Carbohydrate-Based Small-Molecule Scaffolds for the Construction of Universal Pharmacophore Mapping Libraries

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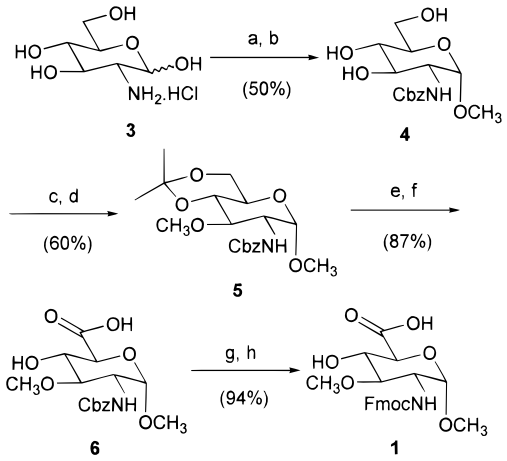
Combinatorial chemistry occupies a prominent position in the modern drug discovery process.[1] Because of its ability to generate large numbers of structurally diverse molecules, combinatorial chemistry has been able to reduce the drug discovery timeline by meeting the compound needs of high throughput screening programs. Continued success will rely heavily on the development of new chemical platforms for constructing useful combinatorial molecular diversity. By rapidly defining novel three-dimensional functional group relationships, i.e., pharmacophores, the ideal combinatorial chemical platform will allow access to broad diversity space, thus facilitating the identification of tight binding ligands against a wide variety of biomolecular targets.

Monosaccharides possess a unique set of characteristics, which makes them particularly attractive as platforms around which to design primary screening libraries. Hexoses are enantiomerically pure and conformationally rigid. They provide a defined three-dimensional spatial arrangement of substituents, are highly functionalized, and therefore, provide high intrinsic combinatorial density. The unique characteristics of monosaccharides were first recognized by Hirschmann, Nicolaou, and Smith in their successful use of β-D-glucose as a β-turn mimetic in the design of nonpeptide somatostatin mimetics and were later exploited by others.[2] The discovery that hexose derivatives also bind with high affinity to several pharmacologically important receptors suggests that, as priviledged platforms, monosaccharide systems are valuable for generating combinatorial libraries. However, readily accessible carbohydrate-based combinatorial platforms have yet to be described.

In this report, we describe the first effective solid-phase chemical method for the preparation of carbohydrate-based universal pharmacophore mapping libraries as a new strategy for identifying novel receptor ligands.

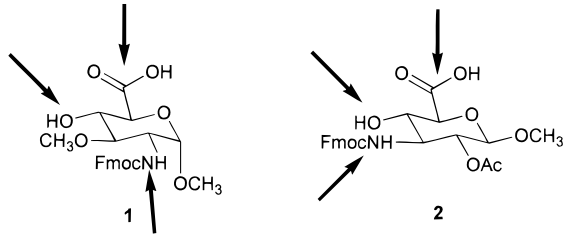
To investigate the potential of carbohydrates for the preparation of universal pharmacophore mapping libraries, two monosaccharide scaffolds **1** and **2** were prepared as outlined in Schemes 1 and 2. Three sites of diversification were incorporated into each scaffold to provide the minimal

Scheme 1[a]



[a] Reagents and conditions: (a) Na_2CO_3, BnOCOCl, H_2O, 4 °C; (b) CH_3OH, HCl−dioxane, 60 °C; (c) $(CH_3O)_2C(CH_3)_2$, *p*-TsOH, DMF, rt; (d) NaH, CH_3I, THF, rt; (e) *p*-TsOH, Amberlite, rt; (f) TEMPO[3], NaOCl, *n*-Bu_4NCl, KBr, $NaHCO_3$, NaCl, H_2O, 0 °C; (g) 10% Pd−C, H_2 (40 psi), EtOAc; (h) Fmoc-Cl, $NaHCO_3$, DIPEA, dioxane−H_2O, rt. DIPEA = *N*,*N*-diisopropylethylamine; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

requirements needed for pharmacophoric chiral molecular recognition. The desired three-point motif was achieved by a scaffold design that incorporated a carboxylic acid moiety, a free hydroxyl group, and a protected amino group. This functional group triad afforded the chemoselectivity necessary for rapid combinatorial solid-phase synthesis, allowing us to maximize molecular diversity while minimizing the number of solid-phase synthetic steps.



Chemical diversity was introduced at the three combinatorial sites on each scaffold using the solid-phase chemistry exemplified in Schemes 3−5. To minimize the number of solid-phase chemistry steps, the first diversification step occurred by attaching the scaffold to the solid support through a prelinked diversity element. Consequently, each glycocarboxylic acid was linked to the free amine of an amino acid functionalized carboxytrityl Tentagel resin,[5] furnishing the scaffold functionalized resins **12** and **13**. In Schemes 4 and 5, isopropyl isocyanate, 2,4-dimethoxybenzoic acid, and 4-nitrobenzoic acid were used to demonstrate the efficiency of the solid-phase chemistry strategy. Carbamate formation[6] at the free hydroxyl site followed by amide formation at the deprotected amine site produced the desired resin-linked trifunctionalized scaffolds. For scaffold **2**, an additional step was required to remove the acetate protecting group at C-2. All products were cleaved from the solid support with 10%

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(1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, 37, 1385−1400.

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(5) NovasynTGT resin is a Tentagel-based resin that has been amino functionalized and derivatized with a 4-carboxytrityl linker. It is available from Novabiochem.

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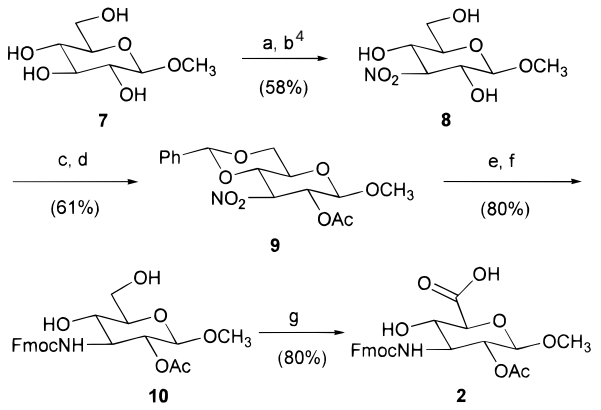
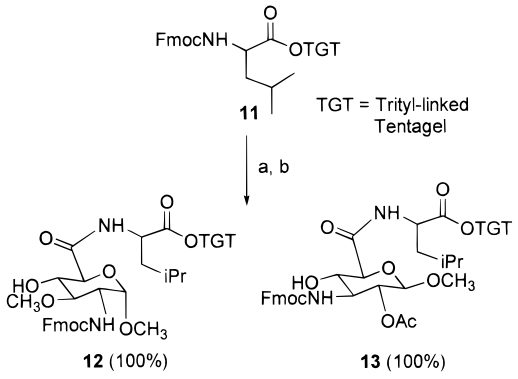
Scheme 2[a]



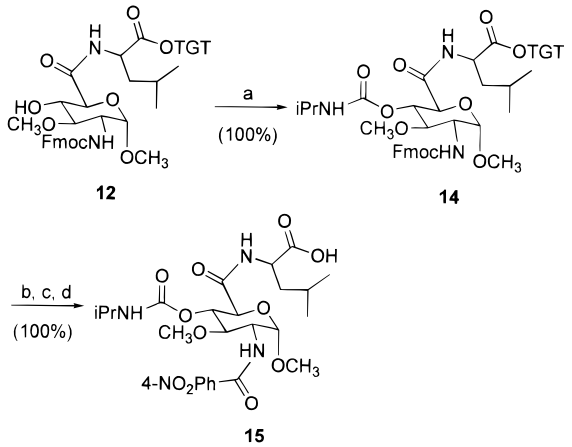
[a] Reagents and conditions: (a) $NaIO_4$, H_2O, 0−25 °C; (b) $NaOCH_3$, CH_3NO_2, CH_3OH, 0 °C to rt; (c) $PhCH(OCH_3)_2$, *p*-TsOH, DMF, 65 °C; (d) Ac_2O, C_6H_5N, 0 °C; (e) 20% $Pd(OH)_2$−C, H_2 (40 psi), AcOH−CH_3OH; (f) FmocONSu, DIPEA, THF, rt; (g) TEMPO, NaOCl, *n*-Bu_4NCl, KBr, $NaHCO_3$, NaCl, H_2O, 0 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) 20% piperidine/DMF, rt; (b) (**1**) or (**2**), HATU, DIPEA, DMF, rt. HATU = [*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate].

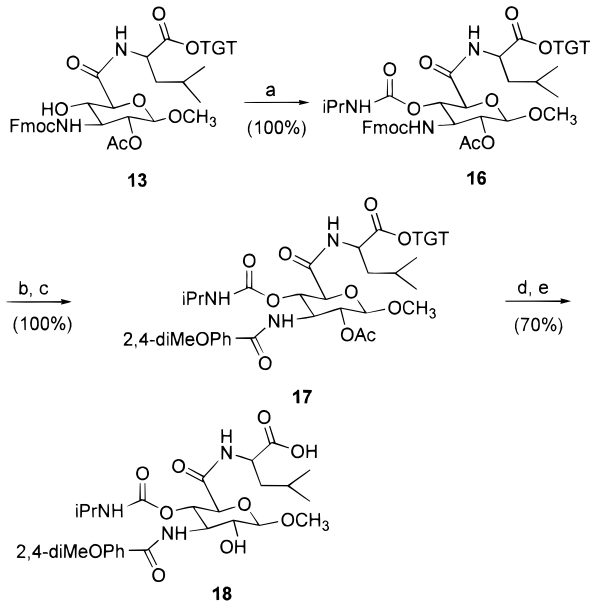
Scheme 4[a]



[a] Reagents and conditions: (a) 0.5 M *i*-PrNCO/DMF, cat. Cu(I)Cl, rt; (b) 20% piperidine/DMF, rt; (c) 4-nitrobenzoic acid, HATU, DIPEA, DMF, rt; (d) 10% TFA/1,2-dichloroethane, rt.

TFA. The trifunctionalized scaffolds **15**[7] and **18**[8] were obtained in 100% and 70% yields, respectively. By LC/MS analysis, the purity of these products was shown to be >90%. We also demonstrated that urea formations, sulfonamide formations, and reductive alkylations at the deprotected amine site of each scaffold occur efficiently on the solid phase (data not shown).

Scheme 5[a]



[a] Reagents and conditions: (a) 0.5 M *i*-PrNCO/DMF, cat. Cu(I)Cl, rt; (b) 20% piperidine/DMF, rt; (c) 2,4-dimethoxybenzoic acid, HATU, DIPEA, DMF, rt; (d) 0.1 M LiOH/THF−CH_3OH, rt; (e) 10% TFA/1,2-dichloroethane, rt.

A library based on scaffolds **1** and **2** was prepared as discrete compounds using the IRORI AccuTag-100 radio frequency tagged solid-phase synthesis system and the directed sorting split-pool method. Scaffolds **1** and **2** were each coupled to eight amino acid-functionalized trityl-Tentagel resins. Each scaffold−amino acid resin was then used to prepare a 48-member sublibrary by reaction with six isocyanates and eight carboxylic acids. Several of the amino acid building blocks contained acid-labile protecting groups. These protecting groups were removed concomitantly with cleavage of the final product from the solid support. In total, 16 48-member sublibraries were prepared. Library analysis by LC/MS showed that 90% of the library products were produced in >80% purity.[9]

A new strategy for the construction of broad screening libraries using a carbohydrate-based universal pharmacophore mapping library strategy has been described. This strategy takes advantage of the unique molecular characteristics of saccharides and the efficiency and speed of solid phase chemistry. By employing a family of trifunctionalized saccharide scaffolds in a combinatorial library strategy, it is possible to rapidly define a pharmacophore map of a biomolecular receptor.

Supporting Information Available: The detailed experimental procedures and characterization data for compounds **1**−**10**, **15**, and **18** and resin cleavage products of **12**−**14**, **16**, and **17**, including representative LC/MS data for library products (28 pages).

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(7) Compound **15**: ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6/D_2O) δ 8.16 (d, 2, J = 9.7 Hz), 8.0 (d, 2, J = 9.7 Hz), 7.83 (d, 1, J = 8.7 Hz), 4.85 (m, 2), 4.7 (br.s, 1), 4.4 (m, 2), 4.05 (d, 1, J = 12 Hz), 3.75 (dd, 1, J = 12 Hz), 3.5 (s, 3), 3.5 (m, 2), 3.3 (s, 3), 1.6 (m, 3), 1.25 (m, 1), 1.05 (m, 6), 0.8 (m, 6).

(8) Compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6/D_2O) δ 8.32 (br d, 1), 8.0 (d, 1, J = 9 Hz), 6.47 (dd, 1, J = 9 Hz, 3 Hz), 6.36 (d, 1, J = 3 Hz), 4.85 (dd, 1, J = 9 Hz), 4.75 (br s, 1), 4.46 (m, 1), 4.43 (d, 1, J = 7 Hz), 4.15 (m, 1), 3.83 (s, 3), 3.83 (m, 1), 3.74 (s, 3), 3.5 (s, 3), 3.45 (m, 1), 1.55 (m, 5), 1.2 (d, 1), 1.0 (m, 6), 0.9 (m, 8).

(9) Library building blocks and LC/MS data for representative library products can be found in the provided Supporting Information.