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A peptide-based catalyst approach to regioselective functionalization of carbohydrates

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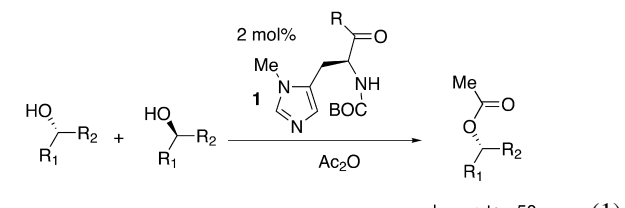
Abstract—Two small peptide libraries (150 members and 36 members) have been subjected to screening experiments to evaluate their potential for regioselective (i.e. site-selective) acylation of carbohydrate monomers. Two substrates, one diol derived from *N*-acetyl glucosamine and one tetraol derived from glucose, have served as the test cases. In each case, the inherent regioselection of catalyzed acylation was defined as that derived from the reaction where *N*-methylimidazole (NMI) is used as the catalyst. With both substrates, peptides were found to perturb the inherent selectivities from those observed with NMI. From the libraries, the catalysts that provide the largest deviation from NMI were subjected to optimization studies. The work sets the groundwork for studies of expanded peptide libraries and development of structure-selectivity relationships to obtain catalysts that can selectively derivatize the unique sites in stereochemically complex polyols.

1. Introduction

The chiral pool continues to represent a tremendous storehouse of useful compounds that often serve as starting places for complex molecule synthesis.[1] Similarly, complex polyfunctional natural products often represent important starting points for the generation of natural product analogs in the search for biologically active molecules with optimized properties. While great strides have been made in the use of the chiral pool for both purposes, there is little doubt that the endeavor is complicated by a large dependence on protecting group manipulations. One approach to the selective functionalization of polyfunctional molecules continues to be the application of enzymes as regioselective catalysts.[2] Indeed, biotechnology continues to make important contributions to this area. But, the specificity of enzymes has led to a situation where enzyme-based methods do not provide a comprehensive set of solutions. Other approaches have included the innovative use of designed protecting-directing groups,[3] and also the exploitation of host–guest interactions.[4] To date, the application of small-molecule catalysts has been fairly limited in scope, with most of the studies focused on the use of chiral nucleophilic catalysts.[5] In particular, both Yoshida[6] and Vasella[7] have made important contributions in this area, studying a set of catalysts for the selective functionalization of a range of minimally protected carbohydrate monomers. The development of a few approaches to efficient manipulation of the chiral pool could have a substantial impact, both on synthesis, and also the generation of libraries of natural products that are unambiguously 'natural-product-like' in their genesis.[8]

Recent studies in our laboratory have demonstrated that small peptides containing modified histidine residues (π-methyl histidine, **1**) are effective catalysts for enantioselective acylation and phosphorylation reactions.[9] Two of the most encouraging cases are shown below. Octapeptide **2** catalyzes kinetic resolution of a range of secondary alcohols with k_{rel} values up to >50 (Eq. (1)).[10] Pentapeptide **3** catalyzes the desymmetrization of *meso* triol **4**, affording product **5** in 65% isolated yield, with >98% ee (Eq. (2)).[11] The fact that peptides in this family are able to convey substantial stereochemical information in these catalytic reactions, in combination with the fact that each was discovered from screening experiments, stimulated us to explore this family of chiral catalysts for its ability to carry out regioselective reactions.



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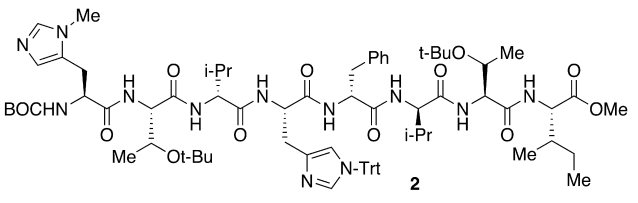

Keywords: regioselectivity; *N*-methylimidazole (NMI); acylation.

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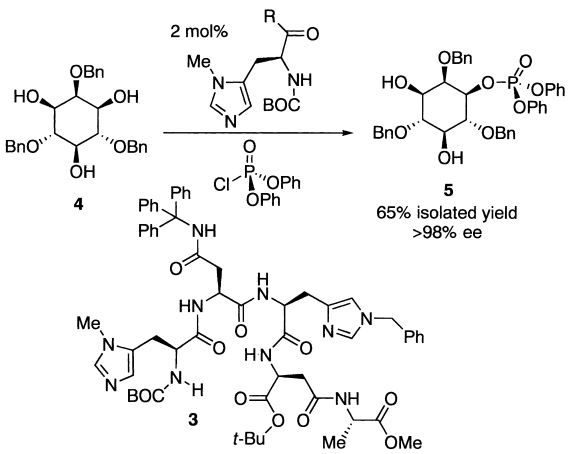
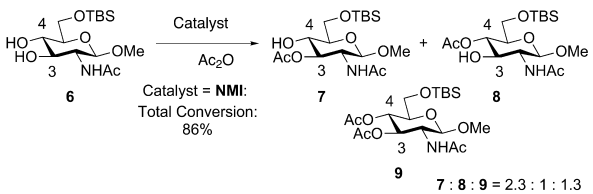


(2)

2. Results and discussion

Our experiments began with an investigation of the acylation reactivity of glucosamine derivative **6** (Eq. (3)).[12] This substrate presents two regiotopic diols that are clearly in different environments. Whereas the 3-hydroxyl is flanked by the 2-acetamide and the 4-secondary hydroxyl, the 4-OH is vicinal to a hydroxyl and two oxygen based substituents. In terms of positional reactivity, when **6** undergoes acylation in the presence of NMI (20 mol%, 1 equiv. Et_3N, toluene, 25°C), a complex reaction mixture is produced (86% conversion). In order to document that the observed product distributions are the product of kinetic selection, isolated samples of each product were obtained, and resubjected to the reaction conditions. In these experiments, the isolated products were found to be stable, and were recovered without modification.



(3)

With the fundamental reactivity of substrate **6** defined under a unique set of conditions, we sought to evaluate a small peptide library to see if there were observable differences in product distribution. We chose 150 peptides that had been prepared in our earlier studies. All peptides were in the family defined by structure **1**, which included tetrapeptides through octapeptides (the sequences may be found in the Section 4.6). The catalysts were then studied under a uniform set of reaction conditions (2 mol%, 1 equiv. Ac_2O, 25°C, 15 h followed by MeOH quench); data are presented in a histogram in Figure 1. The peptides indeed afford a range of product distributions. Several things become clear upon evaluation of the data. First, with all of the peptides, deviations from the selectivity observed with NMI are apparent. Second, the inherently higher reactivity of the 3-OH under the conditions is manifested with essentially all of the catalysts. Indeed, many provide enhanced selectivity for product **7** in comparison to NMI, a result that may reflect an interaction between the acetamide of **6** and the H-bond donors and acceptors of the catalysts. In contrast, very few of the catalysts reverse the inherent selectivity of the peptide, tilting the product ratio toward product **8**. Perhaps also of significance is that with the peptide-based catalysts, very little of the diacetate **9** is typically produced (data not shown). The two most noteworthy catalysts from the initial screen are identified in Figure 1 with bold arrows. For the catalyst labeled **10**, there is a significant increase in selectivity for the C3–OH product **7**. For catalyst **3**, the

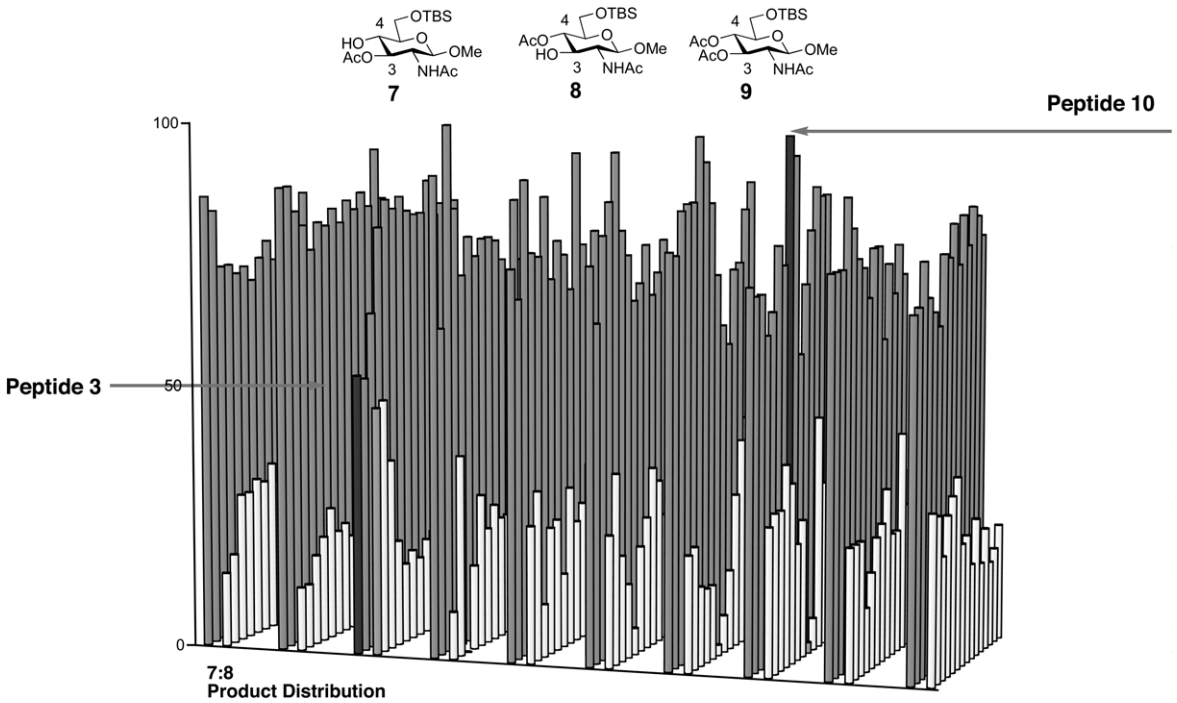
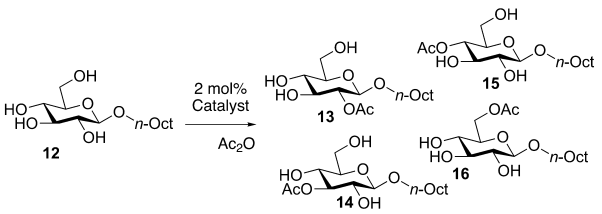


Figure 1. 3D Bar graph showing regioselectivity for acylation of diol **6**. Selectivity for product **7** is shown in grey. Selectivity for product **8** is shown in white. Data for diacetate **9** is not shown. Two catalysts that provide highly disparate selectivity are identified with a red arrow. There are 15 catalysts in each stacked row.

selectivity starts to go the other way, with a near 1:1 **7/8** ratio observed under the reaction conditions. These two catalysts were then selected for further study.

When each was purified and explored in toluene solution, unambiguous deviations from NMI were documented (Table 1). Catalyst **10**, shown below (Table 1), results in highly selective formation of product **7**, affording a 97:3 ratio of products, and diacetate **9** is not observed. In contrast, peptide **3** delivers a near 1:1 mixture (53:47) for the C3–OH (**7**) and C4–OH (**8**) products. Although **3** does not provide high selectivity for product **8**, the fact that it shifts the selectivity to the other side of the ratio afforded by NMI suggests that this peptide-catalyst is overcoming the inherent reactivity biases presented by the substrate. This possibility bodes well for future studies of catalysts in this family for this objective.

Having observed peptides that could deliver product distributions on either side of the ratio delivered by NMI, we wished to establish if such a possibility were specific to glucosamine derivatives like **6**, or if it might be possible with polyols that lacked amides. We thus elected to explore tetraol **12**[13] in the same type of screening study (Eq. (4)). Of note, the product distribution delivered when NMI is used as the catalyst is particularly modest. Under standard conditions (1 equiv. Ac_2O, $CHCl_3$, NaOAc, 0°C), overall reactivity is quite low with only 14% total conversion observed. Furthermore, of the acylated products, the primary acetate **16** is the dominant product (64% of total acetate), followed by 20% of acetate **14** and 16% of acetate **15** (relative to total acetylated product). Of particular note, the 2-OAc product **13** is not observed to an appreciable extent under these conditions.

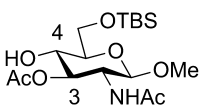
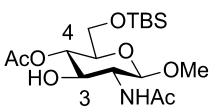
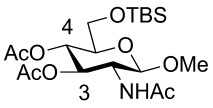


(4)

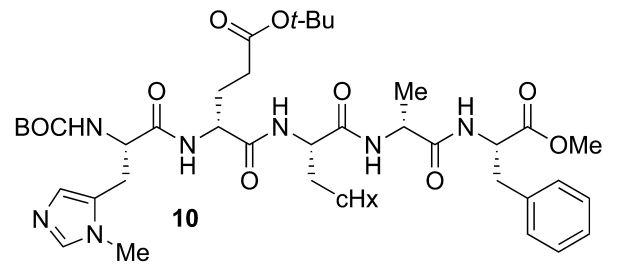
Evaluation of a small peptide library (36 members, Fig. 2) once again showed that the peptides are indeed capable of perturbing the inherent selectivities.[14] Of particular note was that in these experiments, the overall extent of conversion was enhanced in comparison to NMI. In addition, many of the catalysts reversed the inherent selectivity of the reaction away from the primary hydroxyl groups such that one of the secondary alcohols was derivatized to a greater extent. Among the catalysts examined, peptide **17** surfaced as the one that was most distinct from NMI in terms of its selectivity profile.

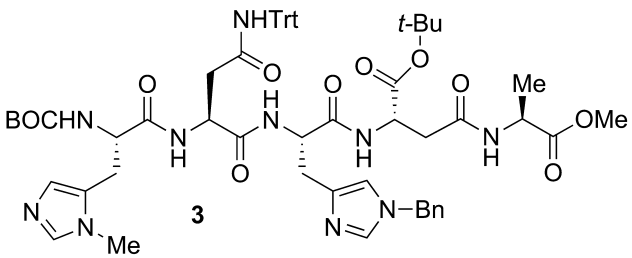
When **17** was employed in the reaction under optimized conditions, complete consumption of the tetraol to acetylated products was observed. Interestingly, 4-OAc product **15** was the dominant product, observed as 58% of the reaction mixture. Primary acetate **16** was the next most abundant component, present as 22% of the mixture. Finally, the 2-OAc product **13** and the 3-OAc product **14** were present at 9 and 11% respectively. That peptide **17** shifts the inherent selectivity observed with NMI from the primary hydroxyl group to one of the secondary sites is particularly intriguing. This observation is one that will

Table 1. 'Hit' catalysts for deviation for NMI derived from the initial peptide library

Catalyst				Total conversion
NMI	50	22	28	86
10	97	3	0	88
3	53	47	0	80

2 mol% catalyst, $PhCH_3$, 25°C, 15 h.





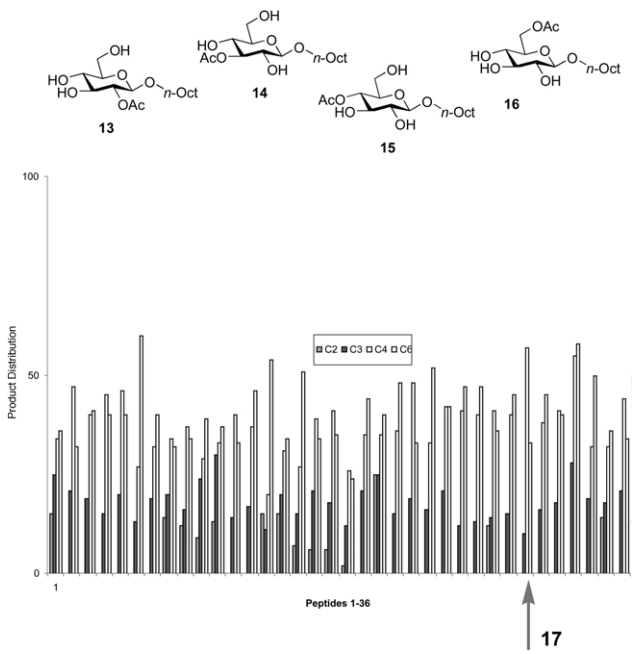


Figure 2. Histogram showing product distribution for regioselectivity observed for acylation of tetraol **12**. Selectivity for product **13** is shown in blue; selectivity for **14** in red; selectivity for **15** in green; selectivity for **16** in violet. Data for polyacetates not shown.

require additional studies to understand and exploit to a more dramatic extent (Table 2).

3. Conclusions

Many challenges remain to achieve a systematic approach to catalytic regioselective carbohydrate acylation. While it is clear that the functionality and chirality endemic to small peptides possess the ability to alter kinetic selectivity in reactions of polyols with Ac_2O, the rules which dictate the perturbations are elusive at this time. One approach to the problem is to apply an expanded diversity-based approach in combination with the development of structure-selectivity relationships to obtain a mechanistic understanding of the selectivity distributions. The development of such a database of results, and its application to the efficient manipulation of the chiral pool are among our current objectives.

4. Experimental

4.1. General procedures

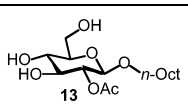
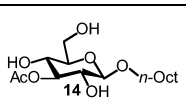
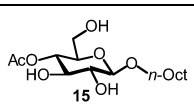
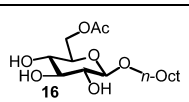
Proton NMR spectra were recorded on Varian 400 or 500 spectrometers. Proton chemical shifts were reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ, 0.0). Spectral data is reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants (J) [Hz], integration). Carbon NMR spectra were recorded on a Varian 400 MHz (100 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to the residual solvent signal ($CDCl_3$, δ 77.16). NMR data were collected at 25°C, unless otherwise indicated. Infrared spectra were obtained on a Perkin–Elmer Spectrum 1000 spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 pre-coated plates (0.25 mm thickness), TLC R_f values are reported and visualization was accomplished by irradiation with a UV lamp and/or staining with cerium ammonium molybdate (CAM) solutions. Flash column chromatography was performed using Silica Gel 60A (40 μ) from Scientific Adsorbents Inc. High resolution mass spectra were obtained from Mass Spectrometry Facilities of Boston College (Chestnut Hill, MA). The method of ionization is given in parentheses. Elemental analyses were obtained from Robertson Microlit Laboratories Inc. (Madison, NJ).

Analytical and preparative HPLC were performed on a Rainin 50–200 chromatograph equipped with a single wavelength UV detector (214 nm).

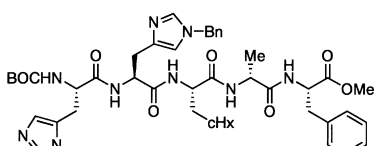
All reactions were carried out under a nitrogen atmosphere employing oven and flame-dried glassware, unless otherwise indicated. All solvents were distilled from appropriate drying agents prior to use. Acetic anhydride was distilled over P_2O_5 prior to use and stored under a nitrogen atmosphere.

Compound **6** was prepared in four steps from commercially

Table 2. 'Hit' catalysts for deviation from NMI derived from the peptide library

Catalysts	 13	 14	 15	 16	Total Conversion
NMI	0	20	16	64	14
17	9	11	58	22	100

2 mol % catalyst, $PhCH_3/CH_2Cl_2$, 0°C, 15 h.



available *N*-acetyl-D-glucosamine. (for procedure see Ref. 12). *N*-Methyl imidazole (NMI) was distilled and stored under an atmosphere of nitrogen prior to use.

4.2. Conditions for high throughput screen for selective acetylation of 6

A stock solution of **6** in methylene chloride (50.0 μL, 0.0286 mmol) was diluted with toluene (2.90 mL). A stock solution of acetic anhydride in methylene chloride (50.0 μL, 0.0286 mmol) was added, followed by the addition of a stock solution of catalyst in methylene chloride (50.0 μL, 0.572 μmol). After stirring for 15 h at 25°C, the reaction was quenched with 50.0 μL of methanol, allowed to stir for an additional 5 min and then concentrated in vacuo. The crude reaction mixtures were then subjected to NMR analysis.

4.3. Assay of product distribution

Product distribution was determined by integration of ^{1}H NMR signals arising from the C3 proton of compound **7** and the C4 proton of compound **8**. Identification of regioisomers was determined by 2D NMR experiments in which proton assignments were made relative to the anomeric proton of compounds **7** and **8**. Conversions relative to diol **6** were calculated employing bromoform as an internal standard.

4.3.1. Data for monoacetate 7. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (d, *J*=9.15 Hz, 1H), 5.04 (t, *J*=9.15 Hz, 1H), 4.39 (d, *J*=8.42 Hz, 1H), 3.99–3.84 (m, 3H), 3.74 (dt, *J*=9.15, 2.56 Hz, 1H), 3.52–3.41 (m, 5H), 2.11 (s, 3H), 1.96 (s, 3H), 0.90 (s, 9H), 0.10 (d, *J*=2.93 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 170.2, 101.9, 75.6, 74.2, 71.7, 64.9, 56.5, 53.8, 26.0, 23.6, 21.3, 18.5, −5.1, −5.2; IR (film, cm^{-1}) 3313, 3093, 2923, 2854, 1746, 1651; TLC R_f 0.47 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{17}H_{34}NO_7Si$] requires *m*/*z* 392.2105. Found 392.2106 (ES+).

4.3.2. Data for monoacetate 8. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (d, *J*=4.03 Hz, 1H), 4.84 (t, *J*=9.52 Hz, 1H), 4.48 (d, *J*=8.06 Hz, 1H), 3.89 (t, *J*=9.52 Hz, 1H), 3.74–3.67 (m, 2H), 3.51–3.43 (m, 5H), 2.11 (s, 3H), 2.05 (s, 3H), 0.89 (s, 9H), 0.059 (d, *J*=1.83 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 170.4, 100.8, 75.3, 73.5, 72.2, 62.9, 58.9, 56.7, 34.8, 26.1, 23.8, 21.3, 18.6, −4.9, −5.1; IR (film, cm^{-1}) 3295, 3100, 2923, 2923, 2955, 2854, 1746, 1658; TLC R_f 0.35 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{17}H_{34}NO_7Si$] requires *m*/*z* 392.2105. Found 392.2086 (ES+).

4.3.3. Data for diacetate 9. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.42 (d, *J*=8.79 Hz, 1H), 5.20 (t, *J*=10.07, 1H), 5.00 (t, *J*=9.70 Hz, 1H), 4.49 (d, *J*=8.42 Hz, 1H), 3.93–3.86 (m, 1H), 3.75–3.67 (m, 2H), 3.55–3.49 (m, 5H), 2.03 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H), 0.88 (s, 9H), 0.056 (d, *J*=3.66 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.0, 169.3, 101.6, 74.9, 73.1, 69.3, 62.8, 56.6, 54.6, 26.1, 23.7, 21.0, 18.6, −5.0; IR (film, cm^{-1}) 3269, 3093, 2930, 2854, 1753, 1658, 1570; TLC R_f 0.53 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{19}H_{35}NO_8NaSi$] requires *m*/*z* 456.2030. Found 456.2037 (ES+).

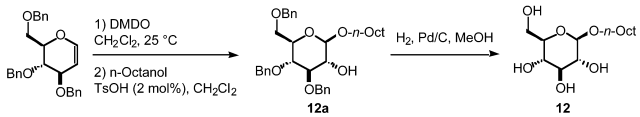
4.3.4. Conditions for high throughput screen for selective acetylation of 12. Initial library screening was accomplished under the conditions of Yoshida and co-workers (Ref. 6): Ac_2O (1 equiv.), 5 mol% catalyst, NaOAc, $CHCl_3$ at 0°C, 1 h.

4.3.5. Analysis of product distribution. Product distributions were determined by integration of the acetate proton signals arising from monoacetates **13**, **14**, **15** and **16**. Spectral data were compared to that reported by Yoshida and co-workers (Ref. 6b). Product yields were determined relative to acetic anhydride employing bromoform as an internal standard.

4.3.6. Optimized conditions for the selective acetylation of 12. A stock solution of **12** in methylene chloride (400 μL, 0.0171 mmol) was added to 2.00 mL of toluene followed by the addition of a stock solution of acetic anhydride in methylene chloride (50.0 μL, 0.0122 mmol). A stock solution of catalyst (20.0 μL, 0.244 μmol) was added to the reaction. Reactions run at 0°C were cooled in an ice bath for 20 min prior to the addition of catalyst. After stirring for 15 h at 25 or 0°C, the reaction was quenched with methanol (50.0 μL), allowed to stir for an additional 5 min and then concentrated in vacuo. The crude reaction mixtures were then subjected to NMR analysis.

4.4. Preparation of 12

Glucose derivative **12** was prepared in three steps from commercially available 3,4,6-tri-*O*-benzyl D-glucal. Synthesis of **12** began with formation of a 1,2-anhydro glycosyl donor from tri-*O*-benzyl D-glucal employing the procedure of Danishefsky (Ref. 13). Glycosylation employing 1-octanol as the glycosyl acceptor followed by hydrogenolysis of the benzyl groups affords **12** (Scheme 1).



Scheme 1.

4.4.1. Synthesis of 12a. To a suspension of 1,2-anhydro-glucal substrate (1.04 g, 2.40 mmol) and 4 Å molecular sieves (0.100 g, pellets) in anhydrous CH_2Cl_2 (10.0 mL) was added 1-octanol (190 μL, 1.20 mmol). *p*-Toluenesulfonic acid (5.0 mg, 0.024 mmol) was then introduced into the reaction. The reaction was allowed to stir at room temperature for 15 h. The reaction was then concentrated in vacuo and purified by silica gel chromatography eluting with a 5–10% EtOAc/hexane gradient to afford each individual anomer. (66% isolated yield, 30/70 α/β desired anomer-β).

Data for **12a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.16 (m, 15H), 4.94 (d, *J*=11.4 Hz, 1H), 4.83 (d, *J*=11.0 Hz, 2H), 4.62 (d, *J*=12.1 Hz, 1H), 4.56–4.52 (m, 2H), 4.24 (d, *J*=7.30 Hz, 1H), 3.94–3.89 (m, 1H), 3.75 (dd, *J*=10.8, 1.92 Hz, 1H), 3.69 (dd, *J*=10.6, 4.76 Hz, 1H), 3.61–3.46 (m, 5H), 2.31 (d, *J*=2.2 Hz, 1H), 1.63 (m, 2H), 1.31 (m, 10H), 0.88 (t, *J*=6.78 Hz, 3H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 138.5, 138.0, 137.9, 128.3, 128.2, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 102.6, 84.5, 77.6, 75.1, 75.0, 75.0, 74.7, 73.5, 70.1, 68.9, 31.9, 29.7, 29.5, 29.3, 26.1, 22.7, 14.2; IR (film, cm^{-1}) 3428, 3066, 3028, 2926, 2855; TLC R_f 0.32 (20% EtOAc/hexane). Anal. calcd for $C_{35}H_{46}O_6$: C, 74.70; H, 8.24. Found C, 74.60; H, 8.24.

4.4.2. Synthesis of 12. A solution of **12a** (0.605 g, 1.14 mmol) in HPLC grade MeOH (15.0 mL) was purged with nitrogen for 2 min and then placed under house vacuum for 1 min. Following three repetitions of this purging cycle was the addition of 10% Pd/carbon (0.240 g, 0.228 mmol). The reaction vessel was placed under an atmosphere of hydrogen (balloon) and stirred at room temperature. Reaction progress was monitored by TLC (20% EtOAc/hexane). Upon consumption of starting material, the suspension was purged with nitrogen for 10 min and then filtered through celite. The resultant solution was concentrated in vacuo to yield a white solid determined to be >98% pure by ^{1}H NMR. (>90% isolated yield).

Data for **12**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (d, J=7.33 Hz, 1H), 3.85 (m, 2H), 3.62–3.28 (m, 4H), 1.62 (m, 2H), 1.28 (m, 12H), 0.88 (t, J=6.77 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.9, 76.4, 75.7, 73.4, 70.6, 69.5, 61.5, 2.1, 29.9, 29.8, 29.6, 26.2, 22.9, 14.4; IR (film, cm^{-1}) 3366, 2921, 1466, 1039; TLC R_f 0.17 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{14}H_{28}O_6Na$] requires m/z 315.1784. Found 315.1769 (ES+).

4.5. Peptide synthesis

The peptide libraries screened for the selective acetylation of **6** and **12** contained peptides synthesized on solid support using commercially available Wang resin preloaded with either FMOC-Phe or FMOC-Ala. Couplings were performed using 5 equiv. amino acid derivative, 5 equiv. HBTU, and 10 equiv. Hunig's base in DMF for 3 h. FMOC-deprotections were performed using 20% piperdine in DMF for 20 min (to minimize diketopiperazine formations, dipeptides were deprotected using 50% piperdine in DMF for 5 min). Peptides were cleaved from solid support using a mixture of MeOH:Et_3N:DMF (9:1:1) for 4d. Initial screening was carried out on crude material (desired sequence identified by mass spectrometry). Selected peptides were resynthesized on solid support in a similar fashion and subjected to preparative HPLC using a reverse phase RP-18 X Terra (Waters) column, eluting with methanol/water at a flow rate of 6 mL/min. The purity was checked by analytical HPLC under similar conditions, and the peptides were characterized by ^{1}H NMR and high resolution mass spectrometry.

4.6. Peptide library members

A list of peptide library members and their performance under the conditions of the high throughput screen is available upon request from the authors.

4.6.1. Data for 'hit' peptides. *Peptide* **10**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (s, 1H), 7.30–7.12 (m, 6H), 6.94 (br s, 1H), 6.79 (s, 1H), 5.61 (br s, 1H) 4.83–4.78 (m, 1H), 4.48–4.28 (m, 4H), 3.70 (s, 3H), 3.66 (br s, 1H), 3.57 (s, 3H), 3.18–2.89 (m, 5H), 2.33–1.87 (m, 9H), 1.71–0.88 (m, 29H); IR (film, cm^{-1}) 3269, 3074, 2974, 2923, 2848, 2357, 2332, 1709, 1627; TLC R_f 0.32 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{43}H_{65}N_7O_{10}Na$] requires m/z 862.4691. Found 862.4705. Analytical HPLC, purity of peptide **10** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.3 mL/min. Retention time=7.8 min.

Peptide **3**. Spectral and chromatography data are available in Ref. 11.

Peptide **17**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (br d, J=5.06 Hz, 1H), 7.49 (s, 1H), 7.39–7.09 (m, 10H), 6.93 (s, 1H), 6.74 (s, 1H), 6.71 (s, 1H), 5.30 (br d, J=6.59 Hz, 1H), 5.12–4.98 (m, 8H), 4.78 (q, J=6.59 Hz, 1H), 4.68–4.47 (m, 3H), 4.31–4.27 (m, 1H), 3.64 (s, 3H), 3.55 (s, 3H), 3.17–2.89 (m, 6H), 1.70–0.85 (m, 25H); IR (film, cm^{-1}) 3288, 2923, 2848, 1740, 1658, 1501; TLC R_f 0.24 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{47}H_{63}N_9O_8Na$] requires m/z 904.4697. Found 904.4722; Analytical HPLC, purity of peptide **17** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.3 mL/min. Retention time=6.2 min.

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