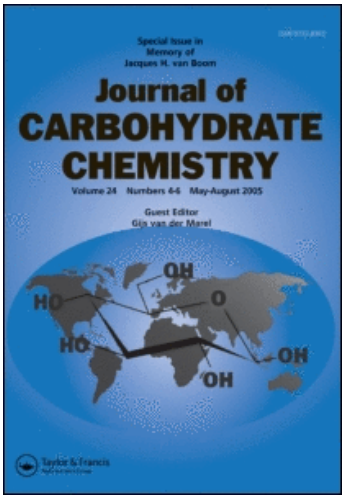


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Triflic Anhydride: An Alternative Promoter in Glycosidations

Alicia Dobarro-Rodriguez[a]; Michel Trumtel[a]; Hans Peter Wessel[a]
[a] Pharma Division, Preclinical Research F. Hoffmann-La Roche Ltd, Basel, CH, Switzerland

To cite this Article Dobarro-Rodriguez, Alicia , Trumtel, Michel and Wessel, Hans Peter(1992) 'Triflic Anhydride: An Alternative Promoter in Glycosidations', Journal of Carbohydrate Chemistry, 11: 3, 255 — 263
To link to this Article: DOI: 10.1080/07328309208017992
URL: http://dx.doi.org/10.1080/07328309208017992

J. CARBOHYDRATE CHEMISTRY, 11(3), 255-263 (1992)

TRIFLIC ANHYDRIDE:

AN ALTERNATIVE PROMOTER IN GLYCOSIDATIONS

Alicia Dobarro-Rodriguez, Michel Trumtel, and
Hans Peter Wessel*

Pharma Division, Preclinical Research
F.Hoffmann-La Roche Ltd
CH 4002 Basel, Switzerland

Received July 24, 1991 - Final form December 30, 1991

ABSTRACT

The activation of glucosyl halides, trichloroacetimidates and of thioglucosides with triflic anhydride has been investigated showing that triflic anhydride promotes glycosidations with trichloracetimidates as well as with fluorides. There is also some potential for the activation of reactive thioglycosides. The role of triflic anhydride as a Lewis acid is likely.

INTRODUCTION

We have recently described trifluoromethanesulfonic (triflic) anhydride as an efficient promoter in *cis*-glucosidation reactions using fluorides as glycosyl donors.[1,2] The reaction proceeds well with glycosyl acceptors of medium or low reactivity, whereas with more reactive acceptors, the formation of acceptor triflates was observed.[3] Glycosidation of unreactive aglycons was also achieved by the use of triflic anhydride as an activator of anomeric sulfoxides.[4] It is assumed[1] that triflic anhydride acts as a Lewis acid in these reactions to activate the anomeric center. We now describe the results of our investigation on the possibility of employing triflic anhydride in the

activation of anomeric species such as halides, trichloroacetimidates, or thioglycosides.

RESULTS AND DISCUSSION

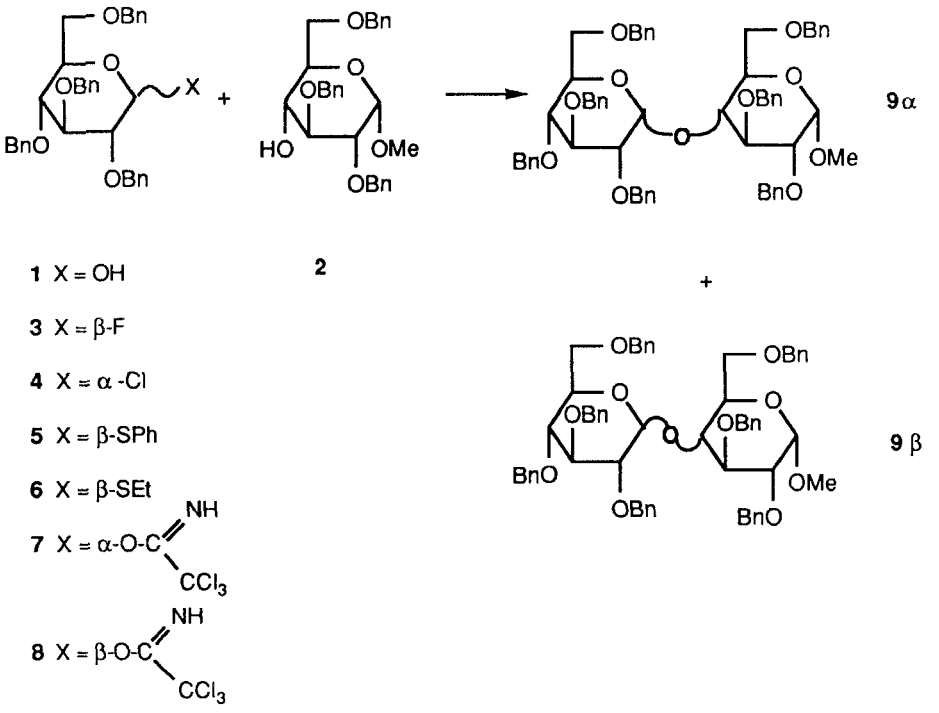
To examine the possible role of triflic anhydride in the activation of different glycosyl donors the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1** was chosen as a common precursor. Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **2**[5] was employed as glycosyl acceptor for its low reactivity.[6] The use of this standard acceptor together with different glucosyl donors has been widely described in literature.[6a,b,7] Diethyl ether favouring the formation of *cis*-glycosides[7c] was the solvent of choice in all glucosidation reactions. Activated powdered molecular sieves (4Å) has been used throughout to trap triflic acid which is formed in the course of the reaction (Scheme **1**).

In a reference experiment involving a fluoride as a donor, reaction of acceptor **2** with **3**[7b] afforded **9**α and **9**β in a very good yield (97%) with a 1.9 : 1 α/β ratio. The two disaccharides **9**α and **9**β were separated by column chromatography on silica gel. Since the NMR data of **9**α were partly at variance with those reported,[7g] the ^{1}H NMR spectrum was analyzed completely (cf. Experimental Part). In particular, we find H-1 at δ 4.60 (Ref. 7g : δ 5.22). Also the isomeric disaccharide **9**β was characterized by ^{1}H NMR spectroscopy using the 1D TOCSY technique.[2,8] This allowed us in the following experiments to obtain **9**α/**9**β ratios from a quantitative analysis of the integrals of the $-OCH_3$ signals (**9**α: $\delta(OCH_3)$ 3.37, **9**β: $\delta(OCH_3)$ 3.36) in the mixture.

Reaction of acceptor **2** with chloride **4**[9] led to **9**α and **9**β in 38% yield, the α/β ratio (cf. Table 1) was comparable to the one obtained with fluoride **3**. This example illustrates a different activation of a glycosyl chloride which usually involves the use of heavy metal salts as promoters[10] in Koenigs-Knorr type glycosidations.

The thiophenyl derivative **5**[11] upon reaction with acceptor **2** afforded **9**α and **9**β in a poor yield (16%), although a comparatively good α selectivity (α/β = 3 : 1) was found. When thioethyl glucoside **6**[11b,12] was used instead of **5**, **9**α and **9**β were obtained in an improved yet moderate yield (53%) and a 1.5 : 1 α/β ratio.

SCHEME 1



Reaction of **2** with either α-trichloroacetimidate **7**[13,14] or β-trichloroacetimidate **8**[14] furnished **9α** and **9β** in virtually quantitative yield (94%) with 1.5 : 1 and 2.3 : 1 α/β ratios, respectively. It is noteworthy that the more reactive β-trichloroacetimidate **8**, which reacts faster and at a lower temperature, gives a better α-selectivity than the α-trichloroacetimidate **7**. These two examples demonstrate that triflic anhydride can be efficiently used as an alternative promoter for the activation of anomeric trichloroacetimidates in the glucosidation of unreactive alcohols.

Promoters commonly used for this purpose are boron trifluoride etherate complex or trimethylsilyl triflate. Less usual promoters are Lewis acids such as zinc chloride,[7e] *t*-butyldimethylsilyl triflate,[7g] zinc chloride etherate,[15] or zinc bromide.[16] With the same donor **7** and acceptor **2** a 50% yield with 5 : 1 α/β-selectivity was described[7g]

TABLE 1. REACTION CONDITIONS AND RESULTS OF GLUCOSIDATION REACTIONS.

EXP.	DONOR	[DONOR]:	[ACCEPTOR]: **2**	[PROMOTER]	TEMP.[a] [°C]	TIME [h]	YIELD [%]	RATIO **9α:9β**
1	**3**	1.7	1	1.8	0	20	97	1.9:1
2	**4**	1.2	1	1.3	10	22	38	1.5:1
3	**5**	1.2	1	1.3	20	10	16	3:1
4	**6**	1.3	1	1.9	20	70	53	1.5:1
5[b]	**1**	1	1	1.1	20	24	no reaction	
6	**7**	2.5	1	2.6	0	16	94	1.5:1
7	**8**	1.2	1	1.3	-20	3	94	2.3:1
8	**7**	2.2	1	0.3[c]	0	20	60	3:1

a. All experiments were started at -20 °C.

b. A minimum amount of dichloromethane was added to solubilize **1**.

c. CF_3SO_3H was used in catalytic amounts instead of triflic anhydride.

employing trimethylsilyl triflate as promoter in ether as solvent. Whether triflic anhydride is a strong promoter also for imidates and even less reactive glycosyl acceptors (as shown for the activation of fluorides[1]) remains to be seen. It is assumed that also in this case triflic anhydride acts as a Lewis acid, i.e., by activation of the nucleophilic nitrogen atom of the imidate with a $CF_3SO_2^{\delta+}$ moiety.

To investigate the possibility that triflic acid formed during the reaction was the active promoter, a control experiment was carried out using triflic acid instead of triflic anhydride. In this case, the yield was considerably lower (cf. Table 1), in keeping with the findings of Schmidt and Michel[7e] that proton acids are less efficient than Lewis acids in the activation of imidates. In a second control experiment, tetra-*O*-benzyl-D-glucose **2** was subjected to triflic anhydride and molecular sieves without bringing about glycosidation. An analogous experiment without molecular sieves was reported by Pavia et al.[17] to furnish a Fischer type glycosidation due to formation of

triflic acid. These comparisons emphasize the action of triflic anhydride as Lewis acid, and point to the role of molecular sieves in our experiments to trap triflic acid.

In conclusion, it is shown that triflic anhydride effectively promotes not only reactions with fluorides as glycosyl donors but also with trichloroacetimidates. There is also some potential for the activation of reactive thioglycosides.

EXPERIMENTAL

General Procedures. Solvents and reagents were obtained from FLUKA (puriss p.a.). Evaporation: Büchi rotary evaporator. TLC: precoated silica gel 60F-254 plates (Merck), detection by UV light (254 nm) and spraying with a 20% solution of concd H_2SO_4 in EtOH followed by charring. MS: MS 902 (FAB) with data system DS 2050 (VG). ^1H NMR: BRUKER AM 400 (400 MHz) with Aspect 3000. Melting points were determined with a Büchi Model 510 capillary apparatus and are uncorrected. Flash column chromatography was performed on Silica Gel 60 (230 - 400 mesh, Merck). Molecular sieves (4 Å) were activated for 3 h at 150 °C under vacuum.

Methyl 4-*O*-(2,3,4,6-Tetra-*O*-benzyl-α and β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**9**α and **9**β). Experiment 1 in Table 1: A soln of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**2**, 302 mg, 0.650 mmol) and 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride **3**[7b] (420 mg, 0.773 mmol) prepared from chloride **4**[9b] in 13 mL of dry diethyl ether was stirred for 30 min together with powdered 4 Å molecular sieves at room temperature under argon atmosphere, cooled to -20 °C, and triflic anhydride (140 µL, 0.852 mmol) was added dropwise. The reaction mixture was monitored by TLC (toluene / ethyl acetate 9 : 1) and was slowly allowed to reach 0 °C; further fluoride **3** (175 mg, 0.322 mmol) and promoter (53 µL, 0.322 mmol) were added. After 20 h of stirring, the reaction mixture was neutralized with Et_3N, filtered over a pad of Celite, and washed with dichloromethane; solvents were evaporated, coevaporated with toluene, acetate 11 : 1) to give **9**α and **9**β (623 mg, 97%).

Experiment 2 in Table 1: 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride[9b] (**4**, 310 mg, 0.554 mmol), **2** (210 mg, 0.452

mmol), triflic anhydride (98 μL, 0.597 mmol), and molecular sieves (4 Å) were reacted in 12 mL of dry ether in the same manner as in experiment 1 to give after chromatography **9α** and **9β** (161 mg, 38%).

Experiment 3 in Table 1: Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[11b] (**5**, 301 mg, 0.475 mmol), **2** (178 mg, 0.383 mmol), triflic anhydride (85 μL, 0.517 mmol) and molecular sieves (4 Å) were reacted in 13 mL of dry ether to give after work-up as described in experiment 1 and chromatography **9α** and **9β** (60 mg, 16%).

Experiment 4 in Table 1: Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[11b] (**6**, 129 mg, 0.221 mmol), **2** (81 mg, 0.174 mmol), triflic anhydride (55 μL, 0.331 mmol), and molecular sieves (4 Å) were reacted in 4 mL of dry ether to give after work-up as in experiment 1 and chromatography **9α** and **9β** (91 mg, 53%).

Experiment 5 in Table 1: Commercial 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**, 233 mg, 0.431 mmol), **2** (200 mg, 0.431 mmol), triflic anhydride (80 μL, 0.487 mmol) were dissolved in 15 mL of dry ether and 5 mL of dichloromethane in the presence of molecular sieves (4 Å). The starting materials were recovered unreacted after 24 h at room temperature.

Experiment 6 in Table 1: 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate[14] (**7**, 628 mg, 0.915 mmol), **2** (168 mg, 0.361 mmol), triflic anhydride (156 μL, 0.950 mmol), and molecular sieves (4 Å) were reacted in 8 mL of dry ether to give after work-up as described in experiment 1 and chromatography **9α** and **9β** (325 mg, 94%).

Experiment 7 in Table 1: 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl trichloroacetimidate[14] (**8**, 306 mg, 0.446 mmol), **2** (170 mg, 0.365 mmol), triflic anhydride (80 μL, 0.487 mmol), and molecular sieves (4 Å) were reacted in 14 mL of dry ether to give after work-up as above and chromatography **9α** and **9β** (339 mg, 94%).

Experiment 8 in Table 1: α-Trichloroacetimidate **7** (549 mg, 0.801 mmol), **2** (169 mg, 0.363 mmol), triflic acid (10 μL, 0.113 mmol), and molecular sieves (4 Å) were reacted in 11 mL of dry ether to give after work-up as above and chromatography **9α** and **9β** (214 mg, 60%).

A sample of **9α/9β** was chromatographed (dichloromethane/diisopropyl ether 40 : 1) to give pure **9α** as an oil; $[\alpha]_{578}^{20}$ + 47.5° (*c* 0.2, chloroform) [ref.7e: $[\alpha]_{578}^{20}$ + 39.5° (*c* 1, chloroform)]; $[\alpha]_{D}^{20}$ + 45.5°

(c 0.2, chloroform) [ref.6a: $[\alpha]_D^{20}$ + 48° (c 1.05, chloroform), ref.7c: $[\alpha]_D^{20}$ + 45.4° (c 0.82, chloroform), ref.7f: $[\alpha]_D$ + 31° (c 1, dichloromethane), ref.7g: $[\alpha]^{20}$ + 50.3° (c 1, chloroform), ref.7m: $[\alpha]_D^{22}$ + 38° (c 0.8, chloroform), ref.7n: $[\alpha]_D^{23}$ + 46.2° (c 1.2, chloroform)]; MS (FAB) 1009.3 $(M + Na)^+$, 1025.3 $(M + K)^+$; ^1H NMR ($CDCl_3$) δ 7.37 - 7.08 (m, 35 H, aromatic), 5.69 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.03, 4.80 (2d, 2H, J = 11.6 Hz, $PhCH_2$), 4.88, 4.77 (2d, 2H, J = 10.8 Hz, $PhCH_2$), 4.78, 4.41 (2d, 2H, J = 10.9 Hz, $PhCH_2$), 4.70, 4.57 (2d, 2H, J = 12.1 Hz, $PhCH_2$), 4.60 (d, 1H, $J_{1,2}$ = 3.5 Hz, H - 1), 4.59, 4.53 (2d, 2H, J = 11.8 Hz, $PhCH_2$), 4.51, 4.27 (2d, 2H, J = 12.2 Hz, $PhCH_2$), 4.49 (m, 2H, $PhCH_2$), 4.09, 4.04 (2 dd~t, 2H, H-3, H-4), 3.90 (1H, $J_{3',4'}$ = 8.7 Hz, H-3'), 3.85 (ddd, 1H, H-5), 3.83 (dd, 1H, $J_{5,6a}$ = 3.8 Hz, H-6a) 3.71 (ddd~br. d, 1H, $J_{4',5'}$ = 9.8 Hz, H-5'), 3.64 (dd~t and dd, 2H, H-4', H-6b), 3.59 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 3.49 (dd, 1H, $J_{2',3'}$ = 9.8 Hz, H-2'), 3.48 (dd, 1H, $J_{5',6a'}$ = 3.6 Hz, $J_{6a',6b'}$ = 10.5 Hz, H-6a'), 3.38 (dd,m 1H, $J_{5',6b'}$ = 1.5 Hz, H-6b'), 3.37 (s, 3H, OMe).

9β was rechromatographed (carbon tetrachloride/ether 4 : 1) to give pure crystalline **9β**, mp 94 - 95 °C from methanol [ref.7e: mp 85 - 88 °C from methanol]; $[\alpha]_{578}^{20}$+20° (c 0.2, chloroform) [ref.7c: $[\alpha]_D^{20}$+ 16.4° (c 2.9, chloroform), ref.7e: $[\alpha]_{578}^{20}$+25.3° (c 1, chloroform), ref.7m: $[\alpha]_D^{22}$+ 13° (c 1.1, chloroform), ref.7k: $[\alpha]_D^{22}$+ 16.9° (c 1.7, chloroform)]; MS (FAB) 1009.3 $(M + Na)^+$, 1025.2 $(M + K)^+$; ^1H NMR ($CDCl_3$) δ 7.46 - 7.17 (m, 35H, aromatic), 5.09 (d, 1H, J = 11.3 Hz, $PhCH_2$), 4.88 - 4.72 (7d, 7H, $PhCH_2$), 4.62 - 4.53 (3d, 3H, $PhCH_2$), 4.56 (d, 1H, $J_{1,2}$ = 3.5 Hz, H - 1), 4.45 - 4.35 (3d, 3H, $PhCH_2$), 4.38 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H - 1'), 3.96 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H - 4), 3.84 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H - 3), 3.83 (dd, 1H, $J_{5,6a}$ = 3.0 Hz, H - 6a), 3.71 (dd, 1H, $J_{5',6'a}$ = 1.8, $J_{6'a,6'b}$ = 11.0 Hz, H - 6'a), 3.60 (dd, 1H, $J_{3',4'}$ = 9.0, $J_{4',5'}$ = 10.0 Hz, H - 4'), 3.58 (m, 1H, H - 5) 3.54 (dd, 1H, $J_{5',6'b}$ = 4.5 Hz, H - 6'b), 3.48 (dd, 1H, $J_{5,6b}$ = 2.0, $J_{6a,6b}$ = 10.5 Hz, H - 6b), 3.47 (dd, 1H, H - 2), 3.46 (dd, 1H, $J_{2',3'}$ = 8.5 Hz, H - 3'), 3.36 (dd, 1H, H - 2'), 3.36 (s, 3H, OMe), 3.29 (ddd, 1H, H - 5').

ACKNOWLEDGEMENTS

We wish to thank the following colleagues for the determination of physical data: Dr. W. Arnold (NMR), Dr. G. Englert (NMR), Mr. W.

Meister (MS), Dr. W. Vetter (MS), and Mrs. R. Nachbur for typing the manuscript.

REFERENCES AND FOOTNOTES

1. H. P. Wessel, *Tetrahedron Lett.*, **31**, 6863 (1990).
2. H. P. Wessel, G. Englert, and P. Stangier, *Helv. Chim. Acta*, **74**, 683 (1991).
3. H. P. Wessel and N. Ruiz, *J. Carbohydr. Chem.*, in press.
4. D. Kahne, S. Walker, Y. Cheng, and D. Van Engen, *J. Am. Chem. Soc*, **111**, 6881 (1989).
5. P. J. Garegg and H. Hultberg, *Carbohydr. Res.*, **93**, C 10 (1981).
6. a) J.-R. Pougny, J.-C. Jacquinet, M. A. M. Nassr, D. Duchet, M. L. Milat, and P. Sinaÿ, *J. Am. Chem. Soc.*, **99**, 6762 (1977);
   b) J.-R. Pougny, M. A. M. Nassr, N. Naulet, and P. Sinaÿ, *Nouv. J. Chim.*, **2**, 389 (1978);
   c) H. Paulsen and Č. Kolář, *Chem. Ber.*, **114**, 306 (1981).
7. a) T. Mukaiyama, T. Nakatsuka, and S. Shoda, *Chem. Lett.*, 487 (1979);
   b) T. Mukaiyama, Y. Murai, and S. Shoda, *Chem. Lett.*, 431 (1981);
   c) S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrahedron Lett.*, **25**, 1379 (1984);
   d) T. Inazu, H. Hosokawa, and Y. Satoh, *Chem. Lett.*, 297 (1985);
   e) R. R. Schmidt and J. Michel, *J. Carbohydr. Chem.*, **4**, 141 (1985);
   f) J.-R. Pougny, *J. Carbohydr. Chem.*, **5**, 529 (1986);
   g) B. Wegmann and R. R. Schmidt, *J. Carbohydr. Chem.*, **6**, 357 (1987);
   h) B. Fraser-Reid, P. Konradsson, D. R. Mootoo, and U. Udodong, *J. Chem. Soc., Chem. Commun.*, 823 (1988);
   i) G. V. Reddy, V. R. Kulkarni, and H. B. Mereyala, *Tetrahedron Lett.*, **30**, 4283 (1989);
   j) K. Suzuki, H. Maeta, and T. Matsumoto, *Tetrahedron Lett.*, **30**, 4853 (1989);
   k) S. Hashimoto, T. Honda, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 865 (1989);
   l) S. Kobayashi, K. Koide, and M. Ohno, *Tetrahedron Lett.*, **31**, 2435 (1990);
   m) F. Dasgupta and P. J. Garegg, *Carbohydr. Res.*, **202**, 225 (1990);
   n) S. Hashimoto, T. Honda, and S. Ikegami, *Tetrahedron Lett.*, **31**, 4769 (1990);
   o) S. Hashimoto, T. Honda, and S. Ikegami, *Chem. Pharm. Bull.*, **38**, 2323 (1990);
   p) A. Marra, J.-M. Mallet, C. Amatore, and P. Sinaÿ, *Synlett.*, 572 (1990);
   q) R. R. Schmidt, M. Behrendt, and A. Toepfer, *Synlett.*, **1990**, 694.
8. H. Kessler, M. Gehrke, and C. Griesinger, *Angew. Chem., Int. Ed. Engl.*, **27**, 490 (1980).
9. a) P. W. Austin, F. E. Hardy, J. G. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 2128 (1964);
   b) T. Iversen and D. R. Bundle, *Carbohydr. Res.*, **103**, 29 (1982).

10. H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, **21**, 155 (1982).

11. a) P. J. Pfaeffli, S. H. Hixson, L. Anderson, *Carbohydr. Res.*, **23**, 195 (1972);
    b) R. J. Ferrier and R. H. Furneaux, *Carbohydr. Res.*, **52**, 63 (1976).

12. H. Lichti, M. Kuhn, and A. von Wartburg, *Helv. Chim. Acta*, **45**, 868 (1962).

13. R. R. Schmidt and J. Michel, *Angew. Chem.*, **92**, 763 (1980).

14. R. R. Schmidt and J. Michel, *Tetrahedron Lett.*, **25**, 821 (1984).

15. P. Zimmermann, U. Greilich, and R. R. Schmidt, *Tetrahedron Lett.*, **31**, 1849 (1990).

16. F. J. Urban, B. S. Moore, and R. Breitenbach, *Tetrahedron Lett.*, **31**, 4421 (1990).

17. a) A. A. Pavia, J. M. Rocheville, and S. N. Ung, *Carbohydr. Res.*, **79**, 79 (1980);
    b) J. M. Lacombe, A. A. Pavia, and J. M. Rocheville, *Can. J. Chem.*, **59**, 473 (1981);
    c) A. A. Pavia, and S. N. Ung-Chhun, *Can. J. Chem.*, **59**, 482 (1981).