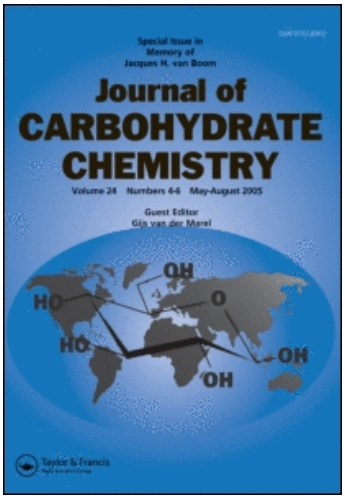

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Solid-Phase Synthesis of a 1-Thio-β-d-GlcNAc Carbohydrate Mimetic Library

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Solid-Phase Synthesis of a 1-Thio-β-D-GlcNAc Carbohydrate Mimetic Library†

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ABSTRACT

The solid phase synthesis of *N*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside derivatives by reacting an immobilized sugar thiol with Michael acceptors and α-chloroketones, followed by ketone reductions, reductive aminations, acylations and alkylations was developed to yield a library of 1088 compounds. Such carbohydrate mimetic libraries are synthesized efficiently on the solid phase without the need for protection of the sugar hydroxyl groups. The library was designed for the identification of potential inhibitors of *β*-D-GlcNAc binding proteins.

INTRODUCTION

The biological significance of oligosaccharides as receptors for the binding of toxins, bacteria, viruses and mammalian cells[1] has suggested their use as pharmaceutical agents.[2] The multiple-step synthesis of oligosaccharides, however, remains very difficult, time-consuming and correspondingly expensive. As a result, there has been an expansion in recent activity aimed at the generation of simpler carbohydrate mimetics.[3–9] Combinatorial carbohydrate chemistry has also been applied to the

†This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

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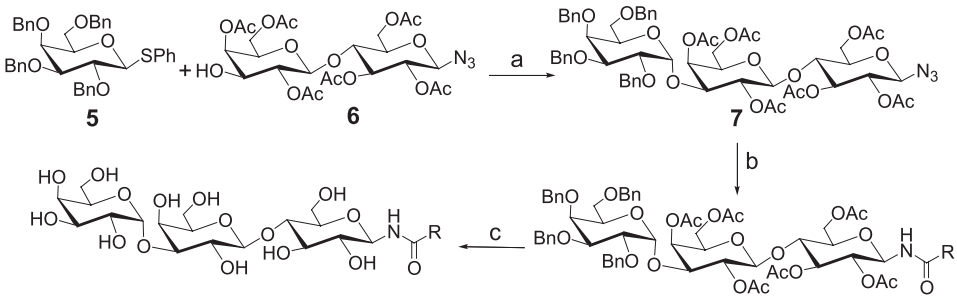
generation of carbohydrate-based ligands, including the use of solid-phase approaches to enhance the affinity of ligands for a target protein.

We recently initiated a combinatorial carbohydrate chemistry program targeting the preparation of very simple monosaccharide derivatives, prepared by tandem Michael additions followed by reductive aminations, to yield panels of thio-sugars functionalized with small cyclic organic aglycones. A 100-member β-Gal carbohydrate mimetic library was prepared by synthesis in solution and purified using a solid-phase extraction protocol to provide potent inhibitors for both a β-galactosidase and a plant toxin.[10,11]

We report here that such carbohydrate mimetic libraries can be much more efficiently synthesized on the solid phase, without the need for protection of the sugar hydroxyl groups. The procedure involves immobilizing an unprotected sugar functionalized at the anomeric position with an unsymmetrical disulfide. The free thio group is then liberated on the immobilized molecule and reacted with a thiophilic reagent to yield coupled products containing carbonyl groups. These groups can then either be reduced to the alcohols, or reductively aminated with a diverse panel of primary amines such as amino acids. The method is validated here for the preparation of 1088 derivatives of *N*-acetylglucosamine.

RESULTS AND DISCUSSION

The 1-thio-β-D-GlcNAc derivative **4** was prepared from 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**1**)[12] (Scheme 1). Compound **1** was



Reagents: (a) NIS, TfOH, CH_2Cl_2, 4 MS, -30 °C, 90%; (b) PtO_2, H_2, MeOH; then RCOCl, Et_3N, CH_2Cl_2, **8a**, 89%, **8b**, 81%, **8c**, 90%, **8d**, 89%; for **8e**, $CH_3OCH_2CH_2OCH_2COOH$, IIDQ, CH_2Cl_2, 54%; (c) Pd/C, H_2, MeOH; then NaOMe, MeOH, **9a**, 97%, **9b**, 91%, **9c**, 91%, **9d**, 96%, **9e**, 81%.

Scheme 1. Reagents and conditions: (a) $SC(NH_2)_2$, acetone, reflux, 15 min, 82%; (b) EtSSEt, MeOH, NEt_3, 20°C, 2 h, 89%; (c) NaOMe, MeOH, 20°C, 2 h, then H^+, IR-120, 96%; (d) Trityl resin, pyridine, DMAP, 60°C, 48 h; (e) DTT, THF, MeOH, NEt_3, 20°C, 18 h.

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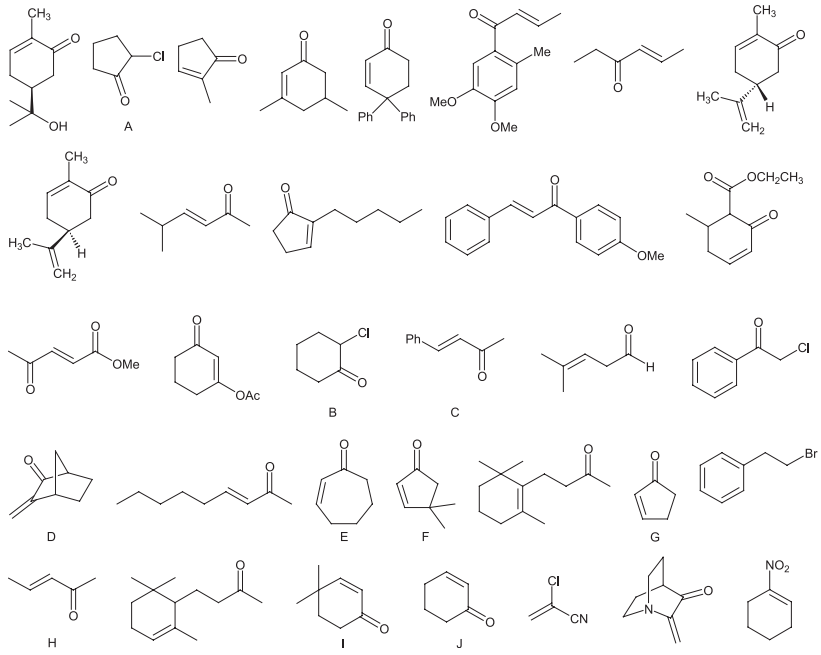

Scheme 2. Commercial Michael acceptors and α-halo ketones used in the present study.

heated with thiourea in acetone for 15 min under reflux to give **2** in 89% yield. Treatment of **2** with diethyl disulfide in methanol and triethylamine followed by deacetylation with sodium methoxide in methanol afforded the unprotected disulfide **3** in 85% yield. Disulfide **3** was immobilized on a trityl chloride derivatized polystyrene resin[a] (1.66 mmol/g). The loading of the disulfide on the solid support was determined by elemental analysis (sulfur content) and was 1.2 mmol/g. The free thiol function was generated on the solid support by reduction of the disulfide with dithiothreitol (DTT) in a mixture of THF, MeOH and Et_3N. The progress of the reduction could be easily monitored by IR spectroscopy directly on a crushed bead (SH-stretch: 2555 cm^{-1}).

Michael Additions and α-Chloro Ketone Substitutions

The highly reactive nucleophilic sugar-1-thiol **4** *without protecting groups* was reacted with 33 different commercially available Michael acceptors and α-halo carbonyl compounds (Scheme 2). Treatment of the resin and the Michael acceptors or α-chloro

[a]The resin is commercially available from Novabiochem. Immobilization was performed using pyridine as solvent in the presence of 4-dimethylaminopyridine (DMAP) for 48 h at 60°C.

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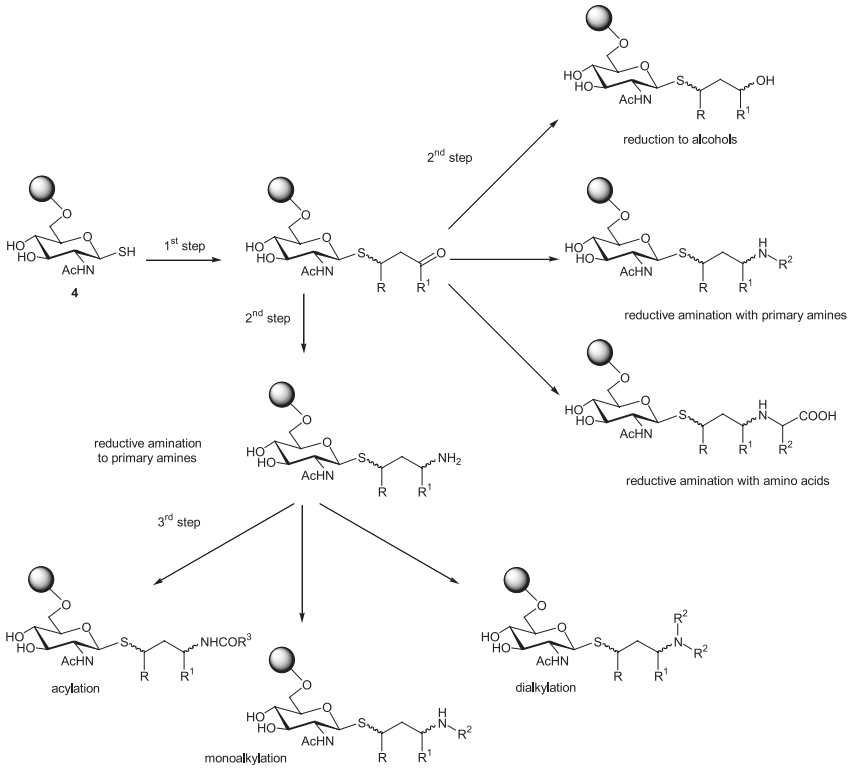

Scheme 3. Parallel solid phase synthesis of a carbohydrate mimetic library.

ketone compounds in DMF[13] in the presence of diethylamine gave the corresponding ketones in quantitative yields. For the final library, we chose two α-chloro ketones **A** and **B** and eight Michael acceptors **C** to **J**. The resulting ketones were split into 28 batches, each of which was further reacted in a parallel fashion (Scheme 3).

Reduction of Ketones to Alcohols

The ketones **A1** to **J1** were reduced to the corresponding alcohols using sodium borohydride in a mixture of methanol and tetrahydrofuran. After cleavage from the resin, the ten alcohols **A2** to **J2** were obtained in high yields (> 90%) (Scheme 4).

Reductive Aminations of Ketones with L-Amino Acid *t*-Butyl Esters

Reductive aminations of the ketones **A1** to **J1** with amino acid *t*-butyl ester hydrochlorides, using sodium triacetoxyborohydride in dichloromethane in the presence of sodium sulfate and acetic acid gave the derivatives in high yields (> 90%) except for the derivatives of ketone **D1**. The only side-products observed in these reactions were

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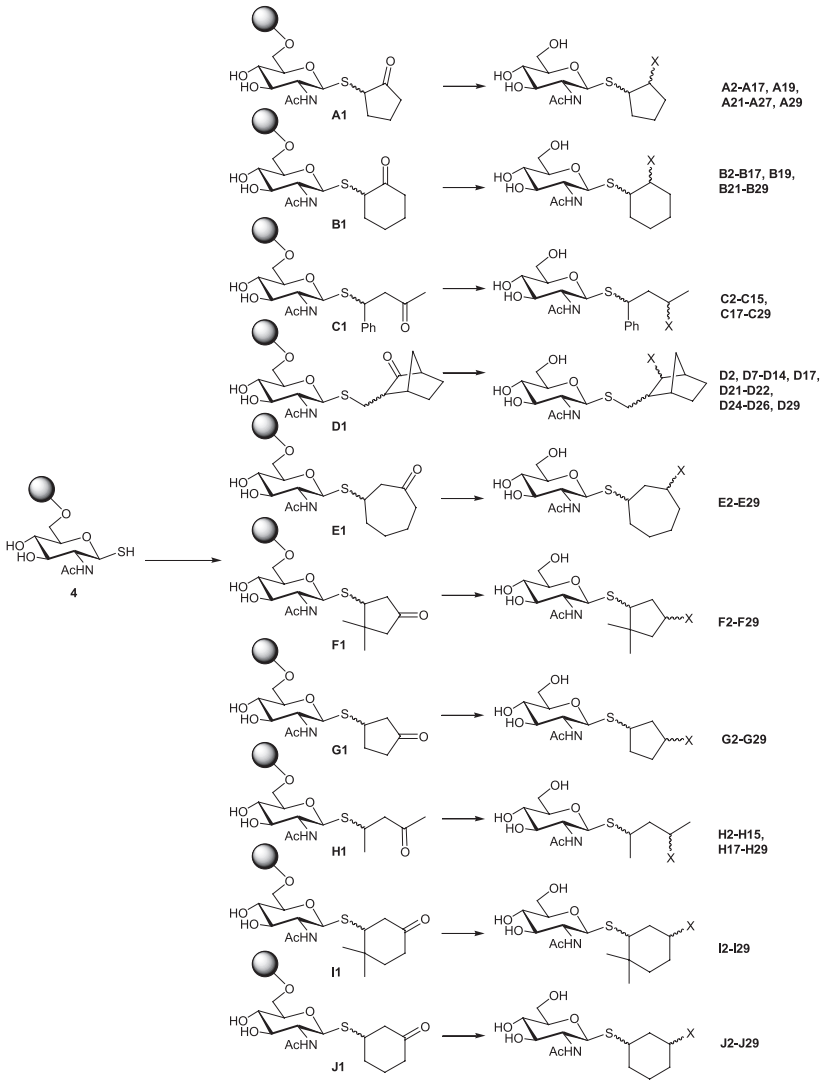

Scheme 4. Each compound is identified by a capital letter (**A–J**), which specifies the type of aglycone, followed by a number (**1–29**), which defines the substituent X. X is defined in the following way: X = OH: **2**; L-Leu: **3**; L-Ile: **4**; L-Val: **5**; L-Asp: **6**; L-Pro: **7**; β-Ala: **8**; L-Ala: **9**; L-Gly: **10**; NH_2: **11**; NHAc: **12**; L-Glu: **13**; L-Phe: **14**; L-Thr: **15**; L-Cys: **16**; L-Asn: **17**; L-Tyr: **18**; L-Met: **19**; L-Arg: **20**; L-Trp: **21**; L-His: **22**; L-Lys: **23**; NHPhth: **24**; NHBnpOH: **25**; NHC_5H_{11}: **26**; $NH(C_4H_7)_2$: **27**; L-Gln: **28**; NHBn: **29**.

the starting ketones. Sodium triacetoxyborohydride,[14,15] as reducing reagent, did not reduce the ketones to the corresponding alcohols (Scheme 4).

Cleavage from the Resin

All derivatives were cleaved from the resin by treatment with 2% TFA in CH_2Cl_2.

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Deblocking of *N*-Alkylated Amino Acid *t*-Butyl Esters

t-Butyl esters were removed from the protected *N*-alkylated amino acids by trifluoroacetic acid after cleavage from the resin.

Reductive Aminations of Ketones with L-Amino Acid Methyl Esters

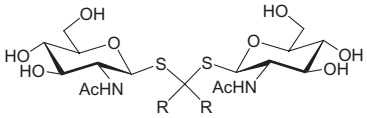
Reductive aminations of the ketones **A1** to **J1** with amino acid methyl ester hydrochlorides, using sodium triacetoxyborohydride in dichloromethane/methanol in the presence of sodium sulfate and acetic acid for 18 h at room temperature gave the corresponding *N*-alkylated L-amino acid derivatives with purities of > 90% and yields from 80–99%. Lower yields were obtained only for derivatives of ketone **D1** and in some case for derivatives of ketones **A1** and **B1** (Scheme 4).

Deblocking of *N*-Alkylated Amino Acid Methyl Esters

Methyl esters were hydrolysed from the protected *N*-alkylated amino acid on the resin using aqueous LiOH in tetrahydrofuran/methanol. An unexpected minor side product was observed by mass spectrometry and ^{1}H NMR spectroscopy in some cases and could be identified as the dithioacetal **5** (Scheme 5). To investigate the formation of this compound, we treated the lithium thiolate on the resin with dichloromethane for 18 h at room temperature, followed by addition of excess ethanethiol. After cleavage from the resin, we obtained the dithioacetal **5** in quantitative yield which suggested that the compound was formed on the solid support. This was further confirmed by performing the same reaction in deuterated dichloromethane which gave the corresponding derivative **6**.

Reductive Aminations of Ketones to Primary Amines

Ketones **A1** to **J1** were reduced to the corresponding primary amines in dichloromethane using a mixture of ammonium acetate, sodium triacetoxyborohydride, triethylamine and methanol in the presence of sodium sulfate. After cleavage from the resin, the amines **A11** to **J11** could be isolated in high yield and purity (> 90% according to ^{1}H NMR and electrospray MS) (Scheme 4).



5 R = H
6 R = D

Scheme 5. Side product formed on the solid support.

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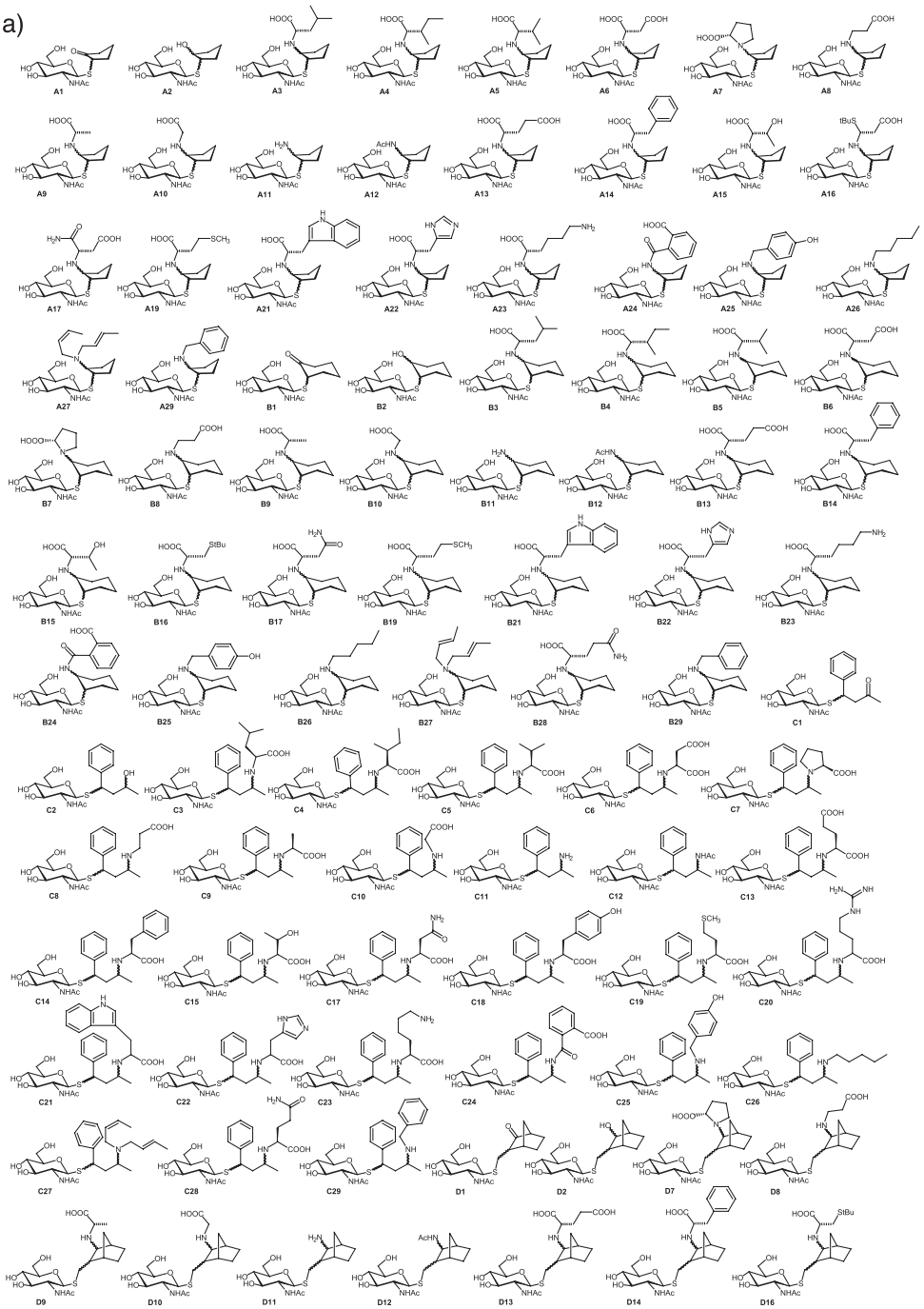

Figure 1. (a–c) 272 Out of the 300 library members were obtained in yields between 72 and 99% and in purities over 80% as judged from ^{1}H NMR analyses.

(*continued*)

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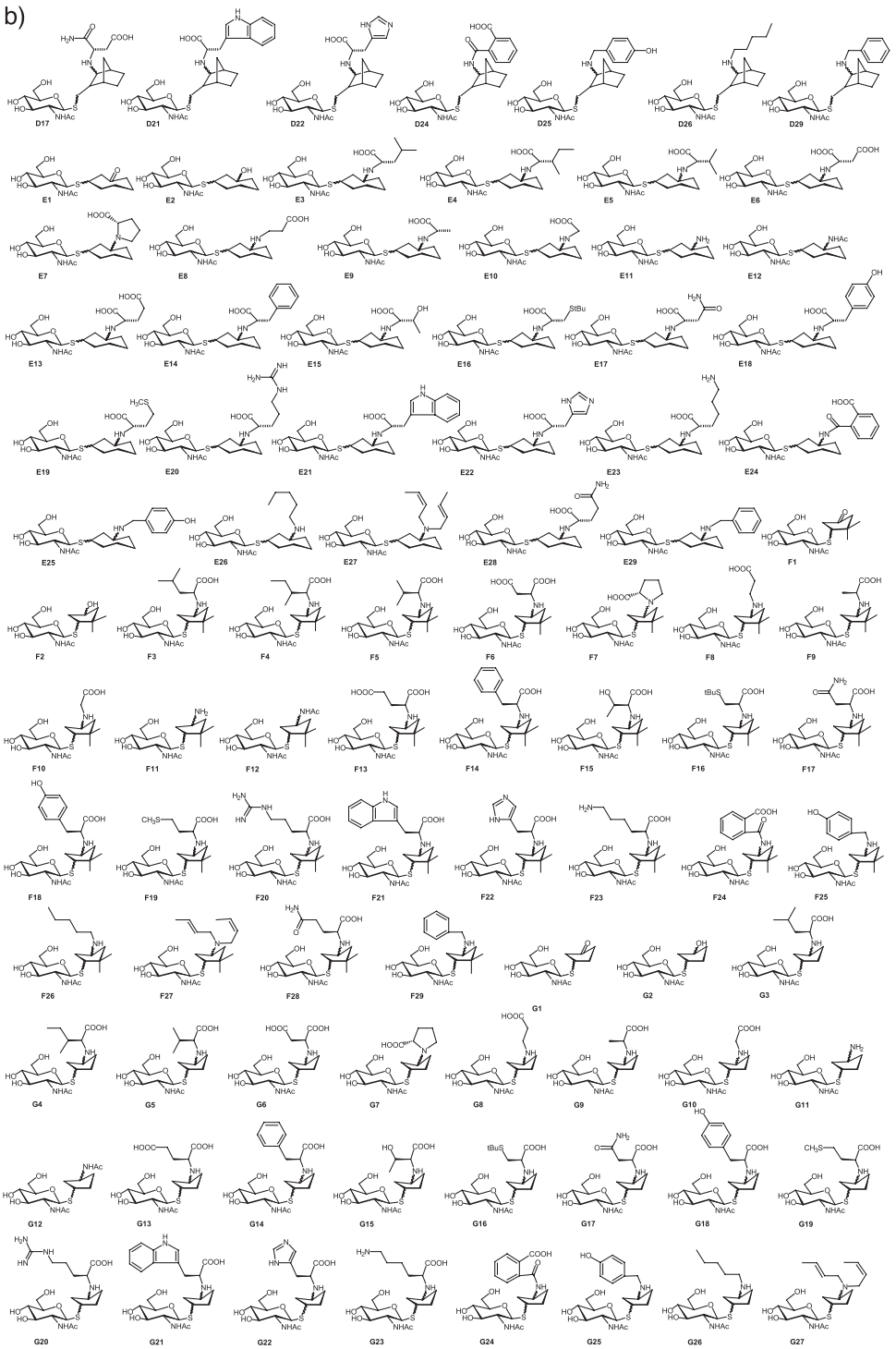

Figure 1. Continued.

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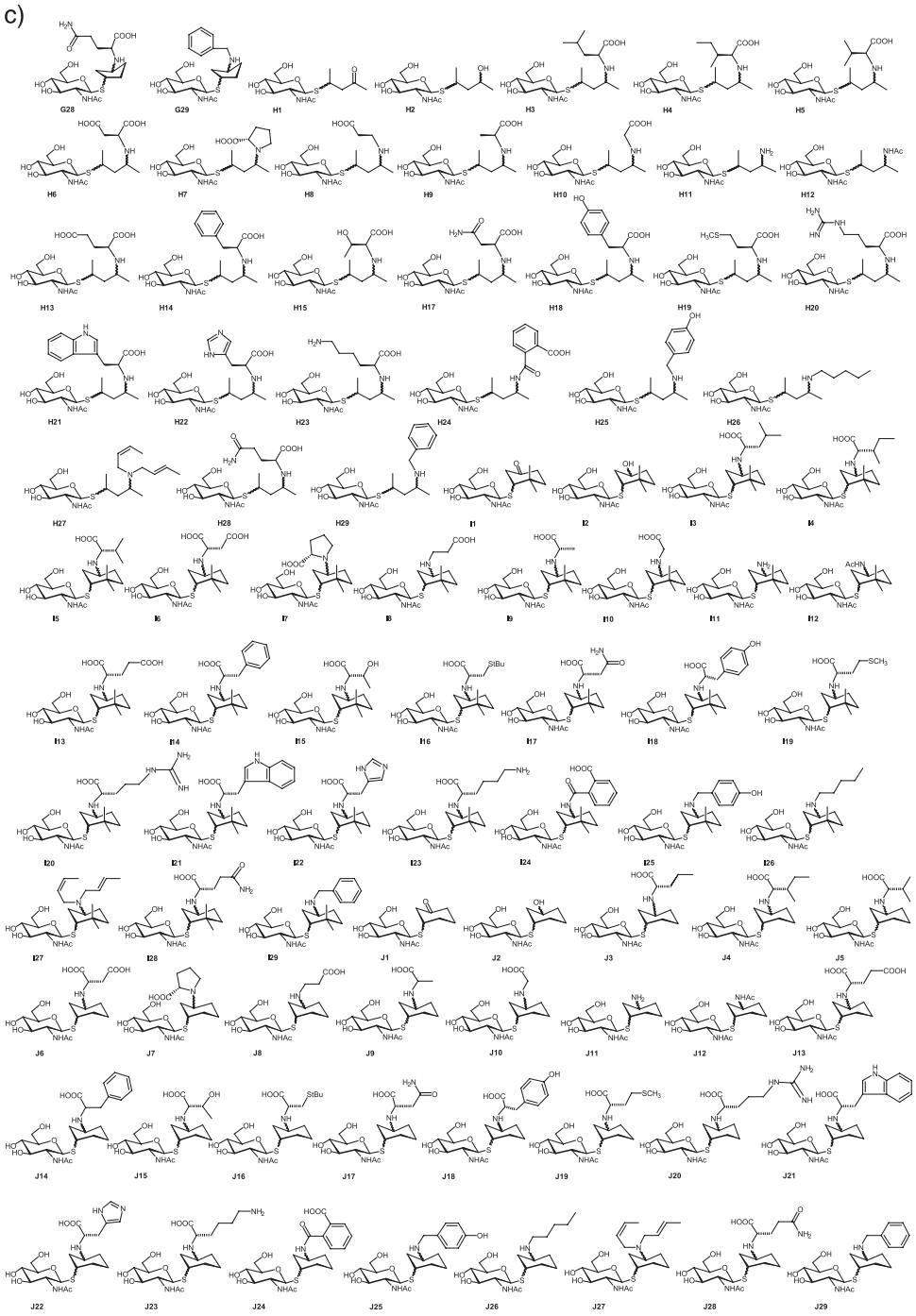

Figure 1. Continued.

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Table 1. Electrospray mass and ^1H NMR (360 MHz, D_2O) spectroscopic data for the GlcNAc library.

Compound	Formula	M calcd	$(M + X)^+$ found[a]	δ/ppm[b]
A1	$C_{13}H_{21}NO_6S$	319.11	320.2, 342.1	4.57, 4.73
A2	$C_{13}H_{23}NO_6S$	321.12	344.0	4.59, 4.62, 4.63
A3	$C_{19}H_{34}N_2O_7S$	434.21	435.1, 457.1	4.59, 4.60
A4	$C_{19}H_{34}N_2O_7S$	434.21	435.2, 457.1	4.55, 4.59, 4.60, 4.62
A5	$C_{18}H_{32}N_2O_7S$	420.19	421.3, 443.2	4.54, 4.56, 4.58, 4.62
A6	$C_{17}H_{28}N_2O_9S$	436.15	437.1, 459.1	4.53, 4.59, 4.60, 4.65
A7	$C_{18}H_{30}N_2O_7S$	418.18	419.0, 441.1	4.53, 4.58
A8	$C_{16}H_{28}N_2O_7S$	392.16	393.1, 415.1	4.50, 4.54, 4.59
A9	$C_{16}H_{28}N_2O_7S$	392.16	393.1, 415.0	4.54, 4.62
A10	$C_{15}H_{26}N_2O_7S$	378.15	379.1, 401.1	4.52, 4.53, 4.59
A11	$C_{13}H_{24}N_2O_5S$	320.14	321.5	4.58, 4.62, 4.63
A12	$C_{15}H_{26}N_2O_6S$	362.15	385.4	4.59, 4.64
A13	$C_{18}H_{30}N_2O_9S$	450.17	451.2, 473.1	4.53, 4.55, 4.63
A14	$C_{22}H_{32}N_2O_7S$	468.19	469.2, 491.1	4.47, 4.53, 4.55
A15	$C_{17}H_{30}N_2O_8S$	422.17	423.5	4.55, 4.57, 4.60
A16	$C_{20}H_{36}N_2O_7S_2$	480.20	481.2, 503.1	4.55, 4.57, 4.63
A17	$C_{17}H_{29}N_3O_8S$	435.17	436.4, 458.3	4.54, 4.57, 4.65
A19	$C_{18}H_{32}N_2O_7S_2$	452.16	453.4	4.55, 4.57
A21	$C_{24}H_{33}N_3O_7S$	507.20	508.3	4.55, 4.58
A22	$C_{19}H_{30}N_4O_7S$	458.18	459.4	4.54, 4.58, 4.63
A23	$C_{19}H_{35}N_3O_7S$	449.22	450.4	4.54, 4.56, 4.60
A24	$C_{21}H_{28}N_2O_8S$	468.16	469.5	4.59, 4.61, 4.62
A25	$C_{20}H_{30}N_2O_6S$	426.18	427.4	4.59, 4.63, 4.75
A26	$C_{18}H_{34}N_2O_5S$	390.22	391.5	4.58
A27	$C_{21}H_{36}N_2O_5S$	428.23	429.5	4.55, 4.60
A29	$C_{20}H_{30}N_2O_5S$	410.18	411.1	4.56, 4.62
B1	$C_{14}H_{23}NO_6S$	333.12	356.1	4.43, 4.53
B2	$C_{14}H_{25}NO_6S$	335.14	336.1, 358.1	4.60, 4.65, 4.67, 4.76
B3	$C_{20}H_{36}N_2O_7S$	448.22	449.1, 471.1	4.58, 4.59, 4.63, 4.65
B4	$C_{20}H_{36}N_2O_7S$	448.22	449.4, 471.3	4.55, 4.59
B5	$C_{19}H_{34}N_2O_7S$	434.21	435.2, 457.1	4.55, 4.57, 4.60
B6	$C_{18}H_{30}N_2O_9S$	450.17	451.1, 473.1	4.55, 4.59, 4.60, 4.61
B7	$C_{19}H_{32}N_2O_7S$	432.19	433.3, 455.1	4.55, 4.59
B8	$C_{17}H_{30}N_2O_7S$	406.17	407.4, 429.1	4.55
B9	$C_{17}H_{30}N_2O_7S$	406.17	407.3	4.54, 4.56, 4.57
B10	$C_{16}H_{28}N_2O_7S$	392.16	393.2, 415.1	4.52, 4.59
B11	$C_{14}H_{26}N_2O_5S$	334.16	335.5	4.56, 4.60, 4.63, 4.65
B12	$C_{16}H_{28}N_2O_6S$	376.17	377.4, 399.4	4.52, 4.57, 4.60, 4.61
B13	$C_{19}H_{32}N_2O_9S$	464.18	465.2, 487.2	4.55
B14	$C_{23}H_{34}N_2O_7S$	482.21	483.4, 505.3	4.42, 4.45, 4.48, 4.53
B15	$C_{18}H_{32}N_2O_8S$	436.19	436.4, 460.2	4.40, 4.54, 4.59
B16	$C_{21}H_{38}N_2O_7S_2$	494.21	495.2, 517.2	4.54, 4.59
B17	$C_{18}H_{31}N_3O_8S$	449.18	450.4, 472.3	4.55, 4.57, 4.58
B19	$C_{19}H_{34}N_2O_7S_2$	466.18	467.2	4.52, 4.58
B21	$C_{25}H_{35}N_3O_7S$	521.22	522.3, 544.3	4.52, 4.54, 4.60

(continued)

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Table 1. Continued.

Compound	Formula	M calcd	$(M + X)^+$ found[a]	δ/ppm[b]
B22	$C_{20}H_{32}N_4O_7S$	472.20	473.4, 495.3	4.52, 4.60, 4.62
B23	$C_{20}H_{37}N_3O_7S$	463.24	464.5	4.54, 4.55, 4.60, 4.61
B24	$C_{22}H_{30}N_2O_8S$	482.17	483.4	4.57, 4.59, 4.61
B25	$C_{21}H_{32}N_2O_6S$	440.20	441.4	4.55, 4.57, 4.63, 4.65
B26	$C_{19}H_{36}N_2O_5S$	404.23	405.5, 427.4	4.50, 4.55
B27	$C_{22}H_{38}N_2O_5S$	442.25	443.5	4.58, 4.60, 4.61
B28	$C_{19}H_{33}N_3O_8S$	463.20	464.4, 486.4	4.56, 4.58
B29	$C_{21}H_{32}N_2O_5S$	424.20	425.2, 447.2	4.54, 4.55, 4.59, 4.61
C1	$C_{18}H_{25}NO_6S$	383.14	384.2, 406.1	4.49, 4.51
C2	$C_{18}H_{27}NO_6S$	385.16	408.1	4.41, 4.46
C3	$C_{24}H_{38}N_2O_7S$	498.24	499.4, 521.3	4.63, 4.64, 4.65
C4	$C_{24}H_{38}N_2O_7S$	498.24	499.2, 521.2	4.48, 4.53, 4.61
C5	$C_{23}H_{36}N_2O_7S$	484.22	485.1, 507.1	4.50, 4.51
C6	$C_{22}H_{32}N_2O_9S$	500.18	501.1, 523.2	4.45, 4.49, 4.52, 4.59
C7	$C_{23}H_{34}N_2O_7S$	482.21	483.3, 505.1	4.50, 4.57, 4.59
C8	$C_{21}H_{32}N_2O_7S$	456.19	457.2, 479.1	4.49, 4.51, 4.57, 4.59
C9	$C_{21}H_{32}N_2O_7S$	456.19	457.4	4.49, 4.51, 4.56, 4.59
C10	$C_{20}H_{30}N_2O_7S$	442.18	443.2, 465.1	4.49, 4.51, 4.58, 4.59
C11	$C_{18}H_{28}N_2O_5S$	384.17	385.4	4.59, 4.61, 4.63, 4.65
C12	$C_{20}H_{30}N_2O_6S$	426.18	449.4	4.43, 4.49
C13	$C_{23}H_{34}N_2O_9S$	514.20	515.2, 537.2	4.49, 4.50, 4.58
C14	$C_{27}H_{36}N_2O_7S$	532.22	555.2	4.49, 4.52, 4.59
C15	$C_{22}H_{34}N_2O_8S$	486.20	509.2	4.59, 4.61, 4.65
C17	$C_{22}H_{33}N_3O_8S$	499.20	500.4, 522.3	4.47, 4.49, 4.52
C18	$C_{27}H_{36}N_2O_8S$	548.22	571.3	4.46, 4.49, 4.51
C19	$C_{23}H_{36}N_2O_7S_2$	516.20	539.3	4.48, 4.50
C20	$C_{24}H_{39}N_5O_7S$	541.26	542.3	4.48, 4.51, 4.56, 4.58
C21	$C_{29}H_{37}N_3O_7S$	571.23	572.3	4.56, 4.63
C22	$C_{24}H_{34}N_4O_7S$	522.21	523.2, 545.3	4.55, 4.60, 4.62
C23	$C_{24}H_{39}N_3O_7S$	513.25	514.3	4.49, 4.52, 4.59, 4.62
C24	$C_{26}H_{32}N_2O_8S$	532.19	533.3	4.57, 4.60
C25	$C_{25}H_{34}N_2O_6S$	490.21	491.4	4.57, 4.60, 4.63, 4.64
C26	$C_{23}H_{38}N_2O_5S$	454.25	455.5	4.51, 4.54
C27	$C_{26}H_{40}N_2O_5S$	492.27	493.5	4.57, 4.63
C28	$C_{23}H_{35}N_3O_8S$	513.21	514.3	4.55, 4.58, 4.59
C29	$C_{25}H_{34}N_2O_5S$	474.21	475.2, 497.1	4.59, 4.61
D1	$C_{16}H_{25}NO_6S$	359.14	382.1	4.54, 4.55
D2	$C_{16}H_{27}NO_6S$	361.16	384.1	4.52, 4.53
D7	$C_{21}H_{34}N_2O_7S$	458.21	459.2, 481.1	4.54, 4.59
D8	$C_{19}H_{32}N_2O_7S$	432.19	433.3, 455.1	4.58, 4.59
D9	$C_{19}H_{32}N_2O_7S$	432.19	433.1, 457.1	4.58, 4.59
D10	$C_{18}H_{30}N_2O_7S$	418.18	419.1, 441.1	4.55, 4.56
D11	$C_{16}H_{28}N_2O_5S$	360.17	383.4	4.56, 4.57
D12	$C_{18}H_{30}N_2O_6S$	402.18	425.4	4.54, 4.55, 4.60
D13	$C_{21}H_{34}N_2O_9S$	490.20	491.2	4.56, 4.58
D14	$C_{25}H_{36}N_2O_7S$	508.22	509.2	4.49, 4.59

(continued)

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Table 1. Continued.

Compound	Formula	M calcd	$(M + X)^+$ found[a]	δ/ppm[b]
D16	$C_{23}H_{40}N_2O_7S_2$	520.23	521.3, 543.2	4.54, 4.55
D17	$C_{20}H_{33}N_3O_8S$	475.20	476.1, 498.2	4.57, 4.59
D21	$C_{27}H_{37}N_3O_7S$	547.23	548.3	4.59, 4.61
D22	$C_{22}H_{34}N_4O_7S$	498.21	499.3	4.59, 4.60
D24	$C_{24}H_{32}N_2O_8S$	508.19	530.2	4.52, 4.59
D25	$C_{23}H_{34}N_2O_6S$	466.21	467.4	4.57, 4.58
D26	$C_{21}H_{38}N_2O_5S$	430.25	431.5	4.64, 4.65
D29	$C_{23}H_{34}N_2O_5S$	450.21	451.2	4.57, 4.59
E1	$C_{15}H_{25}NO_6S$	347.14	348.1, 370.1	4.58, 4.63
E2	$C_{15}H_{27}NO_6S$	349.16	350.1, 372.1	4.60, 4.61, 4.62, 4.65
E3	$C_{21}H_{38}N_2O_7S$	462.24	463.1, 485.2	4.61, 4.65, 4.66
E4	$C_{21}H_{38}N_2O_7S$	462.24	463.3, 485.1	4.57, 4.60
E5	$C_{20}H_{36}N_2O_7S$	448.22	449.2, 471.3	4.60, 4.61
E6	$C_{19}H_{32}N_2O_9S$	464.18	465.2, 487.1	4.59, 4.60, 4.61
E7	$C_{20}H_{34}N_2O_7S$	446.21	448.2, 469.2	4.53, 4.57, 4.60
E8	$C_{18}H_{32}N_2O_7S$	420.19	421.3	4.59, 4.61
E9	$C_{18}H_{32}N_2O_7S$	420.19	421.3, 443.2	4.53, 4.55, 4.59, 4.60
E10	$C_{17}H_{30}N_2O_7S$	406.18	407.3, 429.2	4.57, 4.61
E11	$C_{15}H_{28}N_2O_5S$	348.17	349.5	4.60, 4.61, 4.62, 4.63
E12	$C_{17}H_{30}N_2O_6S$	390.18	413.3	4.50, 4.59, 4.61, 4.62
E13	$C_{20}H_{34}N_2O_9S$	478.20	479.2, 501.2	4.53, 4.56, 4.59
E14	$C_{24}H_{36}N_2O_7S$	496.22	497.2, 519.2	4.52, 4.54, 4.55, 4.59
E15	$C_{19}H_{34}N_2O_8S$	450.20	451.4, 473.4	4.58, 4.60, 4.65
E16	$C_{22}H_{40}N_2O_7S_2$	508.23	509.2, 531.2	4.54, 4.55, 4.59
E17	$C_{19}H_{33}N_3O_8S$	463.20	464.4, 486.3	4.54, 4.59, 4.61, 4.62
E18	$C_{24}H_{36}N_2O_8S$	512.22	513.3, 535.3	4.55, 4.60, 4.61
E19	$C_{20}H_{36}N_2O_7S_2$	480.20	481.4, 503.3	4.54, 4.56, 4.59
E20	$C_{21}H_{39}N_5O_7S$	505.26	506.4	4.58, 4.64, 4.68
E21	$C_{26}H_{37}N_3O_7S$	535.23	536.3, 558.3	4.56, 4.60, 4.64
E22	$C_{21}H_{34}N_4O_7S$	486.21	487.21	4.55, 4.61, 4.63
E23	$C_{21}H_{39}N_3O_7S$	477.25	478.4	4.59, 4.61
E24	$C_{23}H_{32}N_2O_8S$	496.19	497.4	4.60, 4.62, 4.63
E25	$C_{22}H_{34}N_2O_6S$	454.21	455.4	4.63, 4.64, 4.65
E26	$C_{20}H_{38}N_2O_5S$	418.25	419.5	4.58, 4.60
E27	$C_{23}H_{40}N_2O_5S$	456.27	457.5	4.60, 4.61
E28	$C_{20}H_{35}N_3O_8S$	477.21	478.4, 500.4	4.53, 4.59
E29	$C_{22}H_{34}N_2O_5S$	438.21	439.3, 461.2	4.59, 4.63
F1	$C_{15}H_{25}NO_6S$	347.14	370.1	4.55, 4.63
F2	$C_{15}H_{27}NO_6S$	349.16	350.1, 372.1	4.56, 4.57
F3	$C_{21}H_{38}N_2O_7S$	462.24	463.1, 485.1	4.56, 4.57, 4.62, 4.63
F4	$C_{21}H_{38}N_2O_7S$	462.24	463.3, 485.2	4.51, 4.59
F5	$C_{20}H_{36}N_2O_7S$	448.22	449.4, 471.1	4.50, 4.58
F6	$C_{19}H_{32}N_2O_9S$	464.18	465.2, 487.0	4.51, 4.52, 4.58, 4.59
F7	$C_{20}H_{34}N_2O_7S$	446.21	447.4, 469.1	4.47, 4.51, 4.58
F8	$C_{18}H_{32}N_2O_7S$	420.19	422.2, 443.1	4.51, 4.52, 4.58

(continued)

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Table 1. Continued.

Compound	Formula	M calcd	$(M + X)^+$ found[a]	δ/ppm[b]
F9	$C_{18}H_{32}N_2O_7S$	420.19	421.0	4.51, 4.58
F10	$C_{17}H_{30}N_2O_7S$	406.18	408.3, 429.1	4.52, 4.58
F11	$C_{15}H_{28}N_2O_5S$	348.17	349.5	4.55, 4.56, 4.62, 4.63
F12	$C_{17}H_{30}N_2O_6S$	390.18	413.4	4.58, 4.62
F13	$C_{20}H_{34}N_2O_9S$	478.20	479.2, 505.1	4.51, 4.58
F14	$C_{24}H_{36}N_2O_7S$	496.22	497.2, 519.2	4.46, 4.49, 4.57
F15	$C_{19}H_{34}N_2O_8S$	450.20	451.4	4.58, 4.61, 4.68
F16	$C_{22}H_{40}N_2O_7S_2$	508.23	510.2, 531.3	4.52, 4.58
F17	$C_{19}H_{33}N_3O_8S$	463.20	464.4, 486.3	4.51, 4.52, 4.58
F18	$C_{24}H_{36}N_2O_8S$	512.22	513.3, 535.3	4.52, 4.56, 4.58
F19	$C_{20}H_{36}N_2O_7S_2$	480.20	481.4	4.50, 4.52, 4.56, 4.57
F20	$C_{21}H_{39}N_5O_7S$	505.26	506.3	4.59, 4.61, 4.66
F21	$C_{26}H_{37}N_3O_7S$	535.23	536.3	4.60, 4.65
F22	$C_{21}H_{34}N_4O_7S$	486.21	487.4	4.56, 4.60, 4.65
F23	$C_{21}H_{39}N_3O_7S$	477.25	478.4	4.55, 4.60, 4.62
F24	$C_{23}H_{32}N_2O_8S$	496.19	519.2	4.56, 4.60
F25	$C_{22}H_{34}N_2O_6S$	454.21	455.4	4.56, 4.57, 4.62, 4.63
F26	$C_{20}H_{38}N_2O_5S$	418.25	419.5	4.56, 4.63, 4.65
F27	$C_{23}H_{40}N_2O_5S$	456.27	457.3	4.52, 4.53, 4.59, 4.60
F28	$C_{20}H_{35}N_3O_8S$	477.21	478.4, 500.4	4.51, 4.58
F29	$C_{22}H_{34}N_2O_5S$	438.21	439.3, 461.2	4.54, 4.55, 4.58, 4.60
G1	$C_{13}H_{21}NO_6S$	319.11	342.1	4.62, 4.66
G2	$C_{13}H_{23}NO_6S$	321.12	344.1	4.54, 4.55
G3	$C_{19}H_{34}N_2O_7S$	434.21	435.4, 457.4	4.55, 4.64
G4	$C_{19}H_{34}N_2O_7S$	434.21	435.2, 457.1	4.58, 4.59
G5	$C_{18}H_{32}N_2O_7S$	420.19	421.3, 443.1	4.59, 4.61
G6	$C_{17}H_{28}N_2O_9S$	436.15	437.1, 459.9	4.58, 4.59, 4.60
G7	$C_{18}H_{30}N_2O_7S$	418.18	419.1, 441.1	4.54, 4.55, 4.57, 4.59
G8	$C_{16}H_{28}N_2O_7S$	392.16	393.1, 415.1	4.56, 4.57, 4.58
G9	$C_{16}H_{28}N_2O_7S$	392.16	393.2, 415.1	4.55, 4.57
G10	$C_{15}H_{26}N_2O_7S$	378.15	379.1, 401.1	4.56, 4.57
G11	$C_{13}H_{24}N_2O_5S$	320.14	321.5	4.59, 4.61, 4.63
G12	$C_{15}H_{26}N_2O_6S$	362.15	383.4	4.56, 4.57, 4.59, 4.61
G13	$C_{18}H_{30}N_2O_9S$	450.17	473.3	4.52, 4.57
G14	$C_{22}H_{32}N_2O_7S$	468.19	469.2, 491.2	4.51, 4.53, 4.55, 4.59
G15	$C_{17}H_{30}N_2O_8S$	422.17	423.4	4.58, 4.61
G16	$C_{20}H_{36}N_2O_7S_2$	480.20	481.2, 503.1	4.53, 4.55, 4.57, 4.60
G17	$C_{17}H_{29}N_3O_8S$	435.17	436.4, 458.3	4.55, 4.57, 4.58, 4.59
G18	$C_{22}H_{32}N_2O_8S$	484.19	485.4, 507.3	4.52, 4.55, 4.57, 4.59
G19	$C_{18}H_{32}N_2O_7S_2$	452.16	453.4	4.55, 4.56, 4.59
G20	$C_{19}H_{35}N_5O_7S$	477.22	478.4	4.58, 4.63
G21	$C_{24}H_{33}N_3O_7S$	507.20	508.4	4.59, 4.63
G22	$C_{19}H_{30}N_4O_7S$	458.18	459.4	4.55, 4.60, 4.64
G23	$C_{19}H_{35}N_3O_7S$	449.22	450.5	4.55, 4.59, 4.62
G24	$C_{21}H_{28}N_2O_8S$	468.16	491.2	4.60, 4.63
G25	$C_{20}H_{30}N_2O_6S$	426.18	427.4	4.62, 4.63, 4.64

(continued)

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Table 1. Continued.

Compound	Formula	M calcd	$(M + X)^+$ found[a]	δ/ppm[b]
G26	$C_{18}H_{34}N_2O_5S$	390.22	391.5	4.62, 4.64
G27	$C_{21}H_{36}N_2O_5S$	428.23	429.4	4.56, 4.58, 4.60
G28	$C_{18}H_{31}N_3O_8S$	449.18	450.5	4.57, 4.59, 4.60
G29	$C_{20}H_{30}N_2O_5S$	410.18	411.2, 433.1	4.58, 4.59, 4.60, 4.61
H1	$C_{13}H_{23}NO_6S$	321.12	322.2, 344.1	4.62, 4.64
H2	$C_{13}H_{25}NO_6S$	323.14	324.1, 346.1	4.62, 4.64, 4.65
H3	$C_{19}H_{36}N_2O_7S$	436.22	437.1, 459.1	4.62, 4.64, 4.65
H4	$C_{19}H_{36}N_2O_7S$	436.22	437.3, 459.2	4.58, 4.62, 4.63
H5	$C_{18}H_{34}N_2O_7S$	422.21	423.3, 445.2	4.56, 4.60, 4.62, 4.63
H6	$C_{17}H_{30}N_2O_9S$	438.17	439.3, 461.3	4.57, 4.59, 4.61, 4.62
H7	$C_{18}H_{32}N_2O_7S$	420.19	421.4, 443.1	4.55, 4.59
H8	$C_{16}H_{30}N_2O_7S$	394.18	395.2	4.59, 4.61, 4.63
H9	$C_{16}H_{30}N_2O_7S$	394.18	395.2, 417.1	4.57, 4.60, 4.63
H10	$C_{15}H_{28}N_2O_7S$	380.16	381.1, 403.1	4.59, 4.61, 4.62, 4.64
H11	$C_{13}H_{26}N_2O_5S$	322.16	323.5	4.61, 4.62, 4.63, 4.64
H12	$C_{15}H_{28}N_2O_6S$	364.17	387.4	4.59, 4.60, 4.62, 4.63
H13	$C_{18}H_{32}N_2O_9S$	452.19	453.3, 475.2	4.55, 4.59, 4.60, 4.61
H14	$C_{22}H_{34}N_2O_7S$	470.21	471.2; 493.1	4.53, 4.56, 4.57, 4.58
H15	$C_{17}H_{32}N_2O_8S$	424.19	425.4	4.58, 4.61, 4.63
H17	$C_{17}H_{31}N_3O_8S$	437.18	438.4, 460.3	4.58, 4.59, 4.61, 4.63
H18	$C_{22}H_{34}N_2O_8S$	486.20	487.4, 509.3	4.62, 4.65
H19	$C_{18}H_{34}N_2O_7S_2$	454.18	455.2, 477.2	4.55, 4.61
H20	$C_{19}H_{37}N_5O_7S$	479.24	480.4	4.61, 4.65
H21	$C_{24}H_{35}N_3O_7S$	509.22	532.3	4.60, 4.64
H22	$C_{19}H_{32}N_4O_7S$	460.20	461.4	4.55, 4.57, 4.60, 4.64
H23	$C_{19}H_{37}N_3O_7S$	451.24	452.4	4.59, 4.61
H24	$C_{21}H_{30}N_2O_8S$	470.17	471.3	4.59, 4.60
H25	$C_{20}H_{32}N_2O_6S$	428.20	429.4	4.63, 4.64, 4.65, 4.66
H26	$C_{18}H_{36}N_2O_5S$	392.23	393.5	4.62, 4.64
H27	$C_{21}H_{38}N_2O_5S$	430.25	431.5	4.58, 4.59, 4.60
H28	$C_{18}H_{33}N_3O_8S$	451.20	452.4	4.58, 4.59
H29	$C_{20}H_{32}N_2O_5S$	412.20	413.3, 435.1	4.59, 4.60, 4.61, 4.62
I1	$C_{16}H_{27}NO_6S$	361.16	384.1	4.54, 4.57
I2	$C_{16}H_{29}NO_6S$	363.17	364.2, 386.2	4.48, 4.50, 4.52
I3	$C_{22}H_{40}N_2O_7S$	476.26	477.4, 499.4	4.52, 4.55
I4	$C_{22}H_{40}N_2O_7S$	476.26	477.2, 499.2	4.51, 4.54, 4.59
I5	$C_{21}H_{38}N_2O_7S$	462.24	463.3, 485.1	4.53, 4.56, 4.61
I6	$C_{20}H_{34}N_2O_9S$	478.20	479.4, 501.2	4.47, 4.54
I7	$C_{21}H_{36}N_2O_7S$	460.22	461.2, 483.1	4.51, 4.52, 4.55
I8	$C_{19}H_{34}N_2O_7S$	434.21	435.4, 457.1	4.49, 4.52, 4.54, 4.55
I9	$C_{19}H_{34}N_2O_7S$	434.21	435.0, 457.1	4.50, 4.51, 4.54, 4.56
I10	$C_{18}H_{32}N_2O_7S$	420.19	421.3, 443.2	4.53, 4.55
I11	$C_{16}H_{30}N_2O_5S$	362.19	363.5	4.54, 4.55, 4.56, 4.58
I12	$C_{18}H_{32}N_2O_6S$	404.20	405.5, 427.4	4.51, 4.55, 4.57, 4.62
I13	$C_{21}H_{36}N_2O_9S$	492.21	493.3, 515.3	4.50, 4.51, 4.54
I14	$C_{25}H_{38}N_2O_7S$	510.24	511.4, 533.3	4.48, 4.50, 4.51

(continued)

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Table 1. Continued.

Compound	Formula	M calcd	$(M + X)^+$ found[a]	δ/ppm[b]
I15	$C_{20}H_{36}N_2O_8S$	464.22	465.4, 487.4	4.51, 4.52, 4.58, 4.60
I16	$C_{23}H_{42}N_2O_7S_2$	522.24	523.3, 545.3	4.52, 4.55
I17	$C_{20}H_{35}N_3O_8S$	477.21	478.4, 500.3	4.52, 4.53, 4.55
I18	$C_{25}H_{38}N_2O_8S$	526.23	527.3, 549.3	4.46, 4.49, 4.50
I19	$C_{21}H_{38}N_2O_7S_2$	494.21	495.4, 507.4	4.50, 4.54, 4.55
I20	$C_{22}H_{41}N_5O_7S$	519.27	520.3	4.52, 4.55, 4.57, 4.60
I21	$C_{27}H_{39}N_3O_7S$	549.25	550.3, 572.3	4.37, 4.38, 4.44, 4.45
I22	$C_{22}H_{36}N_4O_7S$	500.23	501.4	4.52, 4.54, 4.55
I23	$C_{22}H_{41}N_3O_7S$	491.27	492.4	4.52, 4.54, 4.55, 4.58
I24	$C_{24}H_{34}N_2O_8S$	510.20	533.3	4.56, 4.57, 4.58, 4.60
I25	$C_{23}H_{36}N_2O_6S$	468.23	469.2	4.53, 4.56, 4.57, 4.59
I26	$C_{21}H_{40}N_2O_5S$	432.36	433.5	4.64, 4.65
I27	$C_{24}H_{42}N_2O_5S$	470.28	471.5	4.53, 4.54, 4.55
I28	$C_{21}H_{37}N_3O_8S$	491.23	492.4, 514.3	4.48, 4.49, 4.53, 4.55
I29	$C_{23}H_{36}N_2O_5S$	452.23	453.3, 475.2	4.55, 4.58, 4.59, 4.61
J1	$C_{14}H_{23}NO_6S$	333.12	357.1	4.61, 4.65
J2	$C_{14}H_{25}NO_6S$	335.14	336.1, 358.1	4.62, 4.63, 4.67
J3	$C_{20}H_{36}N_2O_7S$	448.22	449.1, 471.1	4.61, 4.63, 4.65
J4	$C_{20}H_{36}N_2O_7S$	448.22	449.2, 471.3	4.55, 4.57, 4.60
J5	$C_{19}H_{34}N_2O_7S$	434.21	435.2, 457.1	4.55, 4.56, 4.59, 4.63
J6	$C_{18}H_{30}N_2O_9S$	450.17	451.3, 473.3	4.55, 4.61, 4.63
J7	$C_{19}H_{32}N_2O_7S$	432.19	433.1, 455.1	4.57, 4.60, 4.64
J8	$C_{17}H_{30}N_2O_7S$	406.17	407.1, 429.2	4.62, 4.63, 4.65, 4.67
J9	$C_{17}H_{30}N_2O_7S$	406.17	407.1, 429.1	4.54, 4.56, 4.60, 4.62
J10	$C_{16}H_{28}N_2O_7S$	392.16	393.4, 415.4	4.54, 4.55, 4.61, 4.62
J11	$C_{14}H_{26}N_2O_5S$	334.16	335.5	4.59, 4.60, 4.65, 4.66
J12	$C_{16}H_{28}N_2O_6S$	376.17	377.4, 399.4	4.60, 4.61, 4.64, 4.65
J13	$C_{19}H_{32}N_2O_9S$	464.18	465.2, 487.1	4.54, 4.56, 4.62
J14	$C_{23}H_{34}N_2O_7S$	482.21	483.4, 505.4	4.52, 4.53, 4.58, 4.61
J15	$C_{18}H_{32}N_2O_8S$	436.19	437.4	4.58, 4.60, 4.62
J16	$C_{21}H_{38}N_2O_7S_2$	494.21	495.2	4.55, 4.57, 4.60, 4.64
J17	$C_{18}H_{31}N_3O_8S$	449.18	450.4, 472.3	4.52, 4.53, 4.55
J18	$C_{23}H_{34}N_2O_8S$	498.20	499.4, 521.3	4.52, 4.55, 4.58, 4.60
J19	$C_{19}H_{34}N_2O_7S_2$	466.18	467.4	4.53, 4.58, 4.62, 4.64
J20	$C_{20}H_{37}N_5O_7S$	491.24	492.4	4.55, 4.57, 4.60, 4.65
J21	$C_{25}H_{35}N_3O_7S$	521.22	522.3, 544.2	4.45, 4.50, 4.54, 4.56
J22	$C_{20}H_{32}N_4O_7S$	472.20	473.4	4.55, 4.56, 4.62, 4.63
J23	$C_{20}H_{37}N_3O_7S$	463.24	464.4	4.58, 4.62, 4.64, 4.65
J24	$C_{22}H_{30}N_2O_8S$	482.17	483.4	4.59, 4.61, 4.63, 4.65
J25	$C_{21}H_{32}N_2O_6S$	440.20	441.4	4.60, 4.62, 4.65, 4.66
J26	$C_{19}H_{36}N_2O_5S$	404.23	405.5	4.63, 4.64, 4.65
J27	$C_{22}H_{38}N_2O_5S$	442.25	443.5	4.57, 4.58, 4.59, 4.61
J28	$C_{19}H_{33}N_3O_8S$	463.20	464.4, 486.4	4.55, 4.57, 4.59, 4.61
J29	$C_{21}H_{32}N_2O_5S$	424.20	425.2, 447.2	4.57, 4.58, 4.63, 4.65

[a]X = H or Na.

[b]Anomeric protons. J = 9.5–10 Hz. The observation of less than 4 anomeric signals is a consequence of overlapping signals.

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Reductive Amination of Ketones to Secondary Amines

Reductive aminations of ketones **A1** to **J1** with primary amines, using sodium triacetoxyborohydride in dichloromethane/methanol in the presence of acetic acid and sodium sulfate, were high-yielding and produced all four possible diastereomers (except for ketone **D1** which gave a mixture of the desired secondary amine and the ketone) (Scheme 4).

Acylations of Primary Amines

Acylations of amines **A11** to **J11**, with anhydrides and pyridine in dichloromethane followed by treatment with a 1 M solution of sodium methoxide in dichloromethane were high-yielding and produced all four possible diastereomers (Scheme 4).

Monoalkylations of Primary Amines

Monoalkylations of amines **A11** to **J11**, using aldehydes, sodium triacetoxyborohydride[9] in dichloromethane/methanol in the presence of acetic acid and sodium sulfate for 10 h at room temperature, were high-yielding and produced all four possible diastereomers (except for the amine **D11** which gave a mixture of the desired compound and the primary amine) (Scheme 4).

Dialkylations of Primary Amines

Dialkylations of amines **A11** to **J11**, using aldehydes, sodium triacetoxyborohydride in dichloromethane/methanol in the presence of acetic acid and sodium sulfate for five days at room temperature, were high-yielding and produced the four possible diastereomers (except for the amine **D11** which gave only the starting material) (Scheme 4).

Since two new stereocenters were introduced during the synthetic sequence, the carbohydrate mimetic library actually contained 1088 different members (**A1–J29**, Figure 1a–c). The final library members were characterized with electrospray mass spectrometry and ^{1}H NMR spectroscopy (Table 1).

CONCLUSION

The solid phase synthesis of a highly diverse carbohydrate mimetic library has been described. We observed that 272 (Figure 1a–c) out of the target 300 library members were obtained in yields between 72 and 99% and in purities over 80% as judged from ^{1}H NMR experiments. The structures of all of the compounds are shown in Figure 1a–c, and the observed *m*/*z* values and diagnostic H-1 (GlcNAc) signal in their ^{1}H NMR spectra are collected in Table 1. In all cases, at least 2 signals for H-1 of the β-GlcNAc residue were seen, and often all of the signals for the four expected diastereomers were observed. These varied from approximately equal to the presence of two major and two minor signals. In cases where less than all four of the signals could be distinguished, the chemical shifts of the individual H-1 (GlcNAc) signals

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were most likely redundant. The library is therefore expected to contain 272 × 4=1088 structures. These are being evaluated as potential inhibitors of β-D-GlcNAc binding proteins.

EXPERIMENTAL

N-(2-ethyldisulfanyl-4,5-dihydroxy-6-hydroxymethyltetrahydropyran-3-yl)acetamide **3** (7.8 g, 24.89 mmol) was dissolved in dry pyridine (180 mL). Trityl chloride resin (10 g, loading 1.66 mmol/g of active chlorine, polymer matrix: copolystyrene, 1% DVB, 200–400 mesh, Novabiochem) and DMAP (40 mg) were added, and the mixture was heated for 48 h at 60°C. After cooling to room temperature, methanol (5 mL) was added, and after 1 h the resin was filtered off and washed successively with *N*, *N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (50 mL each, the whole cycle repeated three times) and dried under high vacuum.

The loading of the resin was determined by elemental analysis (sulfur content) and was 1.2 mmol/g.

The resin (10 g) was swollen in dry tetrahydrofuran (300 mL). Dry methanol (60 mL), dithiothreitol (15 g) and triethylamine (35 mL) were added, and the mixture was shaken 18 h at room temperature. The resin was filtered off and washed successively with *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (30 mL each, the whole cycle repeated three times) and dried under high vacuum to give **4**.

General procedure for Michael addition and α-halocarbonyl substitution. Resin **4** (400 mg, loading 1.2 mmol/g) was swollen in dry *N*,*N*-dimethylformamide (8 mL). Michael acceptor or α-haloketone here described for 2-cyclohexen-1-one (465 μL, 0.36 mmol, 10 eq) and diethylamine (220 μL) were added, and the mixture was shaken 18 h at room temperature. The resin was filtered off and washed successively with *N*, *N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (20 mL each, the whole cycle repeated three times) and dried under high vacuum.

The different analogs were synthesized using the general procedure.

General procedure for reduction of ketones to alcohols. The immobilized ketones (**A1**–**J1**, 30 mg, loading 1.2 mmol/g) were swollen in a mixture of dry tetrahydrofuran (1.5 mL) and dry methanol (150 μL). Sodium borohydride (14 mg, 0.36 mmol, 10 eq) was added and the reaction was shaken 18 h at room temperature. The resin was filtered off and washed successively with *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for reductive amination with amino acid *t*-butyl esters. The immobilized ketones (**A1**–**J1**, 30 mg, loading 1.2 mmol/g) were swollen in dry dichloromethane (1.5 mL), and sodium sulfate (200 mg) was added. The amino acid, described here with L-Gly-*t*-butyl ester hydrochloride (60 mg, 0.36 mmol, 10 eq), sodium triacetoxyborohydride (76 mg, 0.36 mmol, 10 eq) and acetic acid (40 μL) were added, the mixture was shaken 18 h at room temperature. Water (1.5 mL) was added, the resin filtered off and washed successively with water, *N*,*N*-dimethylformamide,

methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for deblocking of *N*-alkylated amino acid *t*-butyl esters. After cleavage from the resin (see general procedure), the compound was dissolved in trifluoroacetic acid (1 mL). The solution was shaken 18 h at room temperature, concentrated, dissolved in water (2 mL), passed through a 0.22 μm filter unit (Millipore filter) and lyophilized.

General procedure for reductive amination with amino acid methyl esters. The resin (ketones **A1**–**J1**, 30 mg, loading 1.2 mmol/g) was swollen in a mixture of dry dichloromethane (3 mL) and dry methanol (300 μL) with sodium sulfate (200 mg). The amino acid, described here with L-Lys methyl ester dihydrochloride (84 mg, 0.36 mmol, 10 eq), sodium triacetoxyborohydride (76 mg, 0.36 mmol, 10 eq) and acetic acid (40 μL) were added and the mixture was shaken 48 h at room temperature. Water (1.5 mL) was added, the resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for deblocking of *N*-alkylated amino acid methyl esters. The resin (ketones **A1**–**J1**, 30 mg, loading 1.2 mmol/g) was swollen in tetrahydrofuran (2 mL). Methanol (200 μL) and then a 1 M solution of lithium hydroxide (200 μL) were added and the mixture was shaken 18 h at room temperature. The resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for cleavage from the resin. A solution of 2% trifluoroacetic acid in dichloromethane (1 mL) was added to the resin (30 mg). The mixture was shaken 30 min at room temperature. After filtration, the resin was washed with methanol and dichloromethane (4 mL each) and the filtrate was concentrated. The residue was dissolved in water (2 mL), passed through a 0.22 μm filter unit (Millipore filter) and lyophilized.

General procedure for reductive amination of ketones to primary amines. The resin (ketones **A1**–**J1**, 200 mg, loading 1.2 mmol/g) was swollen in dry dichloromethane (6 mL) with sodium sulfate (400 mg). A solution of ammonium acetate in methanol (20 eq, 720 mg of ammonium acetate in 2.4 mL of methanol), sodium triacetoxyborohydride (510 mg, 2.40 mmol, 10 eq) and triethylamine (220 μL) were added. The mixture was shaken 48 h at room temperature. Water (5 mL) was added, the resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (10 mL each, the whole cycle repeated three times) and dried under high vacuum. The whole cycle of the reductive amination was repeated two more times to drive the reaction to completeness.

General procedure for reductive amination of ketones to secondary amines. The resin (ketones **A1**–**J1**, 30 mg, loading 1.2 mmol/g) was swollen in a mixture of

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dry dichloromethane (2 mL) and dry methanol (200 μL) with sodium sulfate (200 mg). The amine, described here with benzylamine (40 μL, 0.36 mmol, 10 eq), sodium triacetoxyborohydride (76 mg, 0.36 mmol, 10 eq) and acetic acid (160 μL) were added. The reaction was shaken 18 h at room temperature. Water (1.5 mL) was added, the resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for acylation of primary amines. The resin (amines **A11**–**J11**, 30 mg, loading 1.2 mmol) was swollen in dichloromethane (2 mL). Pyridine (200 μL) and anhydride, described here with acetic anhydride (34 μL, 0.36 mmol, 10 eq) were added and the mixture was shaken 18 h at room temperature. The resin was filtered off and washed successively with *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times). The resin was swollen in dichloromethane (1 mL), one molar solution of sodium methoxide in methanol (100 μL) was then added. The mixture was shaken 3 h at room temperature. The resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for monoalkylation of primary amines. The resin (amines **A11**–**J11**, 30 mg, loading 1.2 mmol/g) was swollen in dry dichloromethane (2 mL) with sodium sulfate (200 mg). Dry methanol (200 μL) and the aldehyde, described here with 4-hydroxybenzaldehyde (45 mg, 0.36 mmol, 10 eq), were added and the mixture was shaken 10 min at room temperature. Sodium triacetoxyborohydride (76 mg, 0.36 mmol, 10 eq) and acetic acid (40 μL) were then added and the reaction was shaken 10 h at room temperature. Water (1.5 mL) was added, the resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

General procedure for dialkylation of primary amines. The resin (amines **A11**–**J11**, 30 mg, loading 1.2 mmol/g) was swollen in dry dichloromethane (2 mL) with sodium sulfate (200 mg). Dry methanol (200 μL) and the aldehyde, described here with crotonaldehyde (30 μL, 0.36 mmol, 10 eq) were added and the mixture was shaken 10 min at room temperature. Sodium triacetoxyborohydride (76 mg, 0.36 mmol, 10 eq) and acetic acid (40 μL) were then added and the reaction was shaken 5 days at room temperature. Water (1.5 mL) was added, the resin was filtered off and washed successively with water, *N*,*N*-dimethylformamide, methanol, tetrahydrofuran and dichloromethane (2 mL each, the whole cycle repeated three times) and dried under high vacuum.

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