A Modular System for the Synthesis of Complex *N*-Glycans**

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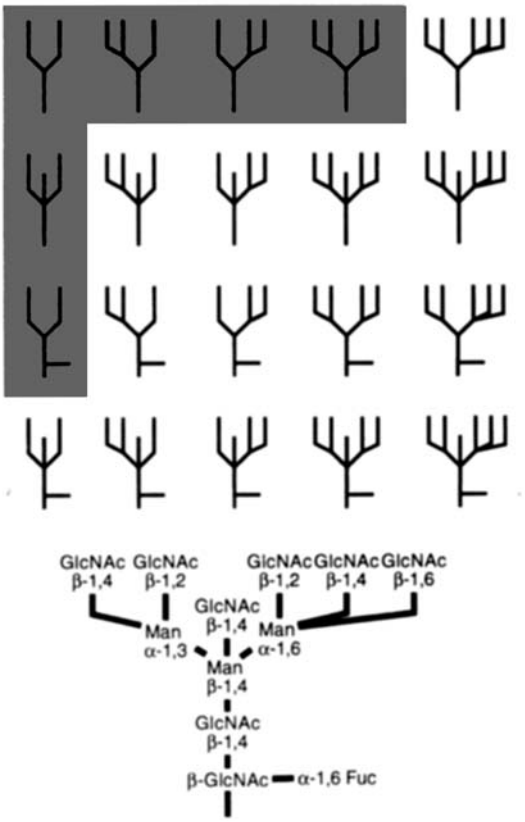
The aparagine-bound oligosaccharides found in glycoproteins (*N*-glycans) vary in their degree of branching, the terminal sugars, and the substitution of the core pentasaccharide.[1] A divergent combination of the possible linkages leads to thousands of related oligosaccharide structures. This phenomenon is also known as microheterogeneity.[2] Therefore, glycoproteins can be viewed as natural libraries, whose elements are very similar but show a high degree of diversity in the detailed structures. Complex *N*-glycans are classified by the number of branches, ranging from two to five, and by characteristic substitutions of the core pentasaccharide (Scheme 1). In the case of the pharmaceutically important glycoprotein hormone erythropoietin (EPO), the in vivo biological activity[3] of the glycoform with tetraantennary *N*-glycans was significanty greater that that of biantennary structures.



Scheme 1. Twenty individual basic structues can be distinguished for complex *N*-glycans. They result from a combination of five different degrees of branching (first row) with core substitutions by "bisecting" GlcNAc residues (second row) or core fucosylation (third row), or both modifications (fourth row). Seven examples of this class of compounds (in the grey box) were synthesized by a flexible system of oligosaccharide building blocks.

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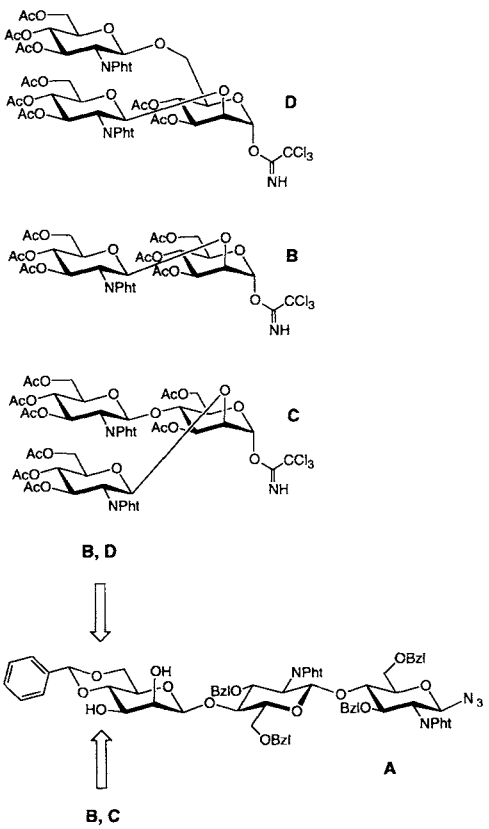
Up to now the synthesis[4] of biantennary sialylated *N*-glycans[5] was only demonstrated in a few examples. Partial structures of complex tri- and tetraantennary *N*-glyans were chemically synthesized.[6] Entire multiantennary *N*-glycans are only accessible in small amounts by tedious isolation procedures[7] from natural sources or by semisynthesis.[8] The biosynthesis of *N*-glycans is carried out stepwise by a number of glycosyltransferases, however, only a few of the *N*-acetylglucosaminyltransferases[2c] responsible for branching have been cloned and overexpressed. In the course of this work a series of modular building blocks which provide access to synthetic tri- and tetraantennary *N*-glycans was devised (Scheme 2).



Scheme 2. The building blocks **A**–**D**; Pht = phthaloyl.

A new strategy was developed recently to obtain biantennary *N*-glycans by chemical synthesis.[9] Starting from core trisaccharide **A** (Scheme 2), positions 3 and 6 of the central β-mannosyl residue were glycosylated regio- and stereoselectively[5c] using donor **B**. Subsequent elongation of the carbohydrate chains by enzymatic synthesis gave sialylated biantennary *N*-glycans.[5c] The concept of double regioselective glycosylation of **A** could be extended and applied to the synthesis of the tri- and tetraantennary *N*-glycans **2**, **5**, and **6**. The products shown in Schemes 3 and 4 represent the most frequently found branching patterns for *N*-glycans. Together with **A** and **B** the newly synthesized trisaccharide building blocks **C** and **D** form a modular system. This allowed the multiple use of valuable intermediates to obtain various basic structures of *N*-glycans. A crucial requisite for the success of this concept was the optimized protecting-group pattern of the building blocks, and the high reactivity at the connection points provided by the vicinal diol structure of the acceptors.

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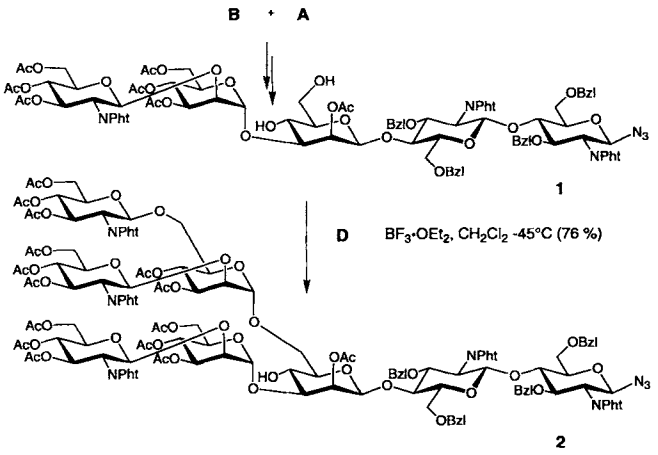
The temporary allyl and benzyl groups required for the synthesis of **C**[10] und **D**[13] were replaced by acetate groups. Benzyl functionalitites in the mannosyl part of the donors may lead to β-configured side products during glycosylation.[6c] The three α-configured imidates **B**–**D** follow the same protecting-group pattern which was expected to facilitate deprotection of these parts of the molecule.

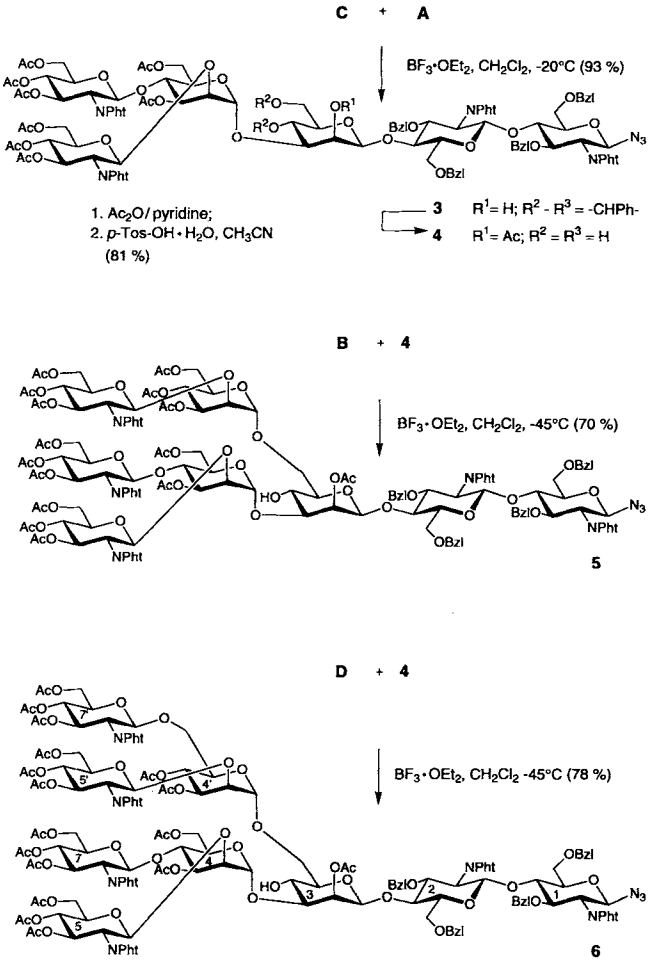
Pentasaccharide **1** was obtained as an intermediate[5c] during the synthesis of biantennary *N*-glycans starting from core trisaccharide **A** and donor **B** (Scheme 3). Elongation of pentasaccharide **1** with the imidate **B** gave the heptasaccharide in 73% yield. To achieve selective reaction at the primary hydroxyl group, the glycosylation was performed under dilute conditions. Otherwise overreaction at the second OH functionality occurred. As an initial test of the glycosylating properties of the branched and thus sterically more demanding trisaccharide imidate **D**, the coupling with pentasaccharide **1** was examined. Activation of the imidate **D** under dilute conditions with $BF_3 \cdot OEt_2$ gave the triantennary octasaccharide **2**[16] in 76% yield (Table 1). The α-1,6-linked product was formed selectively. This was confirmed by the characteristic downfield shift of the ^{13}C NMR signal for C-6^3 (60.4 → 66.3) and a C-1,H-1 coupling constant[17] of 176.2 Hz for C-1$^{4'}$, which is typical for α-mannosides.



Scheme 3. Synthesis of **1** and **2**.

A steric hindrance during the regioselective glycosylation at OH-3^3 of the core trisaccharide **A** with the branched donor **C** was not observed. The coupling to hexasaccharide **3** proceeded with an unexpectedly high yield of 93%(Scheme 4). The newly formed α-1,3-linkage was verified by NMR spectroscopy: the signal for C-3^3 of **3** is shifted from $\delta = 69.9$ to 78.0, and J(C-1,H-1) is 172.7 Hz for C-1^4. Acetylation of the free hydroxyl group in **3** followed by debenzylidenation with *p*-toluenesulfonic acid gave the hexasaccharide diol **4**. These conditions permitted acidic acetal cleavage without affecting the numerous acetyl groups. Subsequently, the linear donor **B** was coupled with the acceptor **4** to the triantennary octasaccharide **5**[16] in 70% yield (Table 1). The presence of the branched mannoside in the 1,3-arm of **4** did not affect the reaction at the primary OH group.

The sterically most demanding glycosylation of the hexasaccharide acceptor **4** also proceeded regio- and stereoselectively with the trisaccharide building block **D** (Scheme 4). Nonasaccharide **6**,[16] a partial structure of tetraantennary *N*-glycans, was obtained in 78% yield (Table 1). Others have reported difficulties in the formation of glycosidic linkages using branched donors.[18]



Scheme 4. Synthesis of **3**–**6**.

Surprisingly, a comparison of the glycosylation yields showed that under identical conditions the branched trisaccharide imidates **C** and **D** gave even higher yields than the linear disaccharide **B**. It may be assumed that the reactivity of the trisaccharides **C** and **D** is lower than that of **B**, and, because of the slower rearrangement to the unreactive trichloroacetamides,[19] higher yields are obtained. However, higher yields should only be observed when steric hindrance is not increased. Therefore, combining donors **C** and **D** with the complex acceptors carrying two adjacent OH groups is favored from a steric point of view. The protected compounds **1**–**6** were purified by flash chromatography and characterized by NMR spectroscopy with HMQC, HMQC-COSY, HMQC-DEPT, HMQC-TOCSY, TOCSY, and NOESY experiments.[20]

The often problematic removal of phthalimido groups was examined for compound **6**, which was converted into the water-soluble nonasaccharide **7** in three steps (Scheme 5). A one-pot reaction with ethylenediamine in *n*-butyl alcohol[21] followed by an acetylation–deacetylation sequence proceeded smoothly, as seen previously for the deprotection of the biantennary parent compound.[5c] Solid-phase extraction furnished the deprotected nonasaccharide **7**[16] in high yield. The remaining protecting groups in the chitobiosyl part are strategically valuable. They allow the construction of glycoconjugates through an *N*-glycosidic bond at the anomeric center, and facilitate purification by reversed-phase HPLC.[5c]

An additional extension of this flexible synthesis concept was demonstrated recently by incorporation of a modified building block **A**, which led to core-fucosylated *N*-glycans.[22] Further-

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Table 1. Physical and spectroscopic data for **2**, **5**, **6**, and **7** [16]. Only representative NMR data are given for compounds **2** and **5** [a].

2: $[\alpha]_D^{23} = -13.3°$ ($c = 0.5$ in dichloromethane); $C_{146}H_{150}N_8O_{60}$ (2976.81); FAB-MS (NBA): $M_{calcd} = 2974.9$, $M_{found} = 2976$ ($M+H^+$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 97.7$ (C-1^4α, J(C-1,H-1) = 176.2 Hz in a coupled HMQC spectrum), 97.6 (C-1$^{7'}$), 96.9 (C-1^3), 96.64 (C-1$^{4'}$$\alpha$, J(C-1,H-1) = 176.2 Hz), 96.62 (C-1^2), 96.0 (C-1^5), 95.9 (C-1$^{5'}$), 84.7 (C-1^1).

5: $[\alpha]_D^{23} = +4.0°$ ($c = 0.5$ in dichloromethane); $C_{146}H_{150}N_8O_{60}$ (2976.81); FAB-MS (NBA): $M_{calcd} = 2974.9$, $M_{found} = 2099.1$ ($M+Na^+$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 97.7$ (C-1^4α, J(C-1,H-1) = 177.6 Hz), 97.1 (C-1$^{4'}$$\alpha$, J(C-1,H-1) = 177.6 Hz), 96.8 (C-1^2), 96.7 (C-1^3), 96.4 (C-1$^{5'}$), 96.2 (C-1^5), 95.3 (C-1^7), 84.8 (C-1^1).

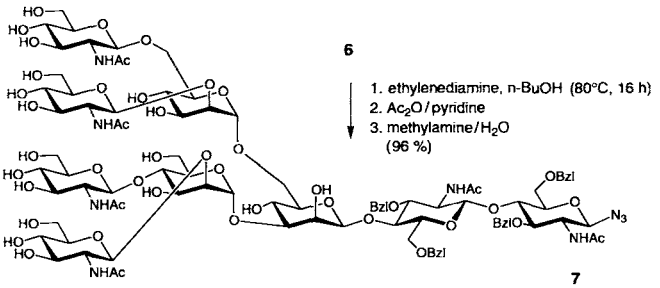
6: $[\alpha]_D^{23} = -2.1°$ ($c = 0.5$ in dichloromethane); $C_{164}H_{167}N_9O_{68}$ (3352.14); FAB-MS (NBA): $M_{calcd} = 3350.0$, $M_{found} = 3377.5$ ($M+Na^+$); ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta = 8.04-7.60$ (m, 24H, Pht), 7.30–6.70 (m, 20H, Ar), 5.64 (m, 1H, H-3^5), 5.62 (m, 1H, H-3^7), 5.48–5.39 (m, 3H, H-1^7, H-3$^{5'}$, H-3$^{7'}$), 5.31 (d, J(1,2) = 8.5 Hz, 1H, H-1^5), 5.29 (d, J(OH-4,4) = 5.2 Hz, 1H, OH-4^3), 5.25 (d, J(1,2) = 9.5 Hz, 1H, H-1^1), 5.18–5.12 (m, 2H, H-1^2, H-1$^{5'}$), 5.04–4.97 (m, 3H, H-2^3, H-4^5, H-4^7), 4.94 (d, J(1,2) = 8.2 Hz, 1H, H-1^7), 4.89 (dd, J(3,4) = J(4,5) = 9.5 Hz, 1H, H-4$^{5'}$), 4.85–4.80 (m, 3H, H-4$^{7'}$, H-3$^{4'}$, CH$_2$O), 4.76–4.70 (m, 3H, H-1^4, H-3^4, H-4$^{4'}$), 4.50–4.42 (m, 3H, H-1^3, CH$_2$O), 4.39 (d, J_{gem} = 12.2 Hz, 1H, CH$_2$O), 4.37–3.82 (m, 25H), 3.80–3.62 (m, 6H, H-2^1, H-2$^{7'}$, H-4^4, H-5^4, H-5$^{4'}$, H-6b$^{5'}$), 3.59 (m, 1H, H-6a^2), 3.57–3.50 (m, 2H, H-5^1, H-5$^{7'}$), 3.48–3.36 (m, 4H, H-6a^1, H-6b^2, H-6b^4, H-6a$^{4'}$), 3.30–3.17 (m, 6H, H-3^3, H-4^3, H-5^2, H-5$^{5'}$, H-6b^1, H-6a^3), 3.04–2.94 (m, 2H, H-6b^3, H-6b$^{4'}$), 2.90 (m, 1H, H-5^3), 2.02, 2.015, 2.01, 2.0, 1.98, 1.96, 1.92, 1.78, 1.77, 1.76, 1.75, 1.74, 1.73, 1.68, 1.63 (15s, 51H, OAc); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 170.1-167.2$ (C=O), 138.3, 138.1, 138.0 (*ipso*-C, Ar), 135.1, 134.9, 134.6 (C-4/5, Pht), 130.9, 130.7, 130.6, 130.5 (C-1/2, Pht), 128.2–127.0 (C-Ar), 123.8, 123.7, 123.4 (C-3/6, Pht), 97.9 (C-1^4α, J(C-1,H-1) = 180.0 Hz), 97.7 (C-1$^{7'}$), 96.70 (C-1^2, C-1^3β, J(C-1,H-1) = 162.7 Hz), 96.65 (C-1$^{4'}$$\alpha$, J(C-1,H-1) = 172.6 Hz), 96.2 (C-1^5), 96.0 (C-1$^{5'}$), 95.3 (C-1^7), 84.7 (C-1^1), 77.0 (C-4^2), 76.8 (C-3^1), 76.6 (C-3^3), 75.7 (C-5^1), 75.5 (C-3^2), 75.3 (C-4^1), 74.3 (C-5^3), 74.2 (C-5^2), 73.9 (CH$_2$O), 73.4 (C-2^4), 73.3 (C-2$^{4'}$), 73.2, 72.3 (CH$_2$O), 71.6 (CH$_2$O, C-4^4), 71.0 (C-5^5), 70.8 (C-5$^{7'}$), 70.7 (C-5$^{5'}$), 70.5 (C-5^7), 70.3 (C-2^3), 70.1 (C-3$^{7'}$), 69.9 (C-3$^{5'}$, C-3^7), 69.8 (C-3^5), 69.6 (C-3$^{4'}$), 68.8 (C-3^4), 68.6 (C-4^5), 68.5 (C-5$^{4'}$), 68.4 (C-4$^{7'}$), 68.3 (C-4$^{5'}$), 68.2 (C-4^7), 67.9 (C-5^4, C-6$^{4'}$), 67.4 (C-6^1, C-6^2), 66.5 (C-6^3), 66.2 (C-4^3), 64.8 (C-4$^{4'}$), 61.9 (C-6^4, C-6^5), 61.5 (C-6$^{7'}$), 61.4 (C-6$^{5'}$, C-6^7), 55.8 (C-2^2), 54.6 (C-2^1), 54.5 (C-2^7), 53.9 (C-2$^{7'}$), 53.8 (C-2^5, C-2$^{5'}$), 20.4, 20.2, 20.1, 20.0, 19.8 (OAc).

7: $[\alpha]_D^{23} = -27.9°$ ($c = 0.5$ in water); $C_{94}H_{133}N_9O_{45}$ (2109.12); ESI-MS (water/methanol, 1/1): $M_{calcd} = 2107.8$, $M_{found} = 1055.4$ [$(M+2H)^+$]; ^1H NMR (500 MHz, D_2O, [D$_6$]acetone as internal standard): $\delta = 7.36-7.12$ (m, 20H, Ar), 4.98 (d, 1H, J(1,2) < 1.0 Hz, H-1^4), 4.78 (d, J_{gem} = 12.2 Hz, 1H, CH$_2$O), 4.68 (d, J_{gem} = 12.0 Hz, 1H, CH$_2$O), 4.61 (d, 1H, J(1,2) < 1.0 Hz, H-1$^{4'}$), 4.53–4.50 (m, 2H), 4.47–4.31 (m, 6H, H-1^3, H-1^5, H-1^7, H-1$^{7'}$, CH$_2$O), 4.25 (m, 3H, H-1^2, CH$_2$O), 4.10 (m, 2H, H-1$^{5'}$, H-2^4), 3.97–3.92 (m, 3H, H-2^3, H-3^4, H-6a$^{4'}$), 3.22–3.18 (m, 2H, H-5^2, H-5^3), 2.86 (m, 1H, H-5$^{5'}$), 1.91, 1.90, 1.89, 1.88, 1.66, 1.62 (6s, 18H, NAc); ^{13}C NMR (125 MHz, D_2O, [D$_6$]acetone as internal standard): $\delta = 174.9-174.0$ (C=O), 138.6, 138.4, 137.7, 137.6 (*ipso*-C, Ar), 129.1–128.2 (C-Ar, C-1^7), 101.8 (C-1$^{7'}$), 100.7 (C-1^2), 100.5 (C-1^3), 100.2 (C-1^5), 99.8 (C-1$^{5'}$), 99.5 (C-1^4), 96.9 (C-1$^{4'}$), 88.8 (C-1^1), 81.0 (C-3^3), 80.4 (C-3^1), 80.3 (C-3^2), 78.4 (C-4^4), 77.6 (C-4^2), 76.9 (C-2$^{4'}$), 76.5 (C-2^4), 76.3 (C-5^1), 76.24 (C-5^7), 76.16 (C-5^5), 76.14 (C-5$^{7'}$), 75.8 (C-5$^{5'}$), 75.4 (C-4^1), 74.6 (C-5^3), 74.2, 74.10 (CH$_2$O), 74.07 (C-5^2, C-3$^{7'}$), 73.9, 73.6 (C-3^5, C-3^7), 73.3 (C-3$^{5'}$, CH$_2$O), 72.1 (C-5^4), 71.8 (C-5$^{4'}$), 70.7 (C-2^3), 70.3, 70.1 (C-4^5, C-4^7, C-4$^{7'}$, C-6$^{4'}$), 69.9 (C-3$^{4'}$, C-4$^{5'}$), 68.4 (C-3^4), 68.3 (C-6^2), 68.0 (C-6^1), 67.8 (C-4$^{4'}$), 65.8 (C-4^3), 65.6 (C-6^3), 61.4 (C-6^4), 61.1, 61.0 (C-6^5, C-6^7, C-6$^{7'}$), 60.5 (C-6$^{5'}$), 55.9 (C-2$^{5'}$, C-2^7, C-2$^{7'}$), 55.7 (C-2^5), 55.3 (C-2^2), 54.0 (C-2^1), 22.8, 22.7, 22.5, 22.3 (NAc).

[a] NBA = *m*-Nitrobenzyl alcohol, Pht = phthaloyl.

more, the glycosylation of the free OH-4^3 functionality of the heptasaccharide[5c] obtained from compounds **A** and **B** gave access to the class of "bisecting" *N*-glycans.[23]

For the first time the most frequently found basic structures of *N*-glycans could be assembled by a single synthetic scheme. The versatile building blocks **A**–**D** provide an efficient chemical equivalent for the modular structure of these natural oligosaccharides. In the future this will facilitate the synthesis of those *N*-glycans that display biological functions and are difficult to isolate. The final compounds were obtained in high yields throughout. After removal of the majority of the protecting groups, the synthetic *N*-glycans are accessible for functionalization at the anomeric center and enzymatic elongation of the oligosaccharide portion.



Scheme 5. Selective cleavage of the protecting groups: synthesis of **7**.

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[1] Review: E. G. Berger, E. Buddecke, J. P. Kamerling, A. Kobata, J. C. Paulson, J. F. G. Vliegenthart, *Experientia* **1982**, *38*, 1129–1162.

[2] Reviews: a) R. A. Dwek, *Chem. Rev.* **1996**, 96, 683–720; b) A. Varki, *Glycobiology* **1993**, *3*, 97–130; c) H. Schachter, *Biochem. Cell. Biol.* **1984**, *64*, 163–181.

[3] M. Takeuchi, N. Inoue, T. W. Strickland, M. Kobuta, M. Wada, R. Shimizu, S. Hoshi, H. Kozutsumi, S. Takasaki, A. Kobata, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 7819–7822.

[4] Review: H. Paulsen, *Angew. Chem.* **1990**, *102*, 851–857; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 823–839.

[5] a) T. Ogawa, M. Sugimoto, T. Kitajma, K. K. Sadozai, T. Nukada, *Tetrahedron Lett.* **1986**, *27*, 5739–5742; b) Y. Nakahara, S. Shibayama, Y. Nakahara, T. Ogawa, *Carbohydr. Res.* **1996**, *280*, 67–84; c) C. Unverzagt, *Angew. Chem.* **1996**, *108*, 2507–2510; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2350–2353.

[6] a) H. Paulsen, B. Helpap, *Carbohydr. Res.* **1991**, *216*, 289–313; b) J. Kerekgyarto, J. P. Kamerling, J. B. Bouwstra, J. F. G. Vliegenthart, A. Liptak, *ibid.* **1989**, *186*, 51–62; c) K. K. Sadozai, Y. Ito, T. Nukada, T. Ogawa, A. Kobata, *ibid.* **1986**, *150*, 91–101; d) K. K. Sadozai, T. Nukada, Y. Ito, Y. Nakahara, T. Ogawa, A. Kobata, *ibid.* **1986**, *157*, 101–123; e) J. Arnarp, M. Haraldsson, J. Lönngren, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1841–1844; f) *Carbohydr. Res.* **1981**, *97*, 307–313; g) J. Arnarp, J. Lönngren, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2070–2074.

[7] a) S. W. Homanns, R. A. Dwek, D. L. Fernandes, T. W. Rademacher, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 6286–6289; b) T. Endo, *J. Chromatogr. A* **1996**, *720*, 251–261; c) K. G. Rice, M. L. Corradi Da Silva, *ibid.* **1996**, *720*, 235–249.

[8] a) M. H. Chiu, T. Tamura, M. S. Wadhwa, K. G. Rice, *J. Biol. Chem.* **1994**, *269*, 16195–16202; b) M. H. Chiu, V. H. Thomas, H. J. Stubbs, K. G. Rice, *ibid.* **1995**, *270*, 24024–24031; c) C.-H. Lin, M. Shimazaki, C.-H. Wong, M. Koketsu, R. R. Juneja, M. Kim, *Bioorg. Med. Chem.* **1995**, *3*, 1625–1630; d) J. Helin, H. Maaheimo, A. Seppo, A. Keane, O. Renkonen, *Carbohydr. Res.* **1995**, *266*, 191–209.

[9] C. Unverzagt, *Angew. Chem.* **1994**, *106*, 1170–1173; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1102–1104.

[10] Donor **C** was obtained by the following reaction sequence: a) benzyl 3,6-di-*O*-allyl-α-D-mannopyranoside [11] and 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-α,β-D-glucopyranosylfluoride [12], CH_2Cl_2, molecular sieves (4 Å), $BF_3 \cdot Et_2O$ (81%); b) 1. $PdCl_2$, NaOAc, AcOH; 2. Ac_2O/pyridine, 4-dimethylaminopyridine (DMAP) (77%); c) 1. Pd/H_2, MeOH; 2. CCl_3CN, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), CH_2Cl_2 (80%).

[11] J. Arnarp, J. Lönngren, *Acta Chem. Scand. B* **1978**, *32*, 696–697.

[12] C. Unverzagt, H. Kunz, *J. Prakt. Chem.* **1992**, *334*, 570–578.

[13] Donor **D** was obtained by the following reaction sequence: a) benzyl 3,4-di-*O*-benzyl-α-D-mannopyranoside [14] and 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-trichloroacetimidate [15], CH_2Cl_2, molecular sieves (4 Å), $BF_3 \cdot Et_2O$ (53%); b) 1. Pd/H_2, MeOH; 2. Ac_2O/pyridine (70%); c) 1. hydrazine acetate, DMF; 2. CCl_3CN, DBU, CH_2Cl_2 (68%).

[14] J. Arnarp, M. Haraldsson, J. Lönngren, *Carbohydr. Res.* **1981**, *97*, 307–313.

[15] R. R. Schmidt, W. Kinzy in *Adv. Carbohydr. Chem. Biochem. Vol. 50* (Ed.: D. Horton), Academic Press, New York, **1994**, pp. 21–123.

[16] The individual residues are assigned according to **6**.

[17] a) K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293–297; b) S. Wolfe, B. M. Pinto, V. Varma, R. Y. N. Leung, *Can. J. Chem.* **1990**, *68*, 1051–1062.

[18] a) Y.-M. Zhang, A. Brodzky, P. Sinai, G. Saint-Marcoux, B. Perly, *Tetrahedron: Asymmetry* **1995**, *6*, 1195–1216; b) P. Grice, S. V. Ley, J. Pietruszka, H. W. M. Priepke, *Angew. Chem.* **1996**, *108*, 206–208; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 197–200.

  0570-0833/97/3618-1991 $ 17.50+.50/0

[19] F. Cramer, N. Hennrich, *Chem. Ber.* **1961**, *94*, 976–989.
[20] a) H. Kessler, M. Gehrke, C. Griesinger, *Angew. Chem.* **1988**, *100*, 507–554; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 490–536; b) H. Kessler, P. Schmieder, M. Kurz, *J. Magn. Reson.* **1989**, *65*, 400–405.
[21] O. Kanie, S. C. Crawley, M. M. Palcic, O. Hindsgaul, *Carbohydr. Res.* **1993**, *243*, 139–164.
[22] J. Seifert, C. Unverzagt, *Tetrahedron Lett.* **1996**, *37*, 6527–6530.
[23] a) C. Unverzagt, *Abstr. Pap. 17th Int. Carbohydr. Symp.* (Ottawa, Canada), **1994**, B1.66; b) C. Unverzagt, J. Seifert, unpublished results.

Phosphorus(v) Nitride Imide HP_4N_7: Synthesis from a Molecular Precursor and Structure Determination with Synchrotron Powder Diffraction**

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The ammonolysis of phosphorus(v) chloride (PCl_5) leads to chlorine-rich compounds such as $[NPClNH_2]_x$ or to totally substituted compounds such as $[NP(NH_2)_2]_x$, depending on the reaction temperature and the distribution ratio NH_3:PCl_5.[1] Already in the last century a polymeric compound HPN_2 was postulated to be the final product of substitution and condensation.[2–4] However, the ammonolysis of PCl_5 leads to countless oligomeric and polymeric phosphazenes; no single-phase and well-defined product HPN_2 was obtained. Pure and crystalline HPN_2 was synthesized recently by heterogeneous pressure ammonolysis of phosphorus(v) nitride [Eq. (a)].[5] Phosphorus(v)

$$P_3N_5 + NH_3 \xrightarrow{580\,^\circ C} 3HPN_2 \qquad (a)$$

nitride imide (HPN_2) has the framework structure $^3_\infty[(PN_{4/2})^-]$ built up of PN_4 tetrahedra linked by corner-sharing through all four vertices. This structure, which is also found in $LiPN_2$,[6] is derived from the isosteric β-cristobalite type.[5] The hydrogen atoms are bound in an ordered manner to half of the nitrogen atoms.[7]

We recently obtained the novel phosphorus(v) nitride imide HP_4N_7[8] by the reaction of P_3N_5 with ammonium chloride in closed, thick-walled quartz ampoules [Eq. (b)]. However, X-ray

$$4P_3N_5 + NH_4Cl \xrightarrow{820\,^\circ C} 3HP_4N_7 + HCl \qquad (b)$$

powder diffraction measurements indicate that HP_4N_7 is not formed as a single-phase product by this reaction. Furthermore, since it was not possible to obtain single crystals of HP_4N_7, the crystal structure could not yet be elucidated. This structure is nevertheless of particular interest, because HP_4N_7, in addition to P_3N_5, is one of a few highly condensed phosphorus(v) nitrides (molar ratio P:N > 1:2). Therefore, the structure of HP_4N_7 should not be analogous to that of silicates.

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While systematically investigating the development of molecular precursors for the synthesis of well-defined, crystalline nonmetal nitrides (molecular preorganization[9, 10]), we obtained $(NH_2)_2P(S)NP(NH_2)_3$ (**1**).[11] According to thermoanalytical investigations diphosphazene **1** loses H_2S already at 145 °C with formation of amorphous poly(aminoiminophosphazene)s. In contrast, the pyrolysis of **1** in closed pressure ampoules at 750 °C (see Experimental Section) leads to pure and crystalline HP_4N_7 [**2**; Eq. (c)]. During this procedure phosphorus(v) nitride imide

$$\underset{\mathbf{1}}{2(NH_2)_2P(S)NP(NH_2)_3} \xrightarrow{750\,^\circ C} \underset{\mathbf{2}}{HP_4N_7} + 2H_2S + 5NH_3 \qquad (c)$$

(**2**) is formed as a microcrystalline, colorless powder. It is stable in a nonoxidizing atmosphere up to 800 °C; further increase of temperature leads to loss of NH_3 and formation of P_3N_5. HP_4N_7 is insoluble in common solvents as well as in hot acids and alkaline solutions.

The determination and refinement of the crystal structure of HP_4N_7 were based on powder X-ray diffraction data. The measurements were made with synchrotron radiation at the National Synchrotron Light Source in Brookhaven, USA (Beamline X7A). The powder pattern obtained (Figure 1) could be indexed unambiguously, and the structure determination by direct methods as well as the subsequent Rietveld refinement were successful (see Experimental Section).

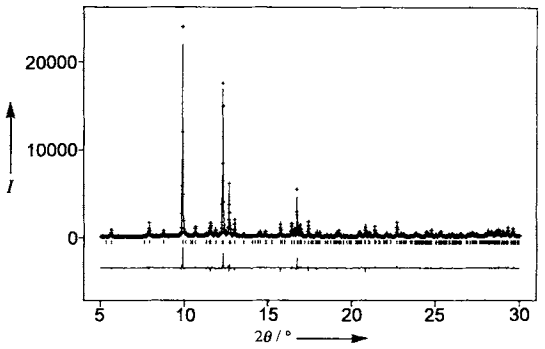

Figure 1. The observed (crosses) and calculated X-ray powder diffraction pattern (line) as well as the difference profile of the Rietveld refinement of HP_4N_7 (only the section until $2\theta = 30°$ is shown). The possible positions of the peaks are marked by vertical lines. The powder pattern was obtained at the National Synchrotron Light Source (NSLS) at Brookhaven, USA, on the Beamline X7A (λ = 69.906 pm). I = intensity in counts.

Solid HP_4N_7 is made up of a three-dimensional network structure of connected PN_4 tetrahedra, according to $^3_\infty[(P^{[4]}_4N^{[2]}_5N^{[3]}_2)^-]$ (Figure 2). Whereas in β-cristobalite-analogous HPN_2[5] the nitrogen atoms are only bound to two phosphorus atoms ($N^{[2]}$), in HP_4N_7 there are also nitrogen atoms connected to three phosphorus atoms ($N^{[3]}$).[*] The situation resembles that in phosphorus(v) nitride $^3_\infty[(P^{[4]}_3N^{[2]}_3N^{[3]}_2)]$.[12] In HP_4N_7 there exist pairs of edge-sharing PN_4 tetrahedra. This structural motive has so far only been found in P_3N_5[12] and P_4N_6O.[13] In the nitridosilicates $Ba_5Si_2N_6$[14] and $BaSi_7N_{10}$[15] analogous edge-sharing pairs of tetrahedra are found, while in oxosilicates a comparable edge linkage has not yet been confirmed.

The three-dimensional network structure of HP_4N_7 may be separated into two different open-branched zweier single chains (Figure 3). The main cords of both arrangements are built up of corner-sharing PN_4 tetrahedra; in one case the branch results by

[*] The superscripted numbers in square brackets define the coordination number of the element.

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