectivity in reactions between chiral boron Lewis acids and aldehydes.[53,54]

One may speculate about the origins of the selectivity differences of the reagents but the situation is complicated due to the presence of multiple coordination sites and the use of excess of the reagents. The cyclic hydrogen-bonded model (Fig. 2) would be favoured over the open-chain alternative due to electrostatic attraction. Thus, the Cram and Felkin–Ahn models of open-

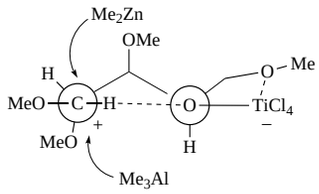
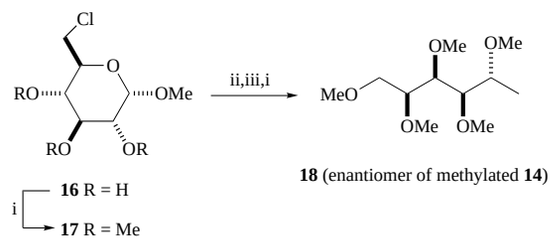


Fig. 2 The tentative intermediate from compound **13** is preferentially attacked at opposite faces depending on the reagent

chain systems would not apply. Besides, both the zinc and the aluminium reagents should be able to form chelates that would lead to the same or similar selectivity in the chelating Felkin–Ahn model, but this was not the case for substrate **13**. The zinc reagent attacks the intermediate originating from compound **13** from above, while the aluminium reagent attacks preferentially from below the average ring plane as depicted in Fig. 2.

The relative configuration of product **14** was determined by GLC/MS comparison of its permethylated derivative with authentic compound **18**, prepared in four steps from chloride **16**[55] as outlined in Scheme 4. Then the absolute configurations



Scheme 4 *Reagents and conditions:* i, NaH, MeI, THF, room temp.; ii, aq. H_2SO_4, 100 °C; iii, $LiAlH_4$, THF, reflux

of compounds **14** and **15** follow from the known configurations of the starting materials. The configuration at C-5 of the individual isomers of the other diastereomeric pairs (**2/3**, **3/4**, **6/7**, **8/9** and **11/12**) could not be determined since the NMR data were not sufficiently informative due to overlapping peaks, and the attempted chromatographic separations were unsuccessful except for compounds **11** and **12**. Other protecting groups than methyl will be needed to solve these problems, *e.g.* by allowing mild removal and the synthesis of cyclic derivatives for structure determination, which will be reported in due course.

Conclusions

The *endo*-C–O bond was cleaved and a new organic group was introduced at C-1 of furanosides by application of a Lewis acid together with a nucleophilic reagent. It was earlier shown that this reaction was feasible for pyranosides. A preliminary mechanistic model, which provides a plausible explanation for the stereoselectivities observed, was suggested. We assume that the reaction proceeds *via* chelation between O-5/O-4 of the furanoside and the Lewis acids ($MeTiCl_3$, $TiCl_4$ and $TiCl_3OPr^i$) followed by transfer of the organic groups by using $ZnMe_2$, $ZnPh_2$, $ZnEt_2$, $AlMe_3$, $AlEt_3$ and $MeTiCl_3$ as nucleophile carriers. In the case of compound β-**1** the cyano group was transferred by using Me_3SiCN and $TiCl_4$. The different selectivities of Me_2Zn and Me_3Al indicated that perhaps the more useful reagent control could be further developed.

Experimental

Column chromatographic separations were performed by using Merck SiO_2 60A (0.035–0.070 nm) silica gel with ethyl acetate–heptane (E/H) mixtures as eluents. TLC analyses were made on Merck SiO_2 60 F254 precoated glass plates and the spots were visualized by charring with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 4H_2O$ (10 g) conc. H_2SO_4 (60 ml) in water (940 ml). NMR spectra were recorded in $CDCl_3$ at 21 °C on a

Bruker DRX 400 NMR spectrometer [(^{1}H) 400 MHz, $CHCl_3$ δ 7.27; and (^{13}C) 100 MHz, $CHCl_3$ δ_C 77.2]. *J*-Values are in Hz. GLC analyses were performed with a DBwax column (J&W Scientific) capillary column (30 m; 0.25 mm i.d., 0.25 μm stationary phase). Mps were measured on a Gallenkamp melting point apparatus and are uncorrected.

IR, mass and optical rotation data were recorded with a Nicolet Impact 410 Infrared Spectrometer, a JEOL JMS-SX 102 mass spectrometer and a Perkin-Elmer 241 Polarimeter, respectively. All reactions were carried out in oven-dried flasks or vials equipped with rubber septa and under an argon atmosphere. The organometallic reagents were transferred by dried, argon-flushed syringes and cannulas. Heptane was distilled from sodium. CH_2Cl_2 was distilled from CaH_2 and stored over molecular sieves. Ethyl acetate was distilled immediately before use. $TiCl_4$ and $Ti(OPr^i)_4$ were purchased from Aldrich and Janssen respectively, and diluted with dry CH_2Cl_2 to 2.0 M before use. $ZnMe_2$ (2.0 M in toluene; Merck), $ZnEt_2$ (1.0 M in hexane; Merck), $ZnPh_2$ (Alfa), $AlMe_3$ (2.0 M in hexane; Aldrich), $AlEt_3$ (1.0 M in hexane; Merck) and Me_3SiCN (Fluka AG) were all used without further purification. $MeTiCl_3$, $Cl_3Ti(OPr^i)$[45] and the substrates **10**[56] and **13**[57] were prepared according to the respective literature procedure.

Methyl 2-deoxy-3,5-di-*O*-methyl-β-D-*erythro*-pentofuranoside and its α-D-anomer α/β-1

A solution of '2-deoxy-D-ribose' (5.0 g, 37.6 mmol) in 0.05% HCl/MeOH (190 ml) was stirred at room temp. for 30 min, followed by addition of Ag_2CO_3 (1.0 g, 3.6 mmol). The resulting solution was stirred for 5 min and was then filtered, evaporated and finally co-evaporated with THF (3 × 10 ml), to afford 6.4 g of an oily mixture of the anomeric methyl glycosides. This mixture was dissolved in THF (85 ml) and the solution was cooled to 0 °C. NaH (60%; 3.3 g, 83 mmol) and MeI (11 g, 5.2 ml, 83 mmol) were alternately added in portions as the temperature was slowly raised to ambient. The resulting slurry was stirred for 60 h, whereafter MeOH (4 ml) was added and the suspension was poured into ice–water (100 ml). CH_2Cl_2 (100 ml) was now added and the aqueous phase was extracted with CH_2Cl_2 (3 × 35 ml). The combined extracts were washed with water (2 × 100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (E/H 3:7 ⟶ 2:3 ⟶ 1:1) afforded the β- (1.6 g, 24%) and α-anomer (2.4 g, 36%) of compound **1**. Spectral data were as reported in the literature.[58]

General procedure for the opening and C-1 alkylation of substrates 1, 10 and 13

A solution of $TiCl_4$ (1.0 mol equiv.; 2.0 M in CH_2Cl_2) was added to a solution of the substrate (0.40 mmol; 0.2 M in CH_2Cl_2) at −72 °C. After a certain time delay (see Table 1) the alkyl donor was added dropwise and 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 2:1). The reaction mixture was quenched by slow addition into a vigorously stirred cold water–ethyl acetate mixture (30:70). Stirring was continued for 1 h. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with water, dried (Na_2SO_4), and gently concentrated at reduced pressure (12 mmHg; water bath ≈35 °C).

(2*R*,3*S*,5*R*)- and (2*R*,3*S*,5*S*)-1,3,5-Trimethoxyhexan-2-ol 2 and 3 (entries 1–6). The general procedure was applied to compound **1** and the methyl-group donors shown in Table 1. Column chromatography (E/H 1:10 ⟶ 1:1) of the crude product gave an inseparable mixture of products **2/3** as a syrup: ν(film)/cm^{-1} 3420; δ_H 3.86 and 3.74 (each 1 H, 2 m), 3.50 (6 H, m), 3.42, 3.40, 3.34, 3.33, 3.32 and 3.32 (each 3 H, 6 s), 2.59 (each 1 H, 2 s), 1.88 and 1.85 (each 1 H, 2 m), 1.67 and 1.58 (each 2 H, 2 m) and 1.17 and 1.16 (each 3 H, 2 d, *J* 6.3 and 6.4); δ_C 79.0, 78.7, 73.8, 73.5, 73.4, 73.0, 71.6, 71.3, 59.2, 59.1, 58.4, 57.4, 55.9 (2 C), 38.3, 35.8 and 19.2 (2 C); HRMS (CI-CH_4): $C_9H_{21}O_4$ (M + H); Found: *m*/*z*, 193.1447. Calc.: *m*/*z*, 193.1440.

(2*R*,3*S*,5*R*)- and (2*R*,3*S*,5*S*)-1,3,5-Trimethoxyheptan-2-ol 4 and 5 (entries 7–12, 15). The general procedure was applied to compound **1** and the ethyl-group donors shown in Table 1. Column chromatography (E/H 1:10 ⟶ 1:1) of the crude product gave an inseparable mixture of products **4/5** as a syrup: ν(film)/cm^{-1} 3440; δ_H 3.87 and 3.72 (each 1 H, 2 m), 3.54 (8 H, m), 3.41, 3.39, 3.38, 3.33, 3.32 and 3.32 (each 3 H, 6 s), 2.57 (each 1 H, 2 s), 1.76 (4 H, m), 1.55 (4 H, m) and 0.88 and 0.87 (6 H, 2 t, *J* 7.5); δ_C 79.0, 78.8, 78.4, 77.8, 73.5, 71.5, 71.3, 59.2, 59.1, 58.3, 57.2, 56.2, 56.1, 35.0, 32.2, 25.8, 25.4, 8.9 and 8.7; HRMS (CI-CH_4): $C_{10}H_{23}O_4$ (M + H); Found: *m*/*z*, 207.1600. Calc.: *m*/*z*, 207.1596.

(2*R*,3*S*,5*R*)- and (2*R*,3*S*,5*S*)-1,3,5-Trimethoxy-5-phenylpentan-2-ol 6 and 7 (entry 13). The general procedure was applied to compound **1** and $ZnPh_2$. Column chromatography (E/H 1:10 ⟶ 1:1) of the crude product gave an inseparable mixture of products **5/6** as a syrup: ν(film)/cm^{-1} 3420 and 3100; δ_H 7.32 (each 5 H, 2 m), 4.39 and 4.33 (each 1 H, 2 dd), 3.88 and 3.82 and 7.32 (each 1 H, 2 m), 3.50 (6 H, m), 3.47, 3.40, 3.39, 3.33, 3.21 and 3.23 (each 3 H, 6 s), 2.63 (each 1 H, 2 s) and 2.18, 1.88, 1.84 and 1.75 (each 1 H, 4 m); δ_C 142.6, 142.0, 128.7 (2 C), 128.6 (2 C), 127.9, 127.7, 126.8 (2 C), 126.6 (2 C), 80.3, 80.0, 79.0, 78.7, 74.0, 73.6, 71.8, 71.3, 59.4, 59.3, 58.8, 57.4, 56.7, 56.6, 40.21 and 37.3; HRMS (CI-CH_4): $C_{14}H_{23}O_4$ (M + H); Found: *m*/*z*, 255.1595. Calc.: *m*/*z*, 255.1597.

(2*R*,4*S*,5*R*)- and (2*S*,4*S*,5*R*)-5-Hydroxy-2,4,6-trimethoxyhexanonitrile 8 and 9 (entry 14). The general procedure was applied to compound **1** and Me_3SiCN. Column chromatography (E/H 1:10 ⟶ 1:1) of the crude product gave an inseparable mixture of products **8/9** as a syrup: ν(film)/cm^{-1} 3460 and 2064; δ_H 4.32 and 4.28 (each 1 H, 2 dd), 3.86 and 3.85 (each 1 H, 2 m), 3.50 (6 H, m), 3.515, 3.505, 3.42, 3.41, 3.405 and 3.40 (each 3 H, 6 s), 2.50 and 2.40 (each 1 H, 2 d) and 2.17 and 2.05 (each 2 H, 2 m); δ_C 118.6, 118.3, 78.8, 77.0, 73.3, 73.2, 70.9, 70.8, 68.1, 67.2, 59.4 (2 C), 58.7, 58.3 (2 C), 58.1, 34.7 and 33.8; HRMS (CI-CH_4): $C_9H_{18}NO_4$ (M + H); Found: *m*/*z*, 204.1236. Calc.: *m*/*z*, 204.1236.

(2*R*,3*R*,4*S*,5*R*)- and (2*R*,3*R*,4*S*,5*S*)-1,3,4,5-Tetramethoxyhexan-2-ol 11 and 12 (entries 16 and 17). The general procedure was applied to compound **10** and the methyl-group donors shown in Table 1. Column chromatography (E/H 1:10 ⟶ 1:1) of the crude product gave compounds **11** and **12** as syrups (H/E 1:2).

Compound **11**: R_f 0.40; $[\alpha]_D^{20}$ +24 (*c* 2.57, $CHCl_3$); ν(film)/cm^{-1} 3430; δ_H 3.89 (1 H, m), 3.55 (3 H, m), 3.47, 3.42, 3.41 and 3.35 (each 3 H, 4 s), 3.35 (2 H, m), 3.27 (1 H, d, *J* 3.5) and 1.21 (3 H, d, *J* 6.3); δ_C 84.0, 80.7, 76.9, 74.0, 71.0, 59.8, 59.6, 59.3, 56.7 and 15.0; HRMS (CI-CH_4): $C_{10}H_{23}O_5$ (M + H); Found: *m*/*z*, 223.1544. Calc.: *m*/*z*, 223.1546.

Compound **12**: R_f 0.35: $[\alpha]_D^{20}$ +13 (*c* 0.58, $CHCl_3$); ν(film)/cm^{-1} 3430; δ_H 4.02 (1 H, m), 3.56 (3 H, m), 3.54, 3.44, 3.42 and 3.38 (each 3 H, 4 s), 3.41 (1 H, m), 3.27 (1 H, dd, *J* 5.7 and 5.8), 3.05 (1 H, d, *J* 3.0) and 1.26 (3 H, d, *J* 6.4); δ_C 84.8, 81.6, 76.9, 74.0, 71.1, 61.3, 59.3, 59.2, 56.9 and 15.7; HRMS (CI-CH_4): $C_{10}H_{23}O_5$ (M + H); Found: *m*/*z*, 223.1545.

(2*R*,3*S*,4*S*,5*R*)- and (2*R*,3*S*,4*S*,5*S*)-1,3,4,5-Tetramethoxyhexan-2-ol 14 and 15 (entries 18–21). The general procedure was applied to anomeric glycosides α-**13** and β-**13**, respectively, and the alkyl donors shown in Table 1. Column chromatography (E/H 1:10 ⟶ 1:1) of the crude product gave compound **15** or a mixture of diastereomers **14/15** as syrups.

Compound **15**: $[\alpha]_D^{20}$ −9 (*c* 2.30, $CHCl_3$); ν(film)/cm^{-1} 3450; δ_H 3.88 (1 H, m), 3.60–3.44 (4 H, m), 3.53, 3.51, 3.38 and 3.32 (each 3 H, 4 s), 3.30 (1 H, m), 2.79 (1 H, d, *J* 5.2) and 1.24 (3 H, d, *J* 6.3); δ_C 84.7, 81.1, 75.9, 74.1, 69.9, 61.0, 60.9, 59.2, 56.6 and 14.8; HRMS (CI-CH_4): $C_{10}H_{23}O_5$ (M + H); Found: *m*/*z*, 223.1544.

Mixture **14/15**: δ_H 3.88 (2 H, m), 3.90–3.44 (8 H, m), 3.54, 3.53, 3.52, 3.51, 3.39, 3.38, 3.32 and 3.30 (each 3 H, 8 s), 3.30 (2 H, m), 2.81 (1 H, d, *J* 4.7), 2.79 (1 H, d, *J* 5.2), 1.24 (3 H, d, *J* 6.3) and 1.23 (3 H, d, *J* 6.3); δ_C 84.7, 84.3, 81.2, 81.1, 77.5, 75.9, 74.1, 74.0, 70.5, 69.9, 61.2, 61.1, 60.9, 60.6, 59.3, 59.2, 56.6, 56.5, 14.9 and 14.8; HRMS (CI-CH_4): $C_{10}H_{23}O_5$ (M + H); Found: *m*/*z*, 223.1545.

Methyl 6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-D-glucopyranoside[59] 17

NaH (60%; 600 mg, 14.5 mmol) and MeI (2.1 g, 14.4 mmol) were added to a solution of methyl 6-chloro-6-deoxy-α-D-glucopyranoside[55] **16** (700 mg, 2.9 mmol) in THF (15 ml). The resulting mixture was stirred at room temp. for 48 h under argon, whereafter water (50 ml) was added. Work-up was as follows: extraction with CH_2Cl_2 (3 × 50 ml), washing of the collected organic extracts sequentially with water (3 × 20 ml), saturated aq. NH_4Cl and brine, followed by drying (Na_2SO_4), and removal of the solvent under reduced pressure. The residue was subjected to column chromatography (H/E 3:1) to give title compound **17** (660 mg, 89%) as a solid; mp 64 °C (lit.,[59] 62–64 °C); $[\alpha]_D^{20}$ +163 (*c* 2.28, $CHCl_3$) [lit.,[59] 162.2 (*c* 1, $CHCl_3$)]; δ_H 4.83 (1 H, d, *J* 3.6), 3.74 (3 H, m), 3.61, 3.57, 3.50 and 3.41 (each 3 H, 4 s), 3.5 (1 H, m) and 3.17 (2 H, m); δ_C 97.7, 83.5, 81.9, 80.3, 69.9, 61.1, 60.9, 59.2, 55.5 and 44.8; HRMS (FAB^+): $C_{10}H_{20}ClO_5$ (M + H); Found: *m*/*z*, 255.0999. Calc.: *m*/*z*, 255.0999. The discrepancies between our NMR data and those reported in the literature[59] are probably due to the different solvents used; $CDCl_3$ *versus* $CDCl_3$–benzene (6:1).

(2*S*,3*R*,4*R*,5*R*)-1,2,3,4,5-Pentamethoxyhexane 18

Compound **17** (500 mg, 2.0 mmol) was added to aq. H_2SO_4 (25 ml; 2 M). The resulting mixture was stirred at 100 °C for 60 h and was then cooled to ambient temperature whereupon the mixture was neutralized by addition of saturated aq. $NaHCO_3$ and worked up as follows: extraction with EtOAc (3 × 50 ml), washing of the collected organic extracts sequentially with water (20 ml) and brine, followed by drying (Na_2SO_4), and removal of the solvent under reduced pressure. The residue was dissolved in THF (15 ml) and then $LiAlH_4$ (300 mg, 8.0 mmol) was added. The resulting mixture was stirred at reflux for 24 h under argon and then was cooled to 0 °C. The excess of $LiAlH_4$ was decomposed by careful addition of water (20 ml) and the mixture was worked up as follows: extraction with EtOAc (4 × 50 ml), washing of the collected organic extracts sequentially with water (20 ml) and brine, followed by drying (Na_2SO_4), and removal of the solvent under reduced pressure. The residue was dissolved in THF (10 ml), whereafter NaH (60%; 320 mg, 8.0 mmol) and MeI (1.1 g, 8.0 mmol) were added. The resulting mixture was stirred at room temp. for 48 h under argon, whereafter water (30 ml) was added. Work-up was as follows: extraction with CH_2Cl_2 (3 × 40 ml), washing of the collected organic extracts sequentially with water (3 × 10 ml), saturated aq. NH_4Cl and brine, followed by drying (Na_2SO_4), and removal of the solvent under reduced pressure. The residue was subjected to column chromatography (H/E 2:1) to give title compound **18** (197 mg, 42%) as a syrup; $[\alpha]_D^{20}$ +6 (*c* 0.40, $CHCl_3$); δ_H 3.61 (2 H, m), 3.50–3.27 (7 H, m) and 3.50, 3.48, 3.46, 3.30 and 3.28 (each 3 H, 5 s); δ_C 82.8, 81.0, 80.6, 77.6, 72.4, 60.8, 60.5, 59.3, 58.9, 56.4 and 15.0; HRMS (CI-CH_4): $C_{11}H_{25}O_5$ (M + H); Found: *m*/*z*, 237.1719. Calc.: *m*/*z*, 237.1702.

Structure determination of compound 14

The 2:1 mixture of diastereomers **14/15** (20 mg, 0.1 mmol) was dissolved in THF (2 ml), and then NaH (60%; 10 mg, 0.2 mmol) and MeI (30 mg, 0.2 mmol) were added. The resulting mixture was stirred at room temp. for 48 h under argon, whereafter water (5 ml) was added. Work-up was as follows: extraction with CH_2Cl_2 (3 × 5 ml), washing of the collected organic extracts sequentially with water (3 × 5 ml), saturated aq. NH_4Cl and brine, followed by drying (Na_2SO_4), and removal of the solvent under reduced pressure, to give a syrup (20 mg). GLC-MS analysis showed a 2:1 mixture of the corresponding methyl ethers of isomers **14/15**. Gas chromatographic co-injection on the non-chiral phase DBwax column with compound **18** showed a perfect overlap of the first peak of the diastereomeric mixture with that of compound **18**, which verified that the methyl ether of stereoisomer **14** was the enantiomer of compound **18**.

Acknowledgements

We thank the Swedish Natural Science Research Council, the Knut and Alice Wallenberg Foundation, and the Crafoord Foundation for financial support. We also thank Dr Ulf Wellmar for a sample of compound **1**.

References

1 A. Alexakis and P. Mangeney, *Tetrahedron: Asymmetry*, 1990, **1**, 477.
2 I. Mori, K. Ishihara, L. A. Flippin, K. Nozaki, Y. Yamamoto, P. A. Bartlett and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 6107.
3 S. E. Denmark and N. G. Almstead, *J. Org. Chem.*, 1991, **56**, 6458.
4 S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, 1991, **113**, 8089.
5 T. Sammakia and R. S. Smith, *J. Am. Chem. Soc.*, 1994, **116**, 7915.
6 T. Sammakia and R. S. Smith, *J. Org. Chem.*, 1992, **57**, 2997.
7 T. Sammakia and R. S. Smith, *J. Am. Chem. Soc.*, 1992, **114**, 10 998.
8 K. Ishihara, N. Hanaki and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 10 695.
9 T.-M. Yuan, S.-M. Yeh, Y.-T. Hsieh and T.-Y. Luh, *J. Org. Chem.*, 1994, **59**, 8192.
10 M. Kinugasa, T. Harada, T. Egusa, K. Fujita and A. Oku, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 3639.
11 S. Hanessian, *Total Synthesis of Natural Products: the Chiron Approach*, Pergamon Press, Oxford, 1983.
12 A. Vasella, in *Modern Synthetic Methods 1980*, ed. R. Scheffold, Salle and Sauerländer, Frankfurt am Main, 1980, vol. 2, p. 173.
13 A. F. Bochkov and G. E. Zaikov, *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*, Pergamon Press, Oxford, 1979.
14 P. M. Collins and R. J. Ferrier, *Monosaccharides: Their Chemistry and Their Roles in Natural Products*, Wiley, Chichester, 1996.
15 D. E. Levy and C. Tang, *The Chemistry of C-Glycosides*, Elsevier Science, Oxford, 1st edn., 1995, vol. 13.
16 *Glycoscience. Synthesis of Oligosaccharides and Glycoconjugates*, ed. H. Driguez and J. Thiem, Springer-Verlag, Berlin, 1997, vol. 186.
17 *Glycoscience. Synthesis of Substrate Analogs and Mimetics*, ed. H. Driguez and J. Thiem, Springer-Verlag, Berlin, 1997, vol. 187.
18 F. Barresi and O. Hindsgaul, *Mod. Synth. Methods*, 1995, **7**, 283.
19 G. Magnusson, A. Y. Chernyak, J. Kihlberg and L. O. Kononov, in *Neoglycoconjugates: Preparation and Applications*, ed. Y. C. Lee and R. T. Lee, Academic Press, San Diego, 1994, p. 53.
20 B. Lindberg, *Acta Chem. Scand.*, 1949, **3**, 1153.
21 M. L. Sinnott, *Bioorg. Chem.*, 1993, **21**, 34.
22 J. L. Liras and E. V. Anslyn, *J. Am. Chem. Soc.*, 1994, **116**, 2645.
23 R. B. Gupta and R. W. Franck, *J. Am. Chem. Soc.*, 1987, **109**, 6554.
24 R. W. Franck, *Bioorg. Chem.*, 1992, **20**, 77.
25 K. Utimoto, Y. Wakabayashi, T. Horiie, M. Inoue, Y. Shishiyama, M. Obayashi and H. Nozaki, *Tetrahedron*, 1983, **39**, 967.
26 J. F. Normant, A. Alexakis and P. Mangeney, *Tetrahedron*, 1989, **45**, 507.
27 A. Ghribi, A. Alexakis and J. F. Normant, *Tetrahedron Lett.*, 1984, **25**, 3075.
28 H. E. Morton and Y. Guindon, *J. Org. Chem.*, 1985, **50**, 5379.
29 Y. Guindon and P. C. Anderson, *Tetrahedron Lett.*, 1987, **28**, 2485.
30 Y. Guindon, M. A. Bernstein and P. C. Anderson, *Tetrahedron Lett.*, 1987, **28**, 2225.
31 Y. Guindon, P. C. Anderson, C. Yoakim, Y. Girard, S. Berthiaume and H. E. Morton, *Pure Appl. Chem.*, 1988, **60**, 1705.
32 M. Kawana, H. Kuzuhara and S. Emoto, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1492.
33 H. Hashimoto and M. Hayakawa, *Chem. Lett.*, 1989, 1881.
34 O. R. Martin, S. P. Rao, T.-F. Yang and F. Fotia, *Synlett*, 1991, 702.
35 T. Inghardt and T. Frejd, *J. Org. Chem.*, 1989, **54**, 5539.

36 R. Olsson, U. Berg and T. Frejd, *Tetrahedron*, submitted.
37 T. Inghardt, T. Frejd and G. Svensson, *Tetrahedron*, 1991, **47**, 6469.
38 M. T. Reetz, B. Raguse and T. Seitz, *Tetrahedron*, 1993, **49**, 8561.
39 V. Jonas, G. Frenking and M. T. Reetz, *Organometallics*, 1995, **14**, 5316.
40 P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117.
41 P. Knochel, *Chemtracts*, 1995, **8**, 205.
42 K. Mauruoka and H. Yamamoto, *Tetrahedron*, 1988, **44**, 5001.
43 H. Yamamoto, in *Organometallics in Synthesis*, ed. M. Schlosser, Wiley, Chichester, 1994, vol. 7, p. 509.
44 B. Weidmann and D. Seebach, *Angew. Chem.*, *Int. Ed. Engl.*, 1983, **22**, 31.
45 M. T. Reetz, in *Organometallics in Synthesis: A Manual*, ed. M. Schlosser, Wiley, Chichester, 1994, vol. 3, p. 195.
46 M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek and S. Maus, *Chem. Ber.*, 1985, **118**, 1421.
47 M. T. Reetz, *Top. Curr. Chem.*, 1982, **106**, 1.
48 M. Bols, *Carbohydrate Building Blocks*, Wiley, New York, 1996.
49 SPARTAN version 4.0 Wavefunction, Inc., 18401 Von Karman Ave., suite 370 Irvine, CA 92715, USA.
50 P. Cossee, *Trans. Faraday Soc.*, 1962, **58**, 1226.
51 U. Berg, R. Olsson and T. Frejd, presented at the *5th European Symposium on Organic Reactivity*, Santiago de Compostela, Spain, 1995, Abstract C1B.
52 R. Olsson, U. Berg and T. Frejd, *Tetrahedron Lett.*, 1997, **38**, 5701.
53 E. J. Corey and J. J. Rohde, *Tetrahedron Lett.*, 1997, **38**, 37.
54 E. J. Corey, J. J. Rohde, A. Fischer and M. D. Azimioara, *Tetrahedron Lett.*, 1997, **38**, 33.
55 R. L. Whistler and A. K. M. Anisuzzaman, *Methods Carbohydr. Chem.*, 1980, **8**, 227.
56 G. R. Barker, *J. Chem. Soc.*, 1948, 2035.
57 E. E. Percival and R. Zobrist, *J. Chem. Soc.*, 1952, 4306.
58 K. Krohn and G. Börner, *J. Org. Chem.*, 1991, **56**, 6038.
59 A. Klemer and G. Mersman, *Carbohydr. Res.*, 1972, **22**, 425.

Paper 7/06166H
Received 22*nd August* 1997
Accepted 22*nd October* 1997