

A convenient synthesis of *N*-acetylactosamine derivatives from lactal[†]

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ABSTRACT

In a thermal inverse-type hetero-Diels–Alder reaction of *O*-silyl-protected lactal **1** and bis(2,2,2-trichloroethyl) azodicarboxylate (**2**), the dihydrooxadiazine derivative **3** was obtained in a very high yield; transesterification with benzyl alcohol furnished the corresponding derivative **4**. Treatment of **3** with methanol in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ afforded the methyl lactoside derivative **5** which, after transesterification with benzyl alcohol, then hydrogenolytic debenzylation and concomitant NN-cleavage with Raney nickel, and *N*-acetylation, furnished methyl *O*-(2,4,6-tri-*O*-*tert*-butyldimethylsilyl- β -D-galactopyranosyl)-(1 \rightarrow 4)-2-acetamido-3,6-di-*O*-*tert*-butyldimethylsilyl-2-deoxy- β -D-glucopyranoside (**7**) in high yield. Desilylation of **4**, then *O*-acetylation, methyl glycoside formation with methanol- $\text{BF}_3 \cdot \text{OEt}_2$, hydrogenolytic debenzylation, and NN-cleavage with Raney nickel, and *N*-acylation afforded methyl *O*-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)-(1 \rightarrow 4)-2-acetamido-3,6-di-*O*-acetyl-2-deoxy- β -D-glucopyranoside (**10**).

INTRODUCTION

Lactosamine is found as a constituent of various oligosaccharides, for example the *lactoneo*-series²; therefore, a convenient synthesis from readily available lactose or lactal would be advantageous. The most common methods used for amino sugar synthesis are $\text{S}_{\text{N}}2$ reaction of epoxides or sulfonates with a nitrogen nucleophile³ (generally azide), reduction of CN-double bonds⁴ as in oximes, and azidonitration of glycals^{5,6}. Rokach and co-workers⁷ employed a photoactivated hetero-Diels–Alder reaction of dibenzyl azodicarboxylate with *O*-silyl-protected lactal for the stereoselective attachment of nitrogen at C-2 with simultaneous generation of glycosyl donor properties at C-1 (formation of an imidate intermediate). However, in our hands, the glycosyl donor properties of this intermediate were insufficient for the synthesis of complex oligosaccharides⁸. Additionally, the photoconversion of the (*E*)-azodicarboxylate into the (*Z*) isomer, required for reactivity increase in the cycloaddition step, limited the large-scale preparation of

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the starting material. Therefore, we envisaged a thermal inverse-type hetero-Diels–Alder reaction with a more electron deficient (more reactive) heterodiene, which should at the same time lead to higher glycosyl donor properties in the cycloadduct. With this aim, we investigated the commercially available (Aldrich) bis(2,2,2-trichloroethyl) azodicarboxylate (**2**) as heterodiene because the cycloadduct is then related to the highly reactive *O*-glycosyl trichloroacetimidates^{9,10}.

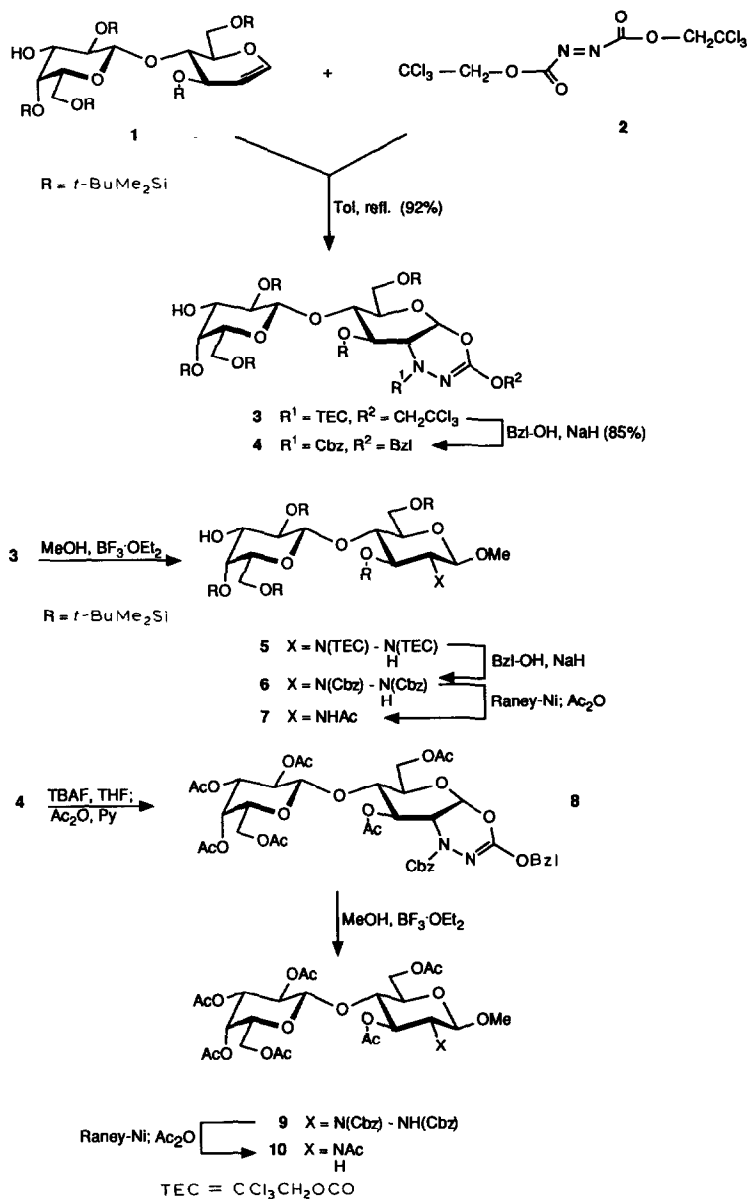
RESULTS AND DISCUSSION

Replacement of the benzyl group by the 2,2,2-trichloroethyl group in the azodicarboxylate led to the expected increase in reactivity towards the *O*-silyl-protected lactal **1**⁷ as heterodienophile. Thus, reaction of **1** and **2** in refluxing toluene afforded stereoselectively the oxadiazine adduct **3** in practically quantitative yield. This reaction could be carried out on any scale. However, reaction of **2** with *O*-benzyl-protected lactal resulted in uncontrolled product formation; this is presumably due to competing ene-type reactions with the benzyl moieties. The structure of **3** was readily confirmed by transesterification with sodium benzyl oxide in benzyl alcohol which provided the known compound **4**⁷ in high yield.

Methyl glycoside formation from **3** in dichloromethane–methanol (1:1) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ gave, by $\text{S}_{\text{N}}2$ -type displacement at the anomeric center, exclusively the β -glycoside **5**. Commonly used methods for the removal of the trichloroethyl group, such as activated zinc in methanol¹¹, in acetic acid¹², or in aqueous buffer¹³, failed in the reaction with **5**. Therefore, exchange of the trichloroethoxy group in **5** by the benzyloxy group was again performed with sodium benzyl oxide–benzyl alcohol, to furnish compound **6**. Hydrogenolytic debenzilation and concomitant cleavage of the NN-bond of the hydrazine moiety were performed with Raney nickel in acetic acid–methanol; ensuing treatment with acetic anhydride furnished the *O*-silyl-protected *N*-acetylactosamine derivative **7**, as confirmed by ¹H NMR data.

Compound **4** was readily transformed into the *O*-acetyl-protected derivative **8** by treatment with tetrabutylammonium fluoride (TBAF) in THF and then with acetic anhydride in pyridine. Methyl glycoside formation from **8** in dichloromethane–methanol in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ gave again exclusively the β -lactoside derivative **9**. Hydrogenolytic debenzilation, cleavage of the NN-bond, and *N*-acylation were carried out as described above, thus providing the *O*-acetyl-protected *N*-acetylactosamine derivative **10** as confirmed by comparison of the ¹H NMR data with the reported data¹⁴.

An investigation employing the oxadiazine derivative **3** as glycosyl donor and various sugars as glycosyl acceptors led only to moderate yields⁸. The best results were obtained in dichloromethane as solvent with $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst. However, even with reactive primary hydroxy groups, the yields never exceeded 50%; therefore, this approach to oligosaccharide synthesis is not competitive with existing methodologies.



EXPERIMENTAL

General methods.—Optical rotations were determined with a Perkin–Elmer 241 MC polarimeter at 20°C. ^1H NMR spectra were recorded for solutions in CDCl_3 (internal Me_4Si) with a Bruker WM 250 (or AC 250) cryospec instrument and a Jeol JNM GX 400 instrument. R_f values refer to TLC performed on Silica Gel 60

F₂₅₄ (Merck). Flash chromatography was performed with Silica Gel (Baker particle size 40 μ m). The bp of the light petroleum (PE) was 35–65°C.

2-(2,2,2-Trichloroethoxy)-4-(2,2,2-trichloroethoxycarbonyl)-[3,6-di-O-tert-butyl-dimethylsilyl-1,2-dideoxy-4-O-(2,4,6-tri-O-tert-butyltrimethylsilyl- β -D-galactopyranosyl)- α -D-glucopyranosyl][2,1e]-1,3,4-oxadiazine (3).—A solution of O-(2,4,6-tri-O-tert-butyltrimethylsilyl- β -D-galactopyranosyl)-(1 \rightarrow 4)-1,5-anhydro-3,6-di-O-tert-butyltrimethylsilyl-2-deoxy-D-arabino-hex-1-enitol⁸ (1) (4.4 g, 5.0 mmol) and bis-(2,2,2-trichloroethyl) azodicarboxylate (2; 3.8 g, 10 mmol) in toluene (100 mL) was heated under reflux for 18 h. Concentration of the mixture in vacuo and flash chromatography of the residue (20:1 PE–MeOAc) yielded 3 (5.8 g, 92%) as a colourless foam; R_f 0.43 (15:1 PE–MeOAc); $[\alpha]_D -287^\circ$ (c 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.00–0.10 (m, 30 H, 10 SiMe), 0.83–0.89 (m, 45 H, 5 *t*-Bu), 1.87 (d, 1 H, $J_{3',OH}$ 6.6 Hz, OH-3'), 3.23 (ddd, 1 H, H-5'), 3.31 (ddd, 1 H, H-3'), 3.56–3.76 (m, 6 H), 3.91 (t, 1 H, J 9.5 Hz), 4.03 (bs, 1 H, H-4'), 4.10 (d, 1 H, J 11.0 Hz), 4.48 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 4.54 (d, 1 H, J 11.7 Hz, CH₂CCl₃), 4.60 (bd, 1 H, H-2), 4.73 (d, 1 H, J 11.7 Hz, CH₂CCl₃), 4.92 (2 d, 2 H, CH₂CCl₃), 5.60 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1). Anal. Calcd for C₄₈H₉₄Cl₆N₂O₁₃Si₅; C, 45.74; H, 7.52; N, 2.22. Found: C, 45.81; H, 7.49; N, 2.32.

2-Benzoyloxy-4-benzoyloxycarbonyl-[3,6-di-O-tert-butyltrimethylsilyl-1,2-dideoxy-4-O-(2,4,6-tri-O-tert-butyltrimethylsilyl- β -D-galactopyranosyl)- α -D-glucopyranosyl][2,1e]-1,3,4-oxadiazine (4).—To benzyl alcohol (50 mL) was added NaH (110 mg, 4.6 mmol), and to the clear solution was added 3 (1 g, 79 mmol). After 7 h at 60°C, the mixture was filtered over a short column of silica gel and concentrated in vacuo (0.1 mbar). Flash chromatography (13:1 PE–MeOAc) gave 4 (791 mg, 85%); R_f 0.61 (5:1 PE–MeOAc); $[\alpha]_D -37.5^\circ$ (c 1, CHCl₃) [lit.⁸ $[\alpha]_D -43.5^\circ$ (c 1, Me₂CO)]. The ¹H NMR data agree with those reported⁸. Anal. Calcd for C₄₅H₁₀₄N₂O₁₃Si₅; C, 59.14; H, 8.90; N, 2.38. Found: C, 59.03; H, 8.89; N, 2.31.

Methyl O-(2,4,6-tri-O-tert-butyltrimethylsilyl- β -D-galactopyranosyl)-(1 \rightarrow 4)-3,6-di-O-tert-butyltrimethylsilyl-2-deoxy-2-[1,2-di(2,2,2-trichloroethoxycarbonyl)hydrazino]- β -D-glucopyranoside (5).—To a solution of 3 (1.0 g, 0.79 mmol) in 1:1 CH₂Cl₂ – MeOH (10 mL) was added dropwise a BF₃ · OEt₂ solution (0.1 M in CH₂Cl₂, 1 mL). After 30 min, the mixture was neutralized with NaHCO₃ (100 mg), filtered, and concentrated in vacuo. Flash chromatography (15:1 PE–MeOAc) afforded 5 (1.02 g, 100%); R_f 0.5 (9:1 PE–MeOAc); $[\alpha]_D -0.5^\circ$ (c 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.01–0.18 (m, 30 H, 10 SiMe), 0.85–0.89 (m, 45 H, 5 *t*-Bu), 1.90 (d, 1 H, J 6.1 Hz, OH-3'), 3.08 (m, 1 H), 3.23 (ddd, $J_{5',6'}$ 9.3, J 4.9 Hz, H-5'), 3.33 (m, 1 H, H-3'), 3.44 (s, 3 H, OMe), 3.53 (dd, J 9.5, J 4.9 Hz), 3.61 (m, 1 H), 3.67 (dd, J 9.5 Hz), 3.77–3.82 (m, 3 H), 4.03 (dd, 2 H, H-4'), 4.51–4.90 (m, 5 H, H-1,1'). Anal. Calcd for C₄₉H₉₈Cl₆N₂O₁₄Si₅; C, 45.54; H, 7.64; N, 2.17. Found: C, 45.54; H, 7.62; N, 2.25.

Methyl O-(2,4,6-tri-O-tert-butyltrimethylsilyl- β -D-galactopyranosyl)-(1 \rightarrow 4)-3,6-di-O-tert-butyltrimethylsilyl-2-deoxy-2-[1,2-di(benzoyloxycarbonyl)hydrazino]- β -D-glucopyranoside (6).—The transesterification of compound 5 (1.0 g, 0.77 mmol) with

sodium benzyl oxide–benzyl alcohol was carried out as described for **4**. Flash chromatography (8:1 PE–MeOAc) yielded **6** (800 mg, 85%); R_f 0.52 (5:1 PE–MeOAc); $[\alpha]_D + 4.6^\circ$ (c 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.00–0.14 (m, 30 H, 10 SiMe), 0.78–0.89 (m, 45 H, 5 *t*-Bu), 1.90 (d, 1 H, *J* 6.1 Hz, OH-3'), 3.07 (m, 1 H), 3.2 (ddd, $J_{5',6'}$ 9.2, *J* 4.9 Hz, H-5'), 3.32 (m, 1 H, H-3'), 3.42 (bs, 3 H, OMe), 3.50–4.03 (m, 9 H), 4.49 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1), 4.52 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 5.06–5.30 (m, 4 H), 7.26–7.35 (m, 10 H, 2 CH₂Ph). Anal. Calcd. for C₅₉H₁₀₈N₂O₁₄Si₅ · 0.67H₂O: C, 57.99; H, 9.02; N, 2.29. Found: C, 58.00; H, 8.99; N, 2.04.

Methyl O-(2,4,6-tri-O-tert-butyltrimethylsilyl-β-D-galactopyranosyl)-(1 → 4)-2-acetamido-3,6-di-O-tert-butyltrimethylsilyl-2-deoxy-β-D-glucopyranoside (7).—To a solution of **6** (500 mg, 0.41 mmol) in dry MeOH (5 mL) was added Raney nickel (1 g) and glacial AcOH (10 drops), and the mixture was treated with H₂ under a pressure of 4 bar. After 24 h, solid NaHCO₃ (0.5 g) was added and the mixture was filtered over Celite. The filtrate was evaporated, and codistilled with toluene and then with Ac₂O. Flash chromatography (3:1 PE–MeOAc) gave **7** (298 mg, 75%); R_f 0.43 (3:1 PE–MeOAc); $[\alpha]_D - 9.5^\circ$ (c 1, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 0.00–0.11 (m, 30 H, 10 SiMe), 0.84–0.90 (m, 45 H, 5 *t*-Bu), 1.90 (d, 1 H, *J* 5.8 Hz, OH-3'), 1.95 (s, 3 H, CH₃CON), 3.20–3.39 (m, 3 H, H-2,2'), 3.40 (s, 3 H, OMe), 3.51–4.00 (m, 6 H), 4.44 (d, 1 H, *J* 7.6 Hz, H-1 or -1'), 4.53 (d, 1 H, *J* 7.0 Hz, H-1' or -1), 5.45 (d, $J_{2,NH}$ 8.5 Hz, NH). Anal. Calcd for C₄₅H₉₇NO₁₁Si₅: C, 55.80; H, 10.09; N, 1.45. Found: C, 55.70; H, 10.10; N, 1.50.

2-Benzoyloxy-4-benzoyloxycarbonyl-[3,6-di-O-acetyl-1,2-dideoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranosyl][2,1e]-1,3,4-oxadiazine (8).—To a solution of **4** (680 mg, 0.58 mmol) in dry THF (10 mL) was added dropwise at 0°C tetrabutylammonium fluoride solution in THF (1 M, 7.5 mL). After 18 h, the mixture was evaporated and the residue dissolved in 1:1 pyridine–Ac₂O (20 mL). After 24 h, the mixture was concentrated and codistilled with toluene. Flash chromatography (1:1 PE–MeOAc) afforded **8** (370 mg, 75%); R_f 0.47 (1:1 PE–MeOAc); $[\alpha]_D - 6.1^\circ$ (c 1, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 1.93–2.12 (6 s, 18 H, 6 CH₃CO), 3.79–4.14 (m, 6 H), 4.44–4.48 (m, 2 H, H-1'), 4.76 (m, 1 H), 4.92 (dd, 1 H, *J* 10.4, *J* 3.4 Hz), 5.04–5.32 (m, 7 H, 2 CH₂Ph), 5.49 (m, 1 H), 7.28–7.45 (m, 10 H, 2 CH₂Ph). Anal. Calcd for C₄₀H₄₆N₂O₁₉ · 0.5 H₂O: C, 55.36; H, 5.46; N, 3.23. Found: C, 55.33; H, 5.44; N, 3.11.

Methyl O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-O-acetyl-2-deoxy-2-[1,2-di(benzoyloxycarbonyl)hydrazino]-β-D-glucopyranoside (9).—Compound **9** was prepared as described for **5**, starting from **8** (200 mg, 230 μmol) in 1:1 CH₂Cl₂–MeOH (2 mL) and BF₃ · OEt₂ (0.1 M solution in CH₂Cl₂, 0.5 mL). Flash chromatography (4:1 toluene–Me₂CO) yielded **9** (176 mg, 85%); R_f 0.41 (3:1 toluene–Me₂CO); $[\alpha]_D + 11.5^\circ$ (c 1, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 1.73–2.12 (6 s, 18 H, 6 CH₃CO), 3.50 (bs, 3 H, OMe), 3.81 (m, 2 H), 4.05 (m, 3 H), 4.25 (m, 1 H), 4.42 (d, 1 H, *J* 7.9 Hz, H-1 or -1'), 4.48 (d, 1 H, *J* 7.9 Hz, H-1' or -1), 4.89–5.32 (m, 8 H, 2 CH₂Ph), 7.27–7.35 (m, 10 H, 2 CH₂Ph). Anal. Calcd for

$C_{41}H_{50}N_2O_{20} \cdot 0.5H_2O$: C, 54.73; H, 5.71; N, 3.11, Found: C, 54.63; H, 5.77; N, 3.04.

Methyl O-(2,3,4,6-tetra-O-acetyl- β -D-galactopyranosyl)-(1 \rightarrow 4)-2-acetamido-3,6-di-O-acetyl-2-deoxy- β -D-glucopyranoside (10).—Hydrogenation and *N*-acetylation of **9** (150 mg, 167 μ mol) was carried out as described for **7**. Flash chromatography (25:1 CH_2Cl_2 –MeOH) gave **10** (82 mg, 75%); R_f 0.65 (9:1 CH_2Cl_2 –MeOH); $[\alpha]_D -16.5^\circ$ (c 1, MeOH) {lit.¹⁴ $[\alpha]_D^{25} -18.0^\circ$ (c 1.3, $CDCl_3$)}; 1H NMR (250 MHz, $CDCl_3$): δ 1.95, 1.95, 2.03, 2.03, 2.05, 2.10, 2.13 (7 s, 21 H, 7 CH_3CO), 3.43 (s, 3 H, OMe), 3.61 (m, 1 H), 3.77 (dd, 1 H, J 8.2 Hz), 3.86 (dd, 1 H, J 6.8 Hz), 4.00–4.15 (m, 4 H), 4.33 (d, 1 H, J 7.5 Hz, H-1 or -1'), 4.48 (d, m, 2 H, J 7.8 Hz, H-1' or -1), 4.95 (dd, 1 H, $J_{2',3'}$ 10.5, $J_{3',4'}$ 3.4 Hz, H-3'), 5.07 (2 dd, 2 H, H-3,2'), 5.34 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{4',5'}$ 1.0 Hz, H-4'), 5.62 (d, $J_{2,NH}$ 9.4 Hz, NH). The 1H NMR data agree with those reported¹⁴. Anal. Calcd for $C_{27}H_{39}NO_{17} \cdot 0.5H_2O$: C, 49.24; H, 6.12; N, 2.23. Found: C, 49.10; H, 6.24; N, 1.97.

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REFERENCES

- 1 B. Haag-Zeino and R.R. Schmidt, *Liebigs Ann. Chem.*, (1990) 1197–1203.
- 2 R. Bommer, W. Kinzy, and R.R. Schmidt, *Liebigs Ann. Chem.*, (1990) 425–433; R.R. Schmidt and A. Toepfer, *Tetrahedron Lett.*, 32 (1990) 3353–3356; A. Toepfer and R.R. Schmidt, *ibid.*, 33 (1992) 5161–5164.
- 3 H. Gnichtel, D. Rebentisch, T.C. Tompkins, and P.H. Gross, *J. Org. Chem.*, 47 (1982) 2691–2697.
- 4 G.S. Hajivarnava, W.G. Overend, and N.R. Williams, *J. Chem. Soc., Perkin Trans. 1*, (1982) 205–214.
- 5 R.U. Lemieux and T.L. Nagabushan, *Can. J. Chem.*, 46 (1968) 401–403; R.U. Lemieux and R.M. Ratcliffe, *ibid.*, 57 (1979) 1244–1251.
- 6 I. Dyong and G. Schulte, *Tetrahedron Lett.*, 21 (1980) 603–606.
- 7 B.J. Fitzsimmons, Y. Leblanc, and J. Rokach, *J. Am. Chem. Soc.*, 109 (1987) 285–286; B.J. Fitzsimmons, Y. Leblanc, N. Chan Wai Ling, and J. Rokach, *ibid.*, 110 (1988) 5229–5231; Y. Leblanc, B.J. Fitzsimmons, J.P. Springer, and J. Rokach, *ibid.*, 111 (1989) 2995–3000; R. Grondin, Y. Leblanc, and K. Hoogsten, *Tetrahedron Lett.*, 32 (1991) 5021–5024.
- 8 A. Toepfer, Dissertation, University of Konstanz, 1992; A. Toepfer and R.R. Schmidt, unpublished results.
- 9 R.R. Schmidt and J. Michel, *Angew. Chem.*, 92 (1980) 763–764; *Angew. Chem. Int. Ed. Engl.*, 19 (1980) 731–732.
- 10 R.R. Schmidt, *Angew. Chem.*, 98 (1986) 213–236; *Angew. Chem. Int. Ed. Engl.*, 25 (1986) 212–235; *Pure Appl. Chem.*, 61 (1989) 1257–1270.
- 11 T. Windholz and T. Johnston, *Tetrahedron Lett.*, (1967) 2555–2558.
- 12 R.B. Woodward, K. Hensler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Am. Chem. Soc.*, 88 (1966) 852–853.
- 13 G. Just and K. Grozinger, *Synthesis*, (1976) 457–458.
- 14 J. Dahmen, G. Gnosspeliuss, A.C. Larsson, T. Lave, G. Noori, K. Paalsson, T. Frejd, and G. Magnusson, *Carbohydr. Res.*, 138 (1985) 17–28.