Synthesis of New Glycopeptidomimetics Based on *N*-Substituted Oligoglycine bearing an *N*-Linked Lactoside Side-chain†

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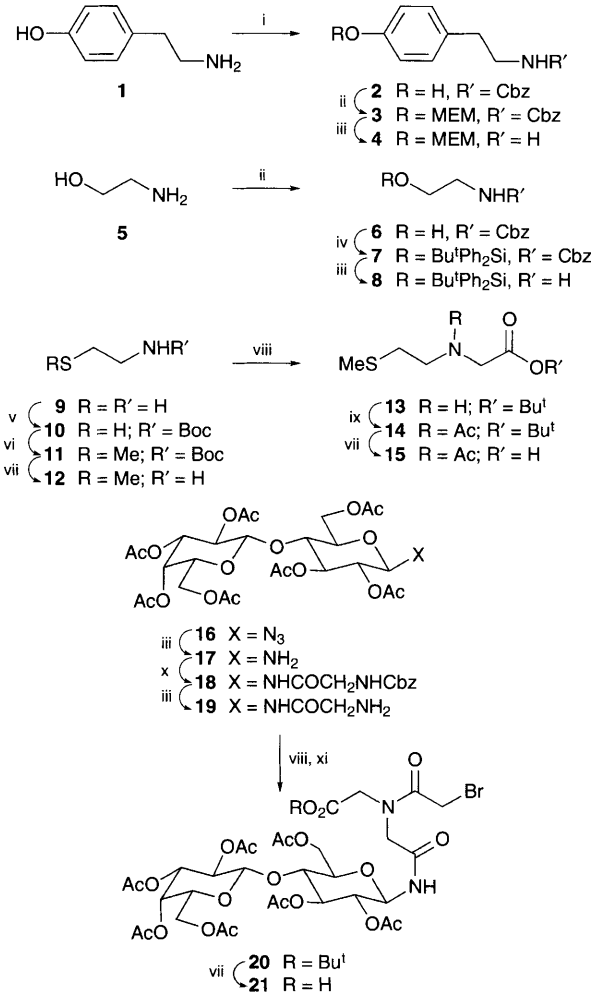
A new family of model *N*-substituted oligoglycines (peptoids) containing an *N*-linked lactoside side-chain was synthesized by a convergent and a reiterative strategy using *tert*-butyl bromoacetate and primary amines as building blocks.

N-Linked and *O*-linked glycans of glycoproteins have been associated with fundamental roles in many different aspects of glycobiology.[1] As a consequence of intense research devoted to an understanding of their exact functions, chemical syntheses of glycopeptides have become routine work.[2–4] Glycopeptides have also been the recent focus of potential pharmaceutical applications.[5,6] Unfortunately, glycopeptides, like their peptide counterparts, are metabolically unstable.[7] Therefore, for therapeutic purposes, it is a natural extension to apply the strategy of peptidomimetics[8] to glycopeptidomimetics, and to this end we recently described the first synthesis of such a *N*-linked glycopeptidomimetic.[9] We used an approach adapted from the synthesis of peptoids which are composed of *N*-substituted oligoglycine (NSGs) residues[10–11] and named this new family of analogues 'glycopeptoids'.[9] We describe herein a second model of a *N*-linked glycopeptoid bearing a lactosyl residue. In this model, the arbitrary hexameric sequence Val-Tyr-Ser-Asn(Lactose)-Glu-Met has been replaced by NVal-NhTyr-NhSer-NAsn(Lactose)-NGlu-NMetNAc.‡

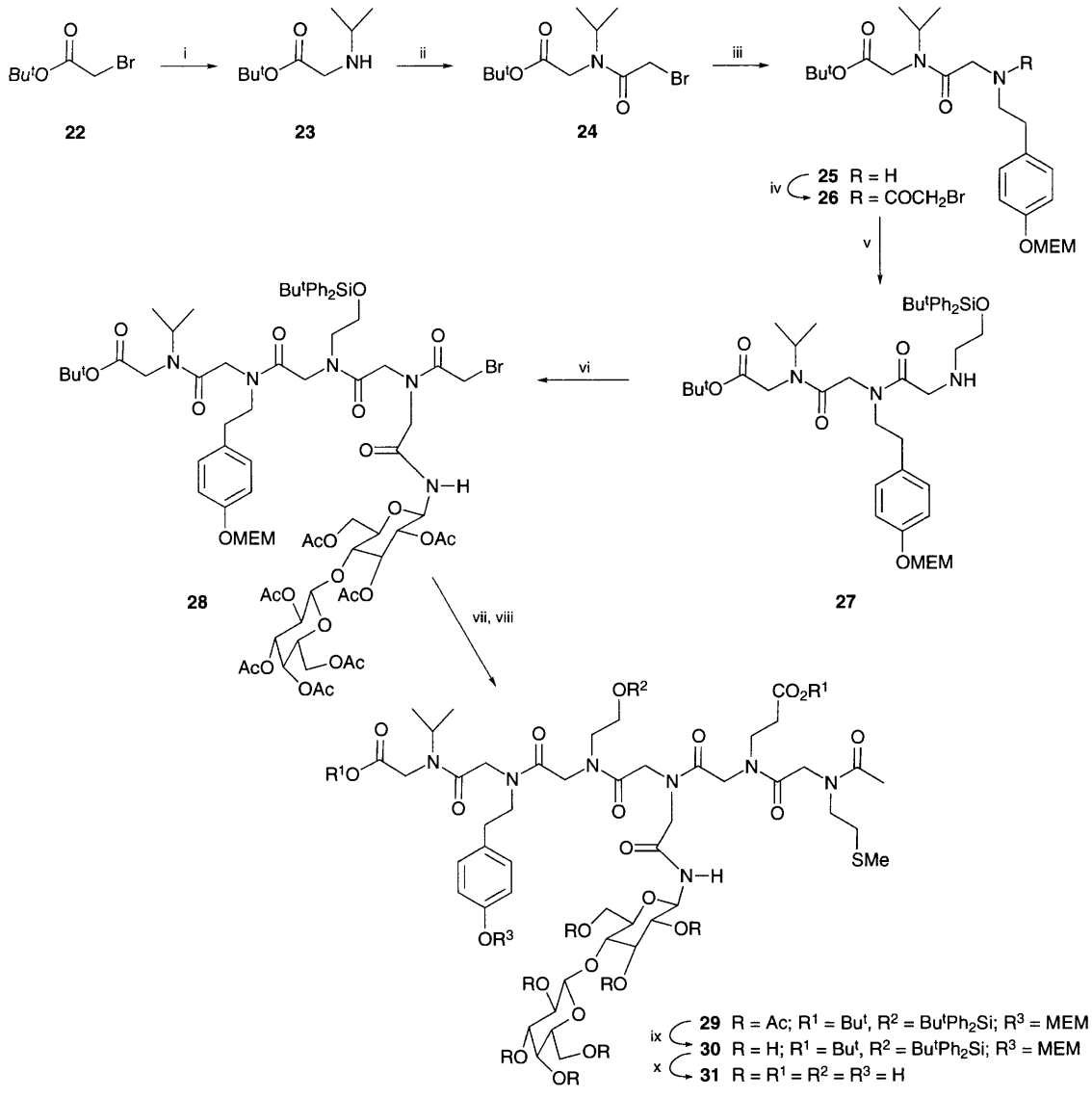
Of particular significance for their applications as therapeutics is the finding that each individual glycopeptoid, by virtue of their intrinsic secondary amide structures, represents a family of rotational isomers in rapid equilibria. This very high flexibility allows glycopeptoids to probe a large conformational space within potential receptors.

The side chain residues were first synthesized according to Scheme 1. Thus, treatment of 4-(2-aminoethyl)phenol (tyramine, **1**) with benzyl chloroformate (CbzCl) gave **2** in 88% yield.§ Phenolic group protection with 2-methoxyethoxymethyl chloride (MEMCl) provided MEM-ether **3** (85% yield). Catalytic hydrogenation over 10% Pd–C afforded homotyrosine analogue precursor **4** in quantitative yield. The homoserine analogue **8** was obtained by transformation of ethanolamine **5** into carbamate **6** using CbzCl (90% yield). Protection of alcohol **6** by *tert*-butyldiphenylsilyl ether formation afforded **7** in 92% yield. Hydrogenation of the benzyloxycarbonyl group of **7** as above gave **8** also in quantitative yield. The methionine side-chain analogue **12** was obtained by first treating 2-aminoethanethiol (cysteamine, **9**) with Boc-anhydride and diisopropylethylamine (DIPEA) in acetonitrile. Without isolation, thiol **10** was then immediately treated with methyl iodide which gave **11** in 85% yield for the two steps. Removal of the Boc-protecting group with trifluoroacetic acid (TFA) in dichloromethane (1 : 2, *v*/*v*) provided the required amine **12** in 94% yield. Since **12** constituted the terminal residue, its amine functionality was initially alkylated with *tert*-butyl bromoacetate **22**. Successful mono *N*-alkylations were usually accomplished in dilute solutions using 1 equiv. of **22** at a temperature ranging from 0 to 25 °C. *N*,*N*-dialkylated byproducts were always formed in varying amounts. The resulting reaction mixtures were directly loaded onto silica gel columns without prior evaporation of the solvent (MeCN). The secondary amine **13**, obtained in 55% yield, was then *N*-acetylated with acetyl chloride in pyridine to give **14** in 93% yield. Removal of the *tert*-butyl ester of **14** with TFA as described above furnished crystalline acid **15** quantitatively. The ^{1}H NMR spectra of **14** and **15** showed that they exist as mixtures of two rotamers in 1.1 : 1 and 1.3 : 1 ratios, as seen from the relative integration of their *tert*-butyl and *N*-acetyl signals respectively.

The key *N*-linked lactosyl glycine moiety **19** was prepared from β-lactosyl azide **16** previously obtained under phase transfer catalysis.[12] Quantitative azide reduction under catalytic hydrogenation in methanol gave amine **17** which was rapidly treated with Cbz-glycine, 1,3-dicyclohexylcarbodiimide (DCC), and 1-hydroxybenzotriazole (HOBt) to provide **18** in 84% yield. Hydrogenolysis of **18** liberated **19** quantitatively. Primary amine **19** was further transformed into secondary amide **20** with *tert*-butyl bromoacetate **22** (78% yield) followed by *N*-bromoacetylation with bromoacetic anhydride in di-



Scheme 1 *Reagents and conditions*: i, CbzCl, DIPEA, DMF, MeCN, room temp., 1 h, 88% for **2**, 90% for **6**; ii, MEMCl, DIPEA, CH_2Cl_2, room temp., 12 h, 85%; iii, H_2, 10% Pd–C, MeOH, quant.; iv, Bu^tPh_2SiCl, imidazole, CH_2Cl_2, room temp., 3 h, 92%; v, Boc_2O, DIPEA, MeCN, 0 °C, 30 min; vi, MeI, DIPEA, MeCN, room temp., 3 h, 85% (2 steps); vii, TFA–CH_2Cl_2 (1 : 2, *v*/*v*), room temp., 3 h, 94% for **11**, quant for **14**, 89% for **20**; viii, $BrCH_2CO_2Bu^t$ (1 equiv.), DIPEA (1.5 equiv.), MeCN, 0–25 °C, 30 min to 3 h, 55% for **12**, 78% for **19**, 89% for **21**; ix, MeCOCl, pyridine, CH_2Cl_2, 93%; x, $CbzNHCH_2CO_2H$, DCC, HOBt, CH_2Cl_2, room temp., 1 h, 84%; xi, $(BrCH_2CO)_2O$, pyridine, CH_2Cl_2, 0 °C, 30 min, 86%.



Scheme 2 *Reagents and conditions*: i, Me_2CHNH_2 (1 equiv.), pyridine, MeCN, 0 °C, 15 min, 75%; ii, $BrCH_2COCl$, pyridine, CH_2Cl_2, 0 °C, 15 min, 90%; iii, **4**, DIPEA, MeCN, 0 °C, 1 h, 70%; iv, $(BrCH_2CO)_2O$, DIPEA, CH_2Cl_2, 0 °C, 30 min, 86%; v, **8**, DIPEA, MeCN, 0 °C, 2 h, 74%; vi, **21**, DCC, HOBt, CH_2Cl_2, room temp., 2 h, 84%; vii, $H_2NCH_2CH_2CO_2$ Bu^t, DIPEA, MeCN, room temp., 1 h, 81%; viii, **15**, DCC, HOBt, CH_2Cl_2, room temp., 2 h, 76%; ix, NaOMe, MeOH, room temp., 1 h, 95%; x, TFA–CH_2Cl_2 (4 : 1, *v/v*), room temp., 12 h, quant.

chloromethane containing pyridine (86% yield). Acid treatment (TFA) of the *tert*-butyl group of **20** as above for **14** gave acid **21** in 89% yield. Secondary amide **20** was also shown to exist as fast equilibrating rotamers in a 1.4 : 1 ratio.

Having secured the preparations of the side-chain residues, the construction of the target hexaglycopeptoid was accomplished following a convergent strategy (Scheme 2). To this end, *tert*-butyl bromoacetate building block **22** was quickly treated with one equivalent of isopropylamine to give secondary amine **23** in 75% yield. *N*-Bromoacetylation of **23** with bromoacetyl chloride gave secondary amide **24** in 90% yield existing as a 1.8 : 1 mixture of rotamers. This *N*-bromoacetylated *N*-valine analogue was alkylated with the tyrosine mimic **4** to provide secondary amine **25** which upon further treatment with bromoacetic anhydride gave intermediate **26** in 86% yield. *N*-Alkylation of **26** with homoserine analogue **8** gave the tripeptoid unit **27** in 74% yield. Coupling of amine **27** with the glycosidic acid unit **21** onto which was preinstalled the necessary *N*-bromoacetamide residue was successfully accomplished in 84% yield using DCC and HOBt. Therefore, utilization of building blocks having both acid and *N*-bromoacetyl moieties constitutes a viable convergent entry into more complex peptoids. Attachment of the glutamic acid side-chain was effected by *N*-alkylation of **28** with the β-alanine *tert*-butyl ester in 81% yield. Merging the resulting amine with acid **15** by DCC–HOBt coupling afforded fully protected hexaglycopeptoid **29** in 76% yield. Sequential deprotection of the sugar residue in **29** under Zemplen conditions (NaOMe, MeOH) gave partially protected intermediate **30** (95%). Acid treatment (TFA, CH_2Cl_2, 4 : 1, *v/v*) of **30** removed all the remaining silyl and MEM ethers, as well as the *tert*-butyl ester in essentially quantitative yield.

Received, 17th August 1995; Com. 5/05489C

Footnotes

† Presented in part at the 8th European Carbohydrate Symposium, Seville, Spain, July 2–7, 1995.

‡ The nomenclature used to design peptoids is the same as that described in ref. 10. Briefly, the monomers are given designations corresponding to the amino acids with similar functionality, with the prefix N. In some cases, the homologous amino acids are made, thus the prefix h for homoserine, homotyrosine, *etc.* were used.

§ All new compounds exhibited consistent spectral (^{1}H, ^{13}C NMR, MS) and analytical data. Obviously, for dipeptoid and higher analogues, the NMR spectroscopic data were rendered complex because of the many rotamers present. For instance, a dipeptoid with two secondary amide bonds exist as 2^2 different rotamers showing accordingly all the possible ^{1}H and ^{13}C NMR signals which were used to determine rotamers ratios. Interestingly, the MS fragmentation patterns coincided with those of the amide bonds as observed in peptides.[9] *Selected data* for **13**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (9 H, s, CMe_3), 1.88 (1 H, s, NH), 1.99 (3 H, s, SMe), 2.55 (2 H, t, *J* 5.3 Hz, CH_2S), 2.66 (2 H, t, *J* 5.3 Hz, CH_2N), 3.20 (2 H, s, CH_2CO_2). For **15**: ^{1}H NMR δ 1.97, 1.98, 2.00, 2.10 (6 H, 4s, NAc, SMe), 2.56 (2 H, m, CH_2S), 3.45 (2 H, t, *J* 7.0 Hz, CH_2NCO), 3.99, 4.00 (2 H, 2s, CH_2CO_2). For **18**: mp 93–94 °C, $[\alpha]_D$ + 3.0 ($CHCl_3$); ^{1}H NMR (500 MHz) δ 5.15 (1 H, dd, $J_{1,2}$ = $J_{1,NH}$ 9.3 Hz, H1), ^{13}C NMR δ 78.0 (C1), 100.8 (C1′). For **20**: ^{1}H NMR (200 MHz) δ 1.37, 1.39 (9 H, 2s, rotamer 1.4 : 1.0, CMe_3), 1.80–2.05 (21 H, 7s, OAc), 3.50–4.40 (14 H, m, 4.65–4.88 (2 H, m), 4.90–5.25 (4 H, m), 7.50, 8.80 (1 H, 2d, *J* 8.5 Hz, NH). For **21**: mp 185–187 °C, $[\alpha]_D$ + 3.9, CHN analyses, *calcd.* C: 44.07, H: 4.97, N: 3.21, *found*, C: 43.98, H: 4.96, N: 3.06. For **24**: ^{1}H NMR δ 1.04, 1.07 (2d, *J* 6.8 Hz, CMe_2), 1.19, 1.22 (6 H, 2d, CMe_2), 1.43, 1.45 (9 H, 2s, rotamer ratio 1 : 1.8, CMe_3). For **26**: ^{1}H NMR δ 0.94, 0.97, 1.05, 1.09, (6 H, 4d, CMe_2), 1.32, 1.33, 1.38 (9 H, 3s, CMe_3), 2.80 (2 H, m,) 3.27 (3 H, s, OMe), 3.40–4.16 (12 H, m, CH_2), 3.95, 4.70 (1 H, 2m, $CHMe_2$), 5.14 (s, CH_2), 6.85 (2 H, m), 7.03 (2 H, m); *m/z* 559 (M^+, 1.2%). For **27**: ^{1}H NMR δ 1.02, 1.03, 1.04, 1.05 (9 H, 4s, $SiCMe_3$), 1.08, 1.12, 1.15, 1.22 (6 H, 4d, CMe_2), 1.38, 1.42, 1.45, 1.46 (9 H, 4s, $OCMe_3$), 2.67 (2 H, t, *J* 5.4 Hz, CH_2), 2.77 (2 H, m, CH_2), 3.33, 3.34, 3.35, 3.36 (3 H, 4s, OMe), 3.51 (4 H, m) 3.65–4.23 (10 H, m), 4.05, 4.80 (1 H, 2m, $CHCMe_2$), 5.19, 5.20, 5.21 (2 H, 3s, MEM–OCH_2O), 6.95 (2 H, m, CH_2Ar), 7.05 (2 H, m), 7.37 (6 H, m), 7.65 (4 H, m, Ar). For **29**, mp 85–87 °C, $[\alpha]_D$ −4.65; HRMS (FAB) *calcd.* for $C_{88}H_{126}N_7O_{32}Si$ (M^+ −SMe) 1822.8373, *found*, 1822.8390. For **31**: ^{1}H NMR δ 1.13–1.31 (6 H, m, CMe_2), 2.06–2.31 (6 H, m, SMe, NAc), 4.50–4.58 (1 H, m, H1′), 5.02–5.11 (1 H, m, H1), 6.92–7.00 (2 H, m, Ar), 7.25–7.30 (2 H, m, Ar); FAB (pos.) *m/z* 1157.3 (M^+ + Na, 6.0%), remaining are fragments occurring at secondary amide bonds, 1123.3 (2.3), 907.0 (2.6), 424 (2.6), 319 (26.4).

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