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Carbohydrate Research 307 (1998) 13–18

CARBOHYDRATE RESEARCH

Organotitanium-induced stereoselective alkylative *endo*-cleavage of benzyl pentopyranosides

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Received 4 August 1997; accepted 3 November 1997

Abstract

The results presented are the first examples where organotitanium reagents induced alkylative *endo*-cleavage of carbohydrates. The best conditions for the alkylative transfer of a methyl group to benzyl 2-deoxy-2-*C*-methyl-4-*O*-(*tert*-butyldimethylsilyl)-α-D-arabinopyranoside (**1**) were the application of one equivalent of $AlMe_3$ followed by four equivalents of $MeTiCl_3$ generated by mixing $TiCl_4$ and $ZnMe_2$ in a ratio 2:1, or, alternatively, treatment of **1** with two equivalents of 1:1 Me_2TiCl_2–$ZnMe_2$. Both the yields and diastereoselectivities were comparable with those of the reaction with $AlMe_3$ but the titanium reagents were more reactive and could be applied at much lower temperatures than the aluminium reagent. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: *Endo*-cleavage; Pentopyranosides; Alkylation; Organotitanium reagents

1. Introduction

Due to the usefulness of acetals in organic chemistry their reactions have attracted considerable attention. One example of this is the substitution at the acetal carbon promoted by Lewis acids in combination with nucleophilic reagents or directly by Lewis acids carrying nucleophilic ligands [1–3]. Mixed acetals of the carbohydrate type may be cleaved either at the *exo* or the *endo* C–O bond (Scheme 1), and hitherto, the main interest has been focused on the cleavage of the *exo*-cyclic C–O bond, as this relates to glycoside synthesis.

Previously we reported, employing organoaluminium reagents, a regio- and stereoselective *C*-alkylative substitution of the *endo* C–O bond in benzyl pentopyranosides to generate chain extended acyclic derivatives [4,5]. To our knowledge, no other examples of the *C*-alkylative regio- and stereoselective substitution reaction of the *endo* C–O bond in pentopyranosides have been reported. A few other non-stereoselective *C*-alkylative *endo* C–O bond substitution reactions of pyranosides [6–11] and some stereoselective chelation controlled *C*-alkylative *endo* C–O bond substitutions on pentofuranosides have been reported [12–14].

In our earlier work with organoaluminium reagents, benzyl 2-deoxy-2-*C*-methyl-4-*O*-(*tert*-butyldimethylsilyl)-α-D-arabinopyranoside (**1**) and

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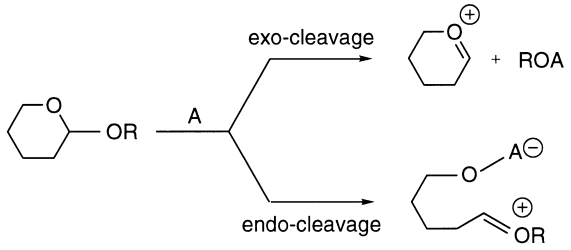
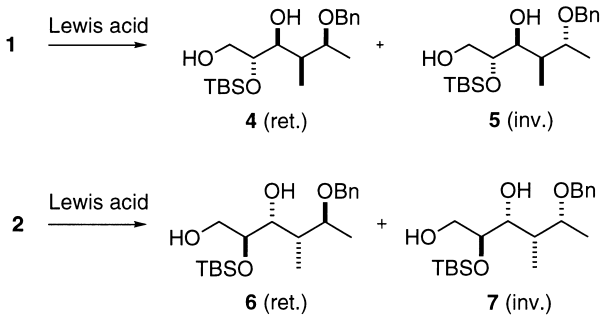
PII S0008-6215(97)10079-9

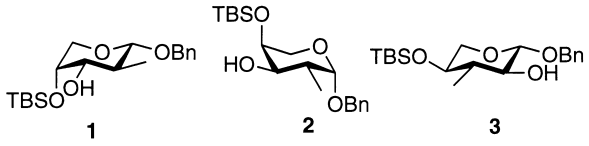


Scheme 1.



Scheme 2.

benzyl 2-deoxy-2-*C*-methyl-4-*O*-(*tert*-butyldimethylsilyl)-β-L-arabinopyranoside (**2**) together with some other pentopyranosides were used as substrates [4]. Thus, in the reaction of **1** with $AlMe_3$ a methyl group was transferred mainly by retention, while the reaction with **2** gave inversion of the stereocenter at C-1 (Scheme 2). The yields were low to moderate but the diastereoselectivities were relatively high, 10:1 (Table 1, entries 1 and 14). Since improvement of both yields and stereoselectivities were desirable we became interested in trying organotitanium reagents. Such reagents have earlier been used for the nucleophilic addition to carbonyl groups by Reetz and co-workers [15–17] and were also shown to cleave acetals based on 1,3-diols with a higher stereoselectivity than the corresponding organoaluminium reagents [18]. An important advantage of titanium reagents over the aluminium reagents is the higher flexibility in modifying the Lewis acidity of the reagent. Here, we report on the application of organotitanium reagents in attempts to C-1-alkylative *endo*-cleavage of benzyl pyranosides **1–3**. Benzyl 3-deoxy-3-*C*-methyl-4-*O*-(*tert*-butyldimethylsilyl)-β-L-xylopyranoside (**3**) was included since only one other ring-opening attempt has been reported of a pyranoside having a free HO-2 group [4].



2. Results and discussion

The methyl-carrying reagents $MeTiCl_3$ and Me_2TiCl_2 were easily accessible via Zn–Ti exchange by mixing $TiCl_4$ and $ZnMe_2$ in stoichiometric amounts [17]. Reaction of **1** using only $MeTiCl_3$ or Me_2TiCl_2 gave complex product mixtures (Table 1, entries 2 and 5). Neither of the expected compounds **4** or **5** could be isolated. As indicated by the formation of gas bubbles, the free hydroxy group at C-3 of **1** formed an alcoholate in contact with $AlMe_3$. In analogy, the titanium reagents probably gave the corresponding titanium alcoholates. The failure of the titanium reagents when used alone, may have been due to their greater Lewis acid strengths in comparison with $AlMe_3$ but also, or in combination with, the greater steric requirements of the titanium alcoholates.

Better results were obtained by first treating the substrate with one equivalent of $AlMe_3$ to form the corresponding aluminium alcoholate and then adding $MeTiCl_3$ or Me_2TiCl_2 (entries 3 and 6). The $AlMe_3$–$MeTiCl_3$ combination gave essentially the same result as when only $AlMe_3$ was used showing that the methyl group of the titanium reagent indeed could be transferred. The low temperature of the reaction excludes the possibility that $AlMe_3$ could be involved since this reagent is too unreactive.

Coordination of Lewis acids with ethers reduces their reactivity and may increase their selectivity. It was recently reported that the $MeTiCl_3(THF)_2$ complex attacked α-phenylthioaldehydes in a highly diastereoselective manner [19]. However, in our case the coordination of $MeTiCl_3$ with THF to give the octahedral bis-etherate, indicated by its red colour [20], lowered the reactivity too much. When applied to **1** only a 10% yield of **4/5** was obtained (entry 4). Replacing the chlorine ligands on titanium by isopropoxy groups in order to lower the Lewis acidity also gave low yields (entries 11—13).

TLC analysis on the reaction mixtures of **1** and Me_2TiCl_2 indicated an initial fast anomerization of **1** possibly caused by minor amounts of unreacted $TiCl_4$. Therefore, an additional equivalent of $ZnMe_2$ was added when forming the reagent in order to consume all "free" $TiC1_4$. It should be noted that $TiMe_4$ is not formed in a 1:1 mixture of

Table 1
Regioselective alkylative cleavage of **1** and **2** using $MeTiCl_xL_{3-x}$ and $Me_2TiCl_xL_{2-x}$[a]

Entry[b]	Substrate	Lewis acid (equiv)	Time (h)/Temp (°C)[c]	Products (ratio)[d]	Isolated yield (%)
1	**1**	$AlMe_3$ (3)	1/reflux	**4:5** (10:1)[e]	69
2	**1**	$MeTiCl_3$ (3)	6/−40	mixture	
3	**1**	$AlMe_3$ (1)/$MeTiCl_3$ (4)	6/−40	**4:5** (9:1)[e]	64
4	**1**	$AlMe_3$ (1)/$MeTiCl_3[THF]_2$ (2)	30/20	**4:5** (4:1)	10
5	**1**	Me_2TiCl_2 (3)	6/−30	mixture	
6	**1**	$AlMe_3$ (1)/Me_2TiCl_2 (4)	2.5/−30	**4:5** (4:1)	29
7	**1**	$AlMe_3$ (1)/Me_2TiCl_2 (2):$ZnMe_2$ (2)	2.5/−30	**4:5** (2:1)	27
8	**1**	$AlMe_3$ (1)/Me_2TiCl_2 (2):$ZnMe_2$ (2)[f]	19/−30	**4:5** (4:1)	36
9	**1**	Me_2TiCl_2 (2):$ZnMe_2$ (2)	5/−30	**4:5** (9:1)[e]	65
10	**1**	$ZnMe_2$ (1)/Me_2TiCl_2 (2)	7/−30	**4:5** (4:1)	49
11	**1**	$AlMe_3$ (1)$TiCl_2$(OiPr) (2)[g]	4/0	**4:5** (4:1)	19
12	**1**	$AlMe_3$ (1)/$MeTiCl(OiPr)_2$ (2)[g]	12/reflux	**4:5** (4:1)	5
13	**1**	$AlMe_3$ (l)/$Me_2Ti(OiPr)_2$ (2)[g]	48/20	**4:5** (4:1)	11
14	**2**	$AlMe_3$ (3)	22/reflux	**6:7** (1:10)[e]	46
15	**2**	$AlMe_3$ (1)/$MeTiCl_3$ (4)	64/−40	**6:7** (1:9)[e]	4
16	**2**	Me_2TiCl_2 (3):$ZnMe_2$ (3)	64/−30	n.r.[h]	—

[a] All reactions were carried out in hexane except for entries 11–13 where CH_2Cl_2 was used. [b]Entry 1 and 14, see ref. [4]. [c]All reactions were started at −72 °C whereafter the temperature was slowly raised to the indicated value and kept there by the aid of a cryostate (±3 °C). [d]Determined by ^1H NMR spectroscopy. [e]Determined by GLC analysis of the acetylated product. [f]Filtration of the organotitanium reagents was performed before use. [g]Structure not elucidated. The reagents were made from $TiCl_4$ and $Ti(OiPr)_4$ as described by Reetz [17] followed by a stoichiometric amount of $ZnMe_2$ as described for generating Me_xTiCl_{4-x} used in entries 2–10. [h]Higher temperature resulted in decomposition.

Me_2TiCl_2 and $ZnMe_2$; only a rapid methyl group exchange takes place [21]. Thus, our reagent was essentially a 1:1 mixture of Me_2TiCl_2 and $ZnMe_2$. This reagent was then added to a preformed mixture of **1** and $AlMe_3$, resulting in a slight increase in yield compared to the previous Me_2TiCl_2 experiment, but the diastereoselectivity was considerably lower (entry 7). Low selectivities in additions to aldehydes have been reported to be due to interference of coexisting salts ($ZnCl_2$, LiCl, MgXCl) [22,23], and also in our case the selectivity was improved, as was the yield, by removal of $ZnCl_2$ by simple filtration (entry 8).

Surprisingly, treatment of **1** with an excess of the reagent mixture consisting of Me_2TiCl_2 and $ZnMe_2$ without the involvement of an aluminium alcoholate, gave one of the best results employing organotitanium reagents (entry 9). Here, it is possible that the $ZnMe_2$ generates a zinc alcoholate, which was in fact indicated by gas evolution on addition of $ZnMe_2$ to **1**. One would therefore expect that preforming the zinc alcoholate by mixing **1** and $ZnMe_2$ and then adding Me_2TiCl_2 a result similar to that of entry 9 would be obtained. As seen in entry 10 this was only almost the case, both the selectivity (4:1) and the yield (49%) were somewhat lower than in entry 9. The alternative explanation of a titanium alcoholate being responsible for the higher yield and selectivity obtained in entry 9 is less likely, since the reaction with only Me_2TiCl_2 (entry 5) gave a rapid conversion of the starting material to an intractable mixture of products. In addition, the results shown in entry 6, where almost certainly an aluminium alcoholate was formed, also gave a 4:1 selectivity albeit in only 29% yield.

The best conditions found for the methyl transfer to **1** as shown in entries 3 and 9 were also applied to **2** (entries 15 and 16). The inverted selectivity seen with **2** compared to that of **1** indicated that methyltitaniumtrichloride reacted in the same way as was earlier observed for $AlMe_3$ [4]. The poor yield reached with the titanium reagents may be explained in terms of the conformational $^4C_1$ preference of substrate **2** placing the glycosidic bond in an axial position [4]. The mechanism of the Lewis acid mediated *exo*- versus *endo*-cleavage of glycosides has been discussed by Guindon et al. [9] and Fraser-Reid et al. [24]. Our results seems to be in best agreement with those of Fraser-Reid et al., i.e., there may be a competition between *endo*- and *exo*-cleavage when the anomeric bond is equatorial but only *exo*-cleavage when axial. Thus, if the Lewis acid is not reactive enough no reaction will occur in the axial case. In addition, PM3 calculations made by us suggested that *endo*-cleavage is greatly favoured when the anomeric benzyloxy group adopts an equatorial position [25]. In the favoured $^4C_1$ conformation of **2** [4], the axial orientation of the anomeric benzyloxy group most

likely prevented *endo*-cleavage by the weak Lewis acid $AlMe_3$, but the low equilibrium concentration of the $^1C_4$ conformer still allowed a slow alkylative *endo*-opening (entry 14).

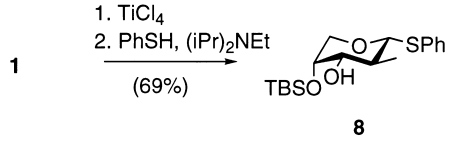
Application of the two best reagents for *endo*-opening of **1** to **2** were very disappointing. A very low yield of the mixture of **6:7** was isolated in the $AlMe_3$-$MeTiCl_3$ case (entry 15). Increase of the reaction temperature resulted in large amounts of byproducts. In the experiments with Me_2TiCl_2–$ZnMe_2$ essentially no reaction was observed at low temperature (−30 °C) while decomposition took place at higher temperatures. The result in entry 14 seems to be in contrast to those in entries 15 and 16; why was no or so very little *endo*-cleavage product formed in the latter cases? We can only speculate about this but we feel that the equilibrium between the $^4C_1$ and the $^1C_4$ conformations of **2** plays an important role. It is possible that this equilibrium is disturbed in the presence of the titanium reagents via complexation so that the $^4C_1$ conformation dominates to the extent that only a very small fraction of the *endo*-cleavage producing $^1C_4$ conformation exists.

According to its NMR spectrum compound **3**, carrying a hydroxy group at C-2, should have the conformation shown, i.e., all groups should be equatorially positioned. In consequence with the discussion about the conformations above, this would favour *endo*-opening. However, treating substrate **3** with $AlMe_3$–$MeTiCl_3$ or Me_2TiCl_2–$ZnMe_2$ did not result in any reaction except for the formation of the corresponding alcoholates. An explanation for this may be that these alcoholates are thermodynamically too stable, perhaps by extra coordination with the anomeric oxygen.

We also examined the possibilities to transfer groups other than methyl. Based on the same method as for the preparation of $MeTiCl_3$ and Me_2TiCl_2, the corresponding reagents $EtTiCl_3$ and Et_2TiCl_2 were assumed to be formed from $ZnEt_2$ and $TiCl_4$. However, only anomerization of **1** was observed in contact with these and the following reagents: $Me_3SiC{\equiv}CTiCl_3$, Et_2AlCl–$TiCl_4$ [21], propylenetri-*n*-butylstannane–$TiCl_4$ [26], and $(Me_3SiC{\equiv}C)_2Ti(OiPr)_2$ [27]. Since steric crowding has been reported to favour anomerisation at the expense of *endo*-alkylative cleavage of furanosides [12], the greater steric bulk of the titanium reagents as compared with the aluminium reagents, may have prevented the transfer of the organic groups also in the cases mentioned here.

In the reactions of **1** with $TiCl_4$ or complexes generated from this reagent, TLC analyses frequently indicated the occurrence of another compound in addition to the anomerized product. This compound could not be detected after the usual ammonolytic work-up. We initially suspected that an *endo*-cleavage had occurred followed by chloride transfer to give the open chain α-chloro ether, which could freely rotate around the C-1/C-2 bond and then recyclize to give the glycoside during work-up. A similar open-chain bromo intermediate was observed and trapped using an excess of a mixture of thiophenol-diisopropylethylamine by Guindon et al. in their work with *endo*-cleavage of D-glucopyranosides using Me_2BBr [28]. In our case, however, the trapping experiment gave the α-thioglycoside **8** in 69% yield (Scheme 3) [29], which excluded an *endo*-cleavage-anomerization route via an acyclic chloro intermediate. Thus, it is more likely that a rapid anomerization via an ion-pair occurs together with generation of a small amount of the corresponding 1-chloro sugar. In the absence of an external nucleophile the only isolated product is the β-anomer of **1**, while the 1-chloro sugar was lost in the ammonolytic work-up procedure.

In conclusion, the results presented here are the first examples where organotitanium reagents induced alkylative *endo*-cleavage of carbohydrates. The best conditions for the alkylative transfer of a methyl group to **1** were the application of one equivalent of $AlMe_3$ followed by four equivalents of $MeTiCl_3$ generated by mixing $TiCl_4$ and $ZnMe_2$ in a ratio 2:1, or, alternatively, treatment of **1** with two equivalents of 1:1 Me_2TiCl_2–$ZnMe_2$ (entries 3 and 9). Both the yields and diastereoselectivities were comparable with those of the reaction with $AlMe_3$ but the titanium reagents were more reactive and could be applied at much lower temperatures than the aluminium reagent. No group other than methyl has hitherto been possible to transfer with the organotitanium reagents, in contrast to the aluminium reagents, which also made possible the transfer of acetylenic residues [4]. In contrast to **1**, methyltransfer to **2** using the titanium reagents was unsuccessful, possibly due to an



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Scheme 3.

unfavourable $^4C_1$–$^1C_4$ equilibrium. Finally, it remains to be seen if the combination of $TiCl_4$ and thiophenol-diisopropylethylamine can be developed into an efficient method for the synthesis of thioglycosides.

3. Experimental

General.—Column chromatography separations were performed by using Merck SiO_2 60A (0.035–0.070 mm) silica gel with EtOAc–heptane (E–H) mixtures as eluents. TLC analyses were made on Merck SiO_2 60 F254 precoated glass plates and the spots were visualised by charring with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2.4H_2O$ (10 g), and conc. H_2SO_4 (60 mL) in H_2O (940 mL). NMR spectra were recorded in $CDCl_3$ at 21 °C [^{1}H, 400 MHz; $CHCl_3$ δ 7.27 and ^{13}C, 100 MHz; $CHCl_3$ δ 77.2]. 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). All reactions were carried out in oven-dried glassware equipped with rubber septa and under Ar. The organometallic reagents were transferred by dried, Ar-flushed syringes and cannulas. Hexane, heptane and THF were distilled from sodium. CH_2Cl_2 was distilled from CaH_2 and stored over molecular sieves. EtOAc was distilled immediately before use. $TiCl_4$ and $Ti(OiPr)_4$ were purchased from Aldrich and Janssen, respectively, distilled and diluted with dry CH_2Cl_2 to give a 2.0 M stock solution before use. $ZnMe_2$ (2.0 M in toluene; Merck), $ZnEt_2$ (1.0 M in hexane; Merck), $AlMe_3$ (2.0 M in hexane; Aldrich), $ClAlEt_2$ (1.0 M in hexane; Aldrich), were all used as delivered. The substrates **1**,**2** and **3** were prepared from commercially available L-(−)- and D-(+)-arabinose as described [30].

General procedure for generation of the organotitanium reagents [17]. *$MeTiCl_3$.*—$ZnMe_2$ (0.313 mmol, 0.156 mL, 2.0 M in toluene) was added dropwise along the side of the flask to a stirred solution of $TiCl_4$ (0.625 mmol, 0.312 mL, 2.0 M in CH_2Cl_2) in hexane (3.0 mL) under Ar at −72 °C. The resulting mixture was kept at −72 °C for 10 min, followed by 30 min at −30 °C. This resulted in a 0.2 M solution of $MeTiCl_3$ (0.625 mmol in 1:20 CH_2Cl_2–hexane). It was finally cooled to −72 °C before the addition of the benzyl glycosides.

The other titanium containing reagents were prepared by the same procedure from 1 equiv of $TiCl_4$ and the reagents in parentheses: Me_2TiCl_2 ($ZnMe_2$); $EtTiCl_3$ (0.5 $ZnEt_2$); Et_2TiCl_2 ($ZnEt_2$); $Me_3SiC{\equiv}CTiCl_3$ ($Me_3SiC{\equiv}CLi$).

General procedure for the pyranose ring opening reactions.—$AlMe_3$ or $ZnMe_2$ (1.0 equiv) was added to the carbohydrate substrate (0.1 M in hexane or CH_2Cl_2) at room temperature. After 30 min, the solution was cooled to −72 °C and then added by cannulation to the solution containing the organotitanium reagents prepared as a 0.2 M solution in hexane or CH_2Cl_2 as described. In the cases of filtration to remove the salt ($ZnCl_2$), the filter paper was snuggled around the flat end of the cannula, and the Lewis acid solution was instead transferred to the substrate. The temperature was then raised to the indicated value (Table 1). The progress of the reaction was monitored by TLC analysis using 1:3 E–H as eluent. After the indicated time, the reaction mixture was quenched by dilution with EtOAc followed by slow addition to an aq solution of NH_4Cl (2 M). After vigorous stirring over night, the aq phase was extracted with EtOAc (3×30 mL) and the combined organic phases were sequentially washed with water (100 mL) and brine (2×100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to column chromatography (1:10 E–H) to give the products as clear oils. Spectral data for **4**, **5**, **6** and **7** were as reported in the literature [4].

*Thiophenyl 2-deoxy-2-*C*-methyl-4-*O*-(*tert*-butyldimethylsilyl)-α-*D*-arabinopyranoside* (**8**).—$TiCl_4$ (0.256 mL, 2.0 M in CH_2Cl_2) was added to a cooled (−72 °C) solution of **1** (0.256 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred for 1 h. $EtN(iPr)_2$ (2.19 mL, 12.8 mmol) followed by PhSH (1.57 mL, 15.3 mmol) were then added and after stirring the resulting mixture at −72 °C for 1 h, the temperature was raised to −30 °C. The progress of reaction was monitored by TLC (1:3 E–H) and when the starting material was consumed (after ca. 3.5 h) the mixture was quenched and worked-up as above. Column chromatography (1:10→1:3 E–H) afforded 81 mg (69%) of **8**; $[\alpha]^{20}_D$ + 68.7° (*c* 0.31, $CHCl_3$); NMR ($CDCl_3$): ^{1}H, δ 7.27 (m, 5 H, C_6H_5), 4.65 (d, 1 H, $J_{1,2}$ 6.9 Hz, H-1), 4.14 (dd, 1 H, $J_{4,5}$ 5.5, $J_{5,5'}$ 12.1 Hz, H-5), 3.90 (dt, 1 H, $J_{3,4}$ 3.1, $J_{4,5}$ 3.1, $J_{4,5'}$ 5.6 Hz, H-4), 3.53 (dd, 1 H, H-5′), 3.45 (m, 1 H, $J_{2,3}$ 7.1, $J_{OH,3}$ 7.1 Hz, H-3), 2.26 (d, 1 H, OH), 2.14 (m, 1 H, $J_{2,Me}$ 6.9 Hz, H-2), 1.16 (d, 3 H, Me), 0.92 (s, 9 H, Me_3CSi), 0.13 (2 s, each 3 H, Me_2Si); ^{13}C, δ 134.9, 131.4, 128.7, and 126.9 (*Ph*C), 88.5 (C-1), 73.4 (C-3), 67.5 (C-4),

66.1 (C-5), 38.9 (C-2), 25.7 (Me_3CSi), 18.0 (Me_3CSi), 15.6 (Me), −4.5 and −4.9 (Me_2Si); MS (CI-NH_3): 372 ($M^+ + 18$), 335 ($M^+ + 1$). HRMS (CI-NH_3): Calcd for $C_{18}H_{34}O_3NSiS$ 372.2029 ($M^+ + 18$). Found 372.2034.

Acknowledgements

The authors thank the Swedish Natural Science Research Council, The Knut and Alice Wallenberg Foundation and The Crafoord Foundation for financial support.

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