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A NEW CATALYST FOR REDUCTIVE CLEAVAGE OF METHYLATED GLYCANS*

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ABSTRACT

Several per-*O*-methylated D-glucans and D-fructans were used as models in an attempt to identify new catalysts for carrying out reductive cleavage. Included in these model studies were several D-glucans that contained 4-linked D-glucopyranosyl residues as well as one having a 4-linked D-glucitol residue, as both types of residue had previously been found to give rise to substantial proportions of artifactual products. These studies led to the development of a new catalyst for carrying out reductive cleavage, namely, a mixture of 5 equivalents of trimethylsilyl methanesulfonate (Me_3SiOSO_2Me) and 1 equivalent of boron trifluoride etherate ($BF_3 \cdot Et_2O$) per equivalent of acetal. This new catalyst was found to accomplish the reductive cleavage of per-*O*-methylated, 4-linked D-glucopyranosyl residues and 4-linked D-glucitol residues, to give only the expected derivatives of 1,5-anhydro-D-glucitol and D-glucitol, respectively. The mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ also catalyzed reductive cleavage of the D-fructofuranosyl residues of per-*O*-methylated sucrose and inulin, to give only the expected derivatives of 2,5-anhydro-D-mannitol and 2,5-anhydro-D-glucitol. Indeed, when used alone, Me_3SiOSO_2Me also rapidly catalyzed the reductive cleavage of D-fructofuranosyl residues, but, under the same conditions, D-glucopyranosyl residues were unaffected. The results of these and other model studies demonstrated that catalysis of reductive cleavage by the mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ occurs in a synergistic manner. Examination of the mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ by ^1H-n.m.r. spectroscopy demonstrated that a reaction occurs to generate trimethylsilyl fluoride and species of the type F_2BOSO_2Me, $FB(OSO_2Me)_2$, or $B(OSO_2Me)_3$ *via* ligand exchange.

INTRODUCTION

Previous reports from this laboratory have described, for determination of

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polysaccharide structure, a new technique that we refer to as the Reductive-Cleavage Method[1], and the suitability of this technique for the analysis of linkage positions and ring forms in polysaccharides containing D-mannopyranosyl[2], D-fructofuranosyl[3], D-glucopyranosyl[4,5], and 2-acetamido-2-deoxy-D-glucopyranosyl[6] residues. Although the expected products were formed in these reactions, two cases were encountered where troublesome amounts of artifactual products were formed. For example, when subjected to sequential methylation and reductive cleavage, a 4-linked D-glucopyranosyl residue, was found to give a small proportion of 1,4-anhydro-2,3,6-tri-*O*-methyl-D-glucitol[4,5,7], suggestive of the presence of a 5-linked D-glucofuranosyl residue, and a 4-linked D-glucitol residue under identical conditions gave a substantial proportion of an unidentified anhydrotetra-*O*-methyl-glucitol[6], suggestive of the presence of a nonreducing (terminal) D-glucosyl group, as well as several other unidentified products. The occurrence of the unexpected products in these reactions prompted us to search for reaction conditions wherein unambiguous results would be obtained. We now describe the results obtained from a study, employing several model glycosides and glycans, that led to the identification of a new catalyst (for carrying out reductive cleavage) that did not give rise to the aforementioned artifactual products.

RESULTS

Chosen for study were several model glycans that were representative of the structural and compositional features previously encountered during the course of development of the reductive-cleavage technique. For comparison purposes, reductive cleavages of the fully methylated glycans were performed with triethylsilane as the reducing agent and either trimethylsilyl trifluoromethanesulfonate or boron trifluoride etherate as the catalyst, as previously reported[1-7]. All mixtures of reaction products were analyzed by gas–liquid chromatography (g.l.c.), g.l.c.–mass spectrometry (g.l.c.–m.s.) in both the chemical ionization (c.i.) and electron ionization (e.i.) modes, and, where appropriate, 300-MHz ^{1}H-n.m.r. spectroscopy. Products were identified on the basis of their co-migration with authentic standards, or comparison of experimental and reported e.i. mass spectra.

*Methyl 2,3,4,6-tetra-*O*-methyl-α-*D*-glucopyranoside* (**1**). — Compound **1** was chosen for study in an attempt to identify potential new catalysts for reductive cleavage of the glycoside. For comparison purposes, all reactions were carried out with 5 equivalents each of reducing agent (Et_3SiH) and catalyst in dichloromethane for 24 h at room temperature. Confirming earlier reports[1,8], both boron trifluoride etherate ($BF_3 \cdot Et_2O$) and trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$) catalyzed the reduction of **1**, to give the 1,5-anhydroalditol **2** in quantitative yield (see Table I). Methanesulfonic acid also gave **2** in quantitative yield, but its trimethylsilylester (Me_3SiOSO_2Me) gave only a trace of product under comparable conditions. In the latter case, however, warming the reaction to ~35° resulted in quantitative reduction. Fluorosulfuric acid–antimony(V) fluoride also

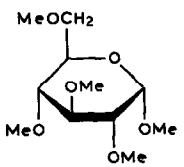
TABLE I

EFFECT OF CATALYST ON THE REDUCTIVE CLEAVAGE[a] OF METHYL 2,3,4,6-TETRA-*O*-METHYL-α-D-GLUCOPYRANOSIDE (**1**)

Catalyst	*Product* **2** *(%)*
$Me_3SiOSO_2CF_3$	100
$BF_3 \cdot Et_2O$	100
$MeSO_3H$	100
Me_3SiOSO_2Me[b]	<1
FSO_3H–SbF_5	58
Me_3SiOSO_2Me (5 equiv.) + FSO_3H–SbF_5 (1 equiv.)	78
Me_3SiOSO_2Me (5 equiv.) + $BF_3 \cdot Et_2O$ (1 equiv.)	100

[a]See Experimental section for reaction conditions. [b]Warming the reaction mixture (~35°) gave **2** in quantitative yield.

catalyzed the reduction of **1** to give **2**, but considerable starting-material (42%) remained after 24 h. A mixture of Me_3SiOSO_2Me (5 equiv.) and FSO_3H–SbF_5 (1 equiv.) was somewhat more effective, but the reaction was still incomplete after 24 h. Interestingly, a mixture of Me_3SiOSO_2Me (5 equiv.) and $BF_3 \cdot Et_2O$ (1 equiv.) gave the expected anhydroalditol (**2**) in quantitative yield.



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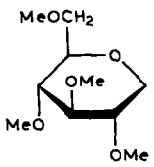

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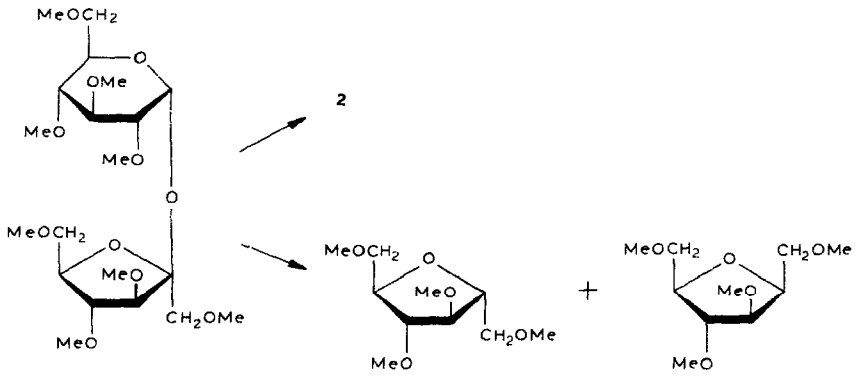
Several other potential catalysts, namely, *p*-toluenesulfonic acid, phosphoric acid, trifluoroacetic acid, magnesium bromide, aluminum iodide, and acetyl iodide, failed to give the expected anhydroalditol. Similarly, a mixture of aluminum chloride (2 equiv.) and lithium aluminum hydride (0.5 equiv.), which has proved effective for the reduction of other acetals[9,10], was ineffective in the reduction of compound **1**.

Sucrose. — Sucrose was chosen as a model for the further evaluation of promising catalysts, because of its content of both a furanosyl and a pyranosyl moiety. Shown in Scheme 1 are the structures of per-*O*-methylated sucrose and the expected reductive-cleavage products.

Reductive cleavage of the per-*O*-methylated disaccharide, with either



Scheme 1 3 4

$Me_3SiOSO_2CF_3$ or $BF_3 \cdot Et_2O$ as the catalyst, indeed gave the expected products (see Table II), in agreement with previous findings[3]. Methanesulfonic acid was also effective in catalyzing complete reductive cleavage, although the proportion of **2** formed was lower than expected, due to evaporative loss during workup.

Very interesting results were obtained when Me_3SiOSO_2Me was used to catalyze reductive cleavage (see Table II). Compounds **3** and **4**, arising from the D-fructofuranosyl moiety, were formed, as expected, but only a very small proportion of **2** was observed. Careful analysis of the reaction products by g.l.c.–m.s. and 300-MHz, ^{1}H-n.m.r. spectroscopy revealed the presence of methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (**1**) in the molar ratio of 0.38:1.00 and of methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside (**5**) in the molar ratio of 0.37:1.00. Decomposition of the 2,5-anhydroalditol products (**3** and **4**) was suspected as the source of the methanol for formation of these methyl glucosides, because the reaction mixture began to turn dark after reaction for ~15 min. This suspicion was confirmed by conducting the reductive cleavage of per-*O*-methylated sucrose in the presence of docosane as an internal standard; integration of the combined areas of (**3** + **4**) relative to docosane gave values of 2.74, 1.75, and 1.11 for reactions terminated after 2, 8, and 24 h, respectively, whereas the integral value of per-*O*-methylated sucrose relative to docosane at zero time was 3.93. The time-course study further established that reductive cleavage of per-*O*-methylated sucrose in the presence of Me_3SiOSO_2Me as the catalyst was complete within 15 min. Analysis of the reaction product revealed the presence of compounds **3** and **4**, the absence of the methyl D-glucosides **1** and **5**, and the presence of other components having molecular weights of 236 and 308. These are the molecular weights expected for 2,3,4,6-tetra-*O*-methyl-D-glucose and its trimethylsilyl glucoside, respectively. Thus, Me_3SiOSO_2Me appeared to hold promise as a catalyst for the selective reductive cleavage of ketofuranosides.

Per-*O*-methylated sucrose was subjected to reductive cleavage in the presence of the mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ that was found to catalyze

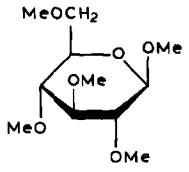


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TABLE II

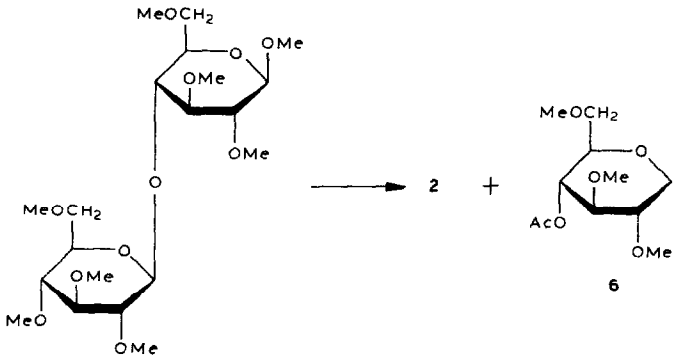
EFFECT OF CATALYST ON THE REDUCTIVE CLEAVAGE OF PER-*O*-METHYLATED SUCROSE[a]

Catalyst	*Molar ratio of compound*[b]		
	2	**3**	**4**
$Me_3SiOSO_2CF_3$	1.00	0.70	0.29
$BF_3 \cdot Et_2O$	0.66	0.75	0.25
$MeSO_3H$	0.84	0.68	0.32
Me_3SiOSO_2Me[c]	0.14	0.80	0.20
Me_3SiOSO_2Me (5 equiv.) + $BF_3 \cdot Et_2O$ (1 equiv.)	1.00	0.82	0.18

[a]See Experimental section for reaction conditions. [b]Normalized to the basis of either **2** or (**3** + **4**) as unity. [c]Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (**1**) and the corresponding β anomer (**5**) were detected in molar ratios of 0.38:1.00 and 0.37:1.00, respectively.

reductive cleavage of **1** (see Table I). Excellent results were also obtained in this case, with compounds **2** and (**3** + **4**) being formed in the molar ratio of 1:1 (see Table II). No decomposition (darkening) was observed in this reaction, in contrast to the reaction catalyzed by Me_3SiOSO_2Me alone.

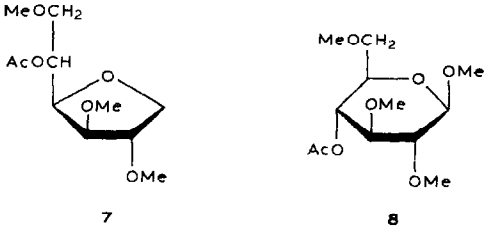
Methyl β-cellobioside. — Per-*O*-methylated methyl β-cellobioside was chosen as a model for the evaluation of potential catalysts, because of the presence of a 4-linked D-glucopyranosyl residue, which had previously been found[7] to give rise to an artifactual product under certain reductive-cleavage conditions. As shown in Scheme 2, the expected products of sequential reductive-cleavage and acetylation are compounds **2** and **6**. The formation of small proportions of **7** from 4-linked D-glucopyranosyl residues had previously been noted to occur, however, as a consequence of the presence of traces of water during reductive cleavage[4,7]. Indeed, reductive cleavage of per-*O*-methylated methyl β-cellobioside in the presence of $Me_3SiOSO_2CF_3$ gave compounds **2** and **6** as the major products, as well as 10% of **7** (see Table III). The formation of **7** was also observed in the $BF_3 \cdot Et_2O$-catalyzed reaction, but, in this case, a substantially smaller proportion of **6** was formed than expected. Analysis of the product mixture by g.l.c.–e.i.m.s. revealed the presence of a substantial proportion (42%, relative to compound **2**) of 4,5-di-*O*-acetyl-1,2,3,6-tetra-*O*-methyl-D-glucitol. The latter must clearly arise from the 4-linked



Scheme 2

D-glucopyranosyl residue by formation, and reduction, of an intermediate acyclic oxonium ion. These results were not unexpected, in view of our previous observation[4] that $BF_3 \cdot Et_2O$ does not catalyze reductive cleavage of the glycosidic linkages of per-*O*-methylated cellulose.

Methanesulfonic acid was found to catalyze complete reductive cleavage of per-*O*-methylated methyl β-cellobioside (see Table III), but, in this case, even greater proportions of **7** were observed than when $Me_3SiOSO_2CF_3$ was used as the catalyst. Trimethylsilyl methanesulfonate failed to catalyze reductive cleavage at room temperature, but cleavage occurred upon warming to ~35°, to yield compounds **2** and **8**. Clearly, the equatorial anomeric group of the methyl glycoside (per-*O*-methylated methyl β-cellobioside) is more resistant to reductive cleavage than the axial one of the methyl glycoside of compound **1** (see Table I). At reflux, Me_3SiOSO_2Me catalyzed the complete reductive cleavage of both glycosidic linkages, to give **2** and **6**, but unacceptable amounts of **7** were also produced. Tetrahydrofuran (THF), CCl_4, and MeCN were also tried as solvents in this reaction, but substantial amounts of compound **7** were formed in reactions in which reductive cleavage occurred.



In contrast to all of the aforementioned results, the mixture of Me_3SiOSO_2Me and $BF \cdot Et_2O$ readily accomplished the complete reductive cleavage of per-*O*-

methylated methyl β-cellobioside at room temperature, to yield only the expected products, compounds **2** and **6** (see Table III). The amount of **2** isolated was somewhat less than expected, however, presumably due to evaporative loss during workup. These results clearly demonstrate that catalysis by the Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$ mixture does not occur simply by the additive effects of the two independent catalysts.

Cyclomaltohexaose. — Per-*O*-methylated cyclomaltohexaose was used as a model for the further evaluation of selected catalysts, because of the presence of α-(1→4)-linked D-glucopyranosyl residues. Reductive cleavage in the presence of $Me_3SiOSO_2CF_3$, $BF_3 \cdot Et_2O$, $MeSO_3H$, or Me_3SiOSO_2Me (35°) gave the expected anhydroalditol **6** as the major product, in addition to the undesired 1,4-anhydroalditol **7** (see Table IV). Trimethylsilyl methanesulfonate failed to catalyze reductive cleavage at room temperature. Mixtures of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ catalyzed complete reductive cleavage of per-*O*-methylated cyclomaltohexaose without giving rise to **7**. Significant demethylation was observed, however, when a mixture containing 5 equiv. each of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ per equiv. of acetal was used to catalyze reductive cleavage (see Table IV). The expected product (**6**) was produced in quantitative yield, however, when reductive cleavage was catalyzed by a mixture containing 5 equiv. of Me_3SiOSO_2Me and 1 equiv. of $BF_3 \cdot Et_2O$ per equiv. of acetal. The latter catalyst mixture was therefore chosen for further evaluation.

Maltitol. — Previous studies[6,11] had indicated that the acyclic, 4-linked penta-*O*-methyl-D-glucitol residues of per-*O*-methylated maltitol (see Scheme 3) and per-*O*-methylated lacto-*N*-tetraitol[6] were substantially degraded during reductive

TABLE III

MOLAR RATIOS OF PRODUCTS (COMPOUNDS **2** AND **6–8**) DERIVED BY REDUCTIVE CLEAVAGE OF PER-*O*-METHYLATED METHYL β-CELLOBIOSIDE UNDER VARIOUS REACTION CONDITIONS[a]

Catalyst	*Solvent*	*Temp.*	*Molar ratio of compound*[b]			
			2	**6**	**7**	**8**
$Me_3SiOSO_2CF_3$	CH_2Cl_2	ambient	1.00	0.91	0.10	—
$BF_3 \cdot Et_2O$[c]	CH_2Cl_2	ambient	1.00	0.24	0.04	—
$MeSO_3H$	CH_2Cl_2	ambient	1.00	0.65	0.45	—
Me_3SiOSO_2Me	CH_2Cl_2	ambient	tr	—	—	tr
Me_3SiOSO_2Me	CH_2Cl_2	~35°	1.00	—	—	1.07
Me_3SiOSO_2Me	CH_2Cl_2	reflux	1.00	0.83	0.23	—
Me_3SiOSO_2Me	THF	reflux	—	—	—	—
Me_3SiOSO_2Me	CCl_4	reflux	1.00	0.51	0.56	—
Me_3SiOSO_2Me	MeCN	reflux	1.00	0.65	0.19	—
Me_3SiOSO_2Me (5 equiv.) + $BF_3 \cdot Et_2O$ (1 equiv.)	CH_2Cl_2	ambient	1.00	1.21	—	—

[a]See Experimental section for reaction conditions. [b]Normalized to the basis of **2** as unity. [c]4,5-Di-*O*-acetyl-1,2,3,6-tetra-*O*-methyl-D-glucitol was also observed as a product, in the molar ratio of 0.42:1.00.

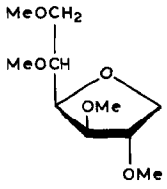
TABLE IV

EFFECT OF CATALYST ON THE REDUCTIVE CLEAVAGE OF PER-*O*-METHYLATED CYCLOMALTOHEXAOSE[a]

Catalyst	*Products (%)*	
	6	**7**
$Me_3SiOSO_2CF_3$	90	10
$BF_3 \cdot Et_2O$	90	10
$MeSO_3H$	70	30
Me_3SiOSO_2Me[b]	—	—
Me_3SiOSO_2Me (5 equiv.)[c] + $BF_3 \cdot Et_2O$ (5 equiv.)	62	—
Me_3SiOSO_2Me (5 equiv.) + $BF_3 \cdot Et_2O$ (1 equiv.)	100	—

[a]See Experimental section for reaction conditions. [b]Warming the reaction (−35°) gave **6** and **7** in yields of 90 and 10%, respectively. [c]2,4-Di-*O*-acetyl-1,5-anhydro-3,6-di-*O*-methyl-D-glucitol, 3,4-di-*O*-acetyl-1,5-anhydro-2,6-di-*O*-methyl-D-glucitol, and 4,6-di-*O*-acetyl-1,5-anhydro-2,3-di-*O*-methyl-D-glucitol were also observed as products, in yields of 9, 3, and 26%, respectively.

cleavage. Because reduced oligosaccharides are frequently used for structural characterization, studies were performed with per-*O*-methylated maltitol in an attempt to define conditions under which the degradation of acyclic residues would not occur. Reactions with $Me_3SiOSO_2CF_3$ as the catalyst were first carried out in the usual way (24 h at room temperature), and were terminated by extraction with aqueous sodium hydrogencarbonate, either with or without prior addition of acetic anhydride (2 h at room temperature). The results (see Table V) established that degradation of the acyclic residue occurs during both reductive cleavage and *in situ* acetylation, as one of the major degradation products (presumed to be compound **9** on the basis of its e.i. mass spectrum) was found to be formed in both reactions, but to be substantially increased in the reaction where *in situ* acetylation was carried out. The product of the reaction in which *in situ* acetylation was performed after reductive cleavage in the presence of $Me_3SiOSO_2CF_3$, or a mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$, was, however, unexpectedly complex. Three other compounds were formed that were each found, by g.l.c.–c.i.m.s. analysis, to have a molecular weight of 248, corresponding to that of a mono-*O*-acetylanhydro-tri-*O*-methylhexitol. The complexity of this reaction precluded its analytical utility, and so the identities of these other products were not pursued. A time-course study established that, in the presence of $Me_3SiOSO_2CF_3$, or a mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$, reductive cleavage was complete within 15 min, and where *in situ* acetylation was not performed, the expected products (**2** and **10**) were produced in excellent yields (see Table V). Acetylation of the product of the latter reaction gave only compounds **2** and **11**, with the latter compound being present in the molar ratio of 0.92:1.00 relative to compound **2**.



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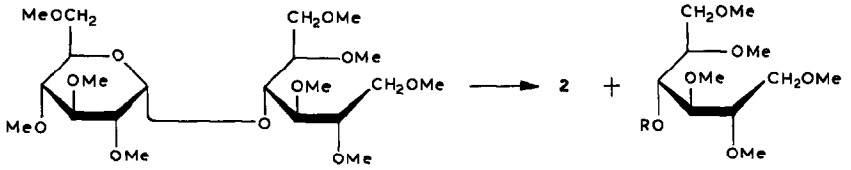
Amylose, cellulose, and pullulan. — Three polysaccharides containing 4-linked D-glucopyranosyl residues were examined by sequential permethylation and reductive cleavage, in order to determine whether these residues would again give rise to only the expected product (**6**) in the Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$-catalyzed reaction, as was observed for per-*O*-methylated cyclomaltohexaose (see Table IV). Amylose and cellulose should give rise to **6** as the major product, whereas pullulan,



Scheme 3

10 R = H
11 R = Ac

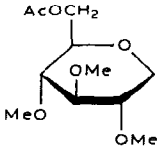
TABLE V

MOLAR RATIOS OF PRODUCTS (COMPOUNDS **2** AND **9–11**) DERIVED BY REDUCTIVE CLEAVAGE OF PER-*O*-METHYLATED MALTITOL UNDER VARIOUS REACTION CONDITIONS[a]

Catalyst	*Time (h)*	*Molar ratio of compound*[b]			
		2	**9**[c]	**10**	**11**
in situ *Acetylation (2 h)*					
$Me_3SiOSO_2CF_3$[d]	24	1.00	0.46	—	0.03
Me_3SiOSO_2Me (5 equiv.)[d] + $BF_3 \cdot Et_2O$ (1 equiv.)	1	1.00	0.02	—	0.48
Without acetylation					
$Me_3SiOSO_2CF_3$	0.25	1.00	0.01	0.93	—
$Me_3SiOSO_2CF_3$	24	1.00	0.25	0.01	—
Me_3SiOSO_2Me (5 equiv.) + $BF_3 \cdot Et_2O$ (1 equiv.)	0.25	1.00	—	1.02	—

[a]See Experimental section for reaction conditions. [b]Normalized to the basis of **2** as unity. [c]The e.i. mass spectrum contained an intense ion at *m/z* 131, which is characteristic of per-*O*-methylated 1,4-anhydroalditols. [d]Three unidentified compounds were formed in these reactions. Each had a molecular weight of 248.

which is comprised of a trisaccharide repeating-unit containing one α-(1→6)-linked D-glucopyranosyl and two α-(1→4)-linked residues, should give rise to compounds **6** and **12** in the relative molar ratio[4] of 2:1. As previously reported[4] (see Table VI), small proportions of the undesired 1,4-anhydro-D-glucitol derivative **7** are formed from these per-*O*-methylated polysaccharides in the $Me_3SiOSO_2CF_3$-catalyzed reductive cleavage, even when care is taken to exclude moisture. Compound **7** was not observed as a product, however, in the Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$-catalyzed reductive cleavage of either per-*O*-methylated amylose or cellulose, and only a trace of **7** was observed in the reductive cleavage of per-*O*-methylated pullulan (see Table VI). Therefore, for all model compounds and polysaccharides examined that contain 4-linked D-glucopyranosyl residues, the Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$ catalyst mixture displayed greater fidelity in the reductive cleavage than catalysts previously used. It is also worth pointing out that the mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ fully catalyzed the reductive cleavage of per-*O*-methylated cellulose, whereas neither $BF_3 \cdot Et_2O$ (ref. 4) nor Me_3SiOSO_2Me when used separately (data not shown), was able to catalyze this reductive cleavage reaction. These results again demonstrate that catalysis of reductive cleavage by the Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$ mixture occurs by a synergistic, rather than an additive, mechanism.



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Inulin. — Per-*O*-methylated inulin (see Scheme 4) was used in a final study in order to compare Me_3SiOSO_2Me and the Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$ mixture as catalysts for the reductive cleavage of a polysaccharide comprised of a high proportion of furanosyl residues. Previous studies[3] had shown that the expected products (**2**, **3**, **4**, **13**, and **14**) are formed in the expected amounts when either $Me_3SiOSO_2CF_3$ or $BF_3 \cdot Et_2O$ is used to catalyze reductive cleavage (see Table VII). Reductive cleavage of per-*O*-methylated inulin with Me_3SiOSO_2Me as the catalyst gave the results expected based on the aforementioned studies with per-*O*-methylated sucrose (see Table II); *i.e.*, complete reductive cleavage of the furanosyl residues occurred, whereas reductive cleavage of the D-glucopyranosyl moiety was not observed. The D-glucopyranosyl group gave rise to the corresponding methyl α- and β-D-glucopyranosides (**1** and **5**, respectively).

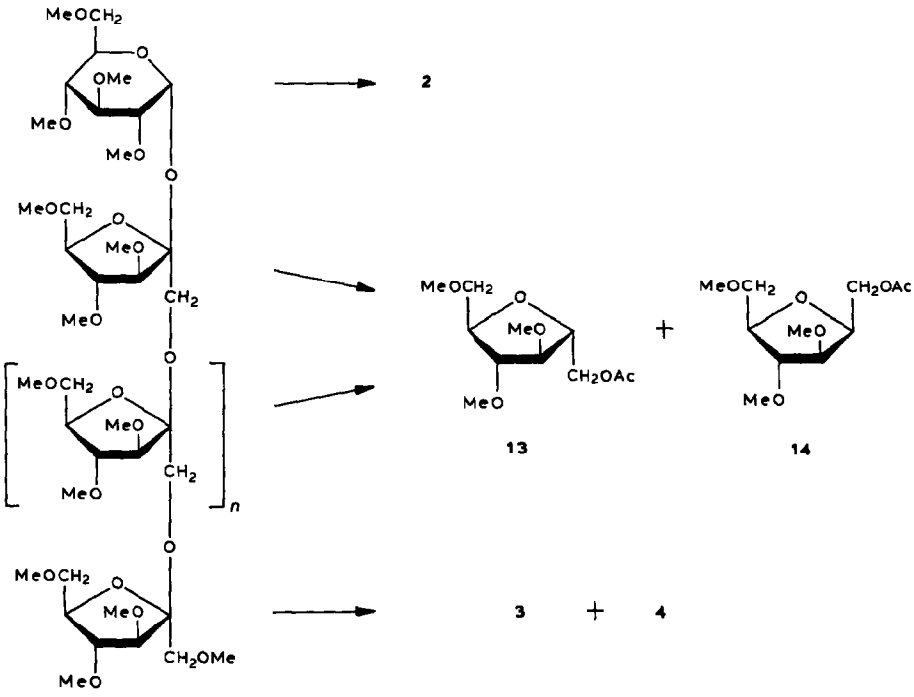
The mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$, however, gave quantitative reductive cleavage of all glycosidic linkages, as expected. Although compounds **13** and **14** were formed in a ratio different from that when either $BF_3 \cdot Et_2O$ or

TABLE VI

MOLAR RATIOS OF PRODUCTS (COMPOUNDS **2**, **6**, **7**, AND **12**) DERIVED BY REDUCTIVE CLEAVAGE OF PER-*O*-METHYLATED AMYLOSE, CELLULOSE, AND PULLULAN

D-*Glucan*	*Catalyst*	*Mole fraction*[a]			
		2	**6**	**7**	**12**
Amylose	$Me_3SiOSO_2CF_3$[b]	tr	0.94	0.04	—
	Me_3SiOSO_2Me[c] + $BF_3 \cdot Et_2O$	tr	0.95	—	—
Cellulose	$Me_3SiOSO_2CF_3$[b]	tr	0.89	0.04	—
	Me_3SiOSO_2Me[c] + $BF_3 \cdot Et_2O$	tr	0.95	—	—
Pullulan	$Me_3SiOSO_2CF_3$[b]	0.02	0.62	0.02	0.33
	Me_3SiOSO_2Me[c] + $BF_3 \cdot Et_2O$	0.03	0.63	<0.01	0.29

[a]Small amounts of products arising from incompletely methylated residues in the polysaccharides were also observed. [b]Data from ref. 4. [c]A mixture containing 5 equiv. of Me_3SiOSO_2Me and 1 equiv. of $BF_3 \cdot Et_2O$ per equiv. of acetal was used.



Scheme 4

TABLE VII

MOLE FRACTIONS OF PRODUCTS (COMPOUNDS **1–5, 13,** AND **14**) DERIVED BY REDUCTIVE CLEAVAGE OF PER-*O*-METHYLATED INULIN

Catalyst	*Mole fraction*						
	1	**2**	**3**	**4**	**5**	**13**	**14**
$Me_3SiOSO_2CF_3$[a]	—	0.05	0.04	0.01	—	0.67	0.22
$BF_3 \cdot Et_2O$[a]	—	0.04	0.05	0.01	—	0.65	0.24
Me_3SiOSO_2Me	0.02	—	0.06	0.01	0.02	0.74	0.15
Me_3SiOSO_2Me[b] + $BF_3 \cdot Et_2O$	—	0.03	0.04	0.01	—	0.75	0.17

[a]Data from ref. 3. [b]A mixture containing 5 equiv. of Me_3SiOSO_2Me and 1 equiv. of $BF_3 \cdot Et_2O$ per equiv. of acetal was used.

$Me_3SiOSO_2CF_3$ was used as the catalyst, the combined mole fraction of (**13** + **14**) relative to the combined mole fraction of (**3** + **4**) was ~18, as expected[3,12].

Nature of the trimethylsilyl methanesulfonate–boron trifluoride etherate catalyst. — In some of the studies reported herein, it was evident that the mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ catalyzes reductive cleavage in a manner independent of that of either catalyst when used separately. These results therefore suggested that Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ react with each other, to give rise to a species that is the actual catalyst in the reductive cleavage process; this was confirmed by a ^{1}H-n.m.r. study of the separate and mixed catalysts. In the 300-MHz, ^{1}H-n.m.r. spectrum of Me_3SiOSO_2Me, the trimethylsilyl singlet was observed at δ 0.40, and the methanesulfonyl methyl singlet, at δ 2.99. The addition of 0.2 equiv. of $BF_3 \cdot Et_2O$ (relative to 1.0 equiv. of Me_3SiOSO_2Me) gave rise to a new trimethylsilyl signal, at δ 0.21 (d, J 7.5 Hz), and a new methanesulfonyl methyl signal, at δ 3.03 (broad s), in addition to the expected resonances of diethyl ether. Integration of the trimethylsilyl signals at δ 0.21 and δ 0.40 gave the ratio of 3:7.

The trimethylsilyl signal at δ 0.21 was readily identified as being due to trimethylsilyl fluoride, because it was a doublet ($^3J_{H,F}$ 7.5 Hz), and this assignment was confirmed by generating Me_3SiF independently from Me_3SiOSO_2Me, and tetrabutylammonium fluoride in a separate experiment. These results therefore indicated that Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ react to form Me_3SiF and F_2BOSO_2Me *via* ligand exchange. The integrated intensity of the Me_3SiF signal (30% of the total trimethylsilyl signals), however, indicated that species of the type $FB(OSO_2Me)_2$, or $B(OSO_2Me)_3$, or both, are present to some extent; *i.e.*, as 0.2 equiv. of $BF_3 \cdot Et_2O$ was added to 1.0 equiv. of Me_3SiOSO_2Me, the integrated intensity of the Me_3SiF doublet would have been only 20% of the total trimethylsilyl signals had all of the $BF_3 \cdot Et_2O$ reacted to give Me_3SiF and F_2BOSO_2Me. Clearly, F_2BOSO_2Me undergoes further ligand exchange in its reaction with $BF_3 \cdot Et_2O$.

DISCUSSION

Described herein is a new catalyst, formed by the reaction between trimethylsilyl methanesulfonate and boron trifluoride etherate, that has been shown to catalyze efficiently the reductive cleavage of a variety of methylated glycans, to give the expected products in quantitative yields. Two particularly troublesome side-reactions previously encountered, namely, the formation of 1,4-anhydro-D-glucitol derivatives from 4-linked D-glucopyranosyl residues, and the cyclization of acyclic, permethylated alditol residues, have been eliminated with the development of this new catalyst. Although most of the reactions reported herein were carried out for 24 h for comparison purposes, it has been found that reductive cleavages with this new catalyst are complete within 1 h. The ease of workup of the reaction mixture, and the short time (0.5 h) needed for subsequent acetylation, make the overall analysis particularly rapid and convenient.

To the best of our knowledge, species of the type F_2BOSO_2Me, formed in the reaction of $BF_3 \cdot Et_2O$ and Me_3SiOSO_2Me, have never been reported. Some related compounds were reported by Olah *et al.*[13], however; dissolution of $Me_3SiOSO_2CF_3$ in neat BCl_3 or BBr_3 was shown to give rise to bimolecular complexes which subsequently underwent ligand exchange to form Me_3SiCl and $Cl_2BOSO_2CF_3$, or Me_3SiBr and $Br_2BOSO_2CF_3$, respectively. Although it is clear that ligand exchange also occurs when Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ are mixed in deuteriochloroform, as judged by the formation of Me_3SiF, it is not clear as to the degree to which the reaction is complete, or the degree to which further ligand exchange occurs to generate $FB(OSO_2Me)_2$ and $B(OSO_2Me)_3$. In contrast to the studies reported by Olah *et al.*[13], the silyl ester (Me_3SiOSO_2Me) was used in excess in our studies, making it more likely that further ligand exchange would occur. The nature of the species present at equilibrium is important, as an equimolar mixture of Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ gave rise to considerable proportions of incompletely methylated anhydroalditols in the reductive cleavage of per-*O*-methylated cyclomaltohexaose (see Table IV). These products clearly arose by demethylation during reductive cleavage, rather than as a result of incomplete methylation prior to reductive cleavage, because they were not observed when the same preparation of per-*O*-methylated cyclomaltohexaose was reductively cleaved in the presence of a 5:1 molar ratio of Me_3SiOSO_2Me to $BF_3 \cdot Et_2O$ (see Table IV). Different "catalysts" are apparently formed, depending on the ratio in which Me_3SiOSO_2Me and $BF_3 \cdot Et_2O$ are mixed.

From studies reported herein, it is also evident that trimethylsilyl methanesulfonate may be useful as a catalyst for the selective, reductive cleavage of methylated ketofuranosyl residues. Although considerable degradation was observed in long-term (24 h) reactions, the reductive cleavage of fructofuranosyl residues was found to be complete within 15 min when Me_3SiOSO_2Me was used as the catalyst and, under these conditions, no cleavage of any methylated pyranosyl residue was observed.

EXPERIMENTAL

General. — Methylation of methyl α-D-glucopyranoside, sucrose, methyl β-cellobioside[14], maltitol, cyclomaltohexaose, amylose, cellulose, pullulan, and inulin was accomplished by the procedure described by Hakomori[15]. Trimethylsilyl methanesulfonate was prepared by refluxing a mixture of methanesulfonic acid (10 mL) and trimethylsilyl chloride (20 mL), and distilling the product at 240 Pa. The fraction boiling at 65–66° had η_D^{20} 1.4235 (lit.[16] 1.4235). Reductive cleavages with either $Me_3SiOSO_2CF_3$, or $BF_3 \cdot Et_2O$ as the catalyst were carried out at room temperature for 24 h, and the products were acetylated as previously described[4]. ^{1}H-N.m.r. spectra were recorded with an IBM NR/300 spectrometer for solutions in $CDCl_3$ as solvent, and were referenced to internal tetramethylsilane. Analytical g.l.c. was performed in a Hewlett–Packard Model 5890A gas–liquid chromatograph equipped with a Hewlett–Packard Model 3392A integrator, a flame-ionization detector, and a Hewlett–Packard fused-silica capillary column (0.2 mm × 25 m) of cross-linked methylsilicone (0.33 μM film thickness). The column was held for 2 min at 110° and then programmed to 300° at 6°/min at a flow rate of 1 mL/min (method 1), or was held for 5 min at 110° and then programmed to 300° at 4°/min at a flow rate of 1 mL/min (method 2). G.l.c.–m.s. analyses were performed in a Finnigan 4000 mass spectrometer equipped with a VG Multispec data system. Column effluents were analyzed by chemical-ionization mass spectrometry, with ammonia as the reagent gas, wherein characteristic $(M + 1)^+$ and $(M + NH_4)^+$ ions were detected, and by electron-impact mass spectrometry in order to verify that eluted components had mass spectra identical to those of independently synthesized standards.

Reductive cleavage with Et_3SiH and Me_3SiOSO_2Me–$BF_3 \cdot Et_2O$. — A sample (5 mg) of the per-*O*-methylated saccharide and a small stirring-bar were added to a *V*-vial, dichloromethane (0.25 mL, predried with CaH_2), Et_3SiH (5 equiv./equiv. of acetal), Me_3SiOSO_2Me (5 equiv./equiv. of acetal), and $BF_3 \cdot Et_2O$ (1 equiv./equiv. of acetal) were sequentially added, the vial was capped, and the contents were stirred for 24 h at room temperature. Methanol (1.0 mL) was then added, stirring was continued for 30 min, and the mixture was de-ionized by passage through a column (0.5 × 5 cm) of Bio-Rad AG501-X8, analytical-grade, mixed-bed resin. Methanol and dichloromethane were removed by evaporation under vacuum, and the product was acetylated by treating with 5 equiv. each of acetic anhydride and 1-methylimidazole in 0.2 mL of dichloromethane for 0.5 h. Acetylation was terminated by the addition of saturated, aqueous sodium hydrogencarbonate (0.5 mL), the aqueous and organic layers were separated, and the dichloromethane layer was washed twice with 1-mL portions of water prior to analysis by g.l.c.

Molar-response values (flame-ionization detection) and g.l.c. retention-times of compounds **1–14**. — The integral values of all g.l.c. peaks were corrected for molar response by the effective carbon-response (e.c.r.) method[17], which had been

TABLE VIII

G.L.C. FLAME-IONIZATION DETECTOR RESPONSE-VALUES AND RETENTION TIMES OF COMPOUNDS **1–14**

Compound	*Normalized e.c.r. value*[a]	*Retention time (min)*	
		Method 1	*Method 2*
1	1.07	10.5	14.3
2	**1.00**	8.2	10.7
3	1.00	8.3	11.0
4	1.00	8.5	11.4
5	1.07	9.7	13.0
6	1.09	11.4	—
7	1.09	12.0	—
8	1.16	12.8	—
9	1.00	9.3	—
10	1.07	11.5	—
11	1.29	13.4	—
12	1.11	11.6	—
13	1.11	—	16.1
14	1.11	—	16.7

[a]Normalized to the basis of compound **2** as unity.

shown[2] to be applicable to anhydroalditols. Calculated e.c.r. values were normalized to the calculated value for compound **2** set at unity. Integrated areas were divided by the appropriate, normalized e.c.r. values, in order to correct for molar response. The normalized e.c.r. values and g.l.c. retention-times of compounds **1–14** are given in Table VIII.

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