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Chee Wee Phoon, and Chris Abell

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Use of Quinic Acid as Template in Solid-Phase Combinatorial Synthesis

Chee Wee Phoon and Chris Abell*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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The use of pentafunctional quinic acid as a polyoxygenated scaffold for combinatorial synthesis is described. Simple protecting group chemistry is used to allow the selective formation of difunctionalized and tetrafunctionalized compounds. The reactions are followed by gel-phase ^{13}C NMR and yield cleaved products of high purity.

Introduction

Early developments in combinatorial chemistry centered on linear oligomeric systems such as peptides and oligonucleotides. However, the search for compounds of pharmaceutical interest has shifted to a broader range of monomeric molecules and, especially, the synthesis of libraries of compounds on multiply substituted templates which can be selectively and sequentially functionalized, e.g., the purine and triazine structures.[1] Much of the early template synthesis was centered around nitrogen-containing compounds, but more recently there has been a growing interest in the use of polyoxygenated scaffolds, e.g., orthogonally protected monosaccharides,[2] shikimic acid,[3] and cholic acid derivatives.[4] In this paper, we report the use of *D*-(−)-quinic acid as a scaffold for library synthesis.

Quinic acid is a readily available, enantiomerically pure compound which has a carboxyl and four hydroxyl groups organized on a cyclohexane core. This molecular complexity has led to it being used as starting material in numerous syntheses, and the chemistry required for selective manipulation is now relatively well established.[5] Quinic acid is an excellent scaffold for the assembly of combinatorial libraries because immense diversity can be achieved in two ways: by varying the number of sites substituted and the number of substituents introduced.

We are systematically developing an efficient solid-phase combinatorial methodology that allows rapid assembly of the quinate-based libraries, using the minimum number of manipulations. To demonstrate the generality of this library synthesis, we have investigated various types of substituents that can be incorporated. Reported herein are our initial studies on the synthesis of the quinate-based libraries which are substituted at C-1 carboxyl and C-3 hydroxyl groups and also at C-1 carboxyl and C-3,4,5 hydroxyl groups. An alternative approach to C-1,3 analogues has recently been reported.[6]

Results and Discussions

Following a published procedure, quinic acid was quadruply protected as its lactone ketal form (**1**) by heating in acetone at reflux with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid (Scheme 1).[7] This left the tertiary hydroxyl group free to serve as the point of attachment onto solid support. The lactone was deprotonated with sodium hydride in anhydrous DMA and then added to bromo-Wang resin, furnishing the resin-bound template (**2**).[8] At this stage, FTIR spectroscopy showed a prominent absorption band at 1789 cm^{-1}, indicating the presence of lactone. Loss of the peak at the benzyl bromide position and the appearance of several peaks associated with the lactone are discernible in the gel-phase ^{13}C NMR spectrum (Figure 1). The loading level was determined to be 90% by TFA cleavage of the supported lactone (**2**) and weighing of the cleaved product, which contained quinic acid and ketal deprotected lactone in a ratio of 91:9, as observed by ^{1}H NMR spectroscopy. This has been taken into account in calculating the percentage loading.

Our initial attempts to open the lactone (**2**) via aminolysis met with limited success. Ring opening was gradually achieved by repeated (3×) addition of lithiated amine (generated from *n*-BuLi and amine). An alternative route using 2-hydroxypyridine as the catalyst proved to be more efficient. Complete aminolysis to form the amide **3** was achieved at ambient conditions with several primary amines, chosen to have different steric demands. It was found that aminolysis proceeded to completion in 2 h when *n*-propylamine was used. However, longer time (18 h) was required in the case of benzylamine and cyclohexylamine. It has previously been shown that this lactone can be opened on solid phase by heating at reflux in dichloromethane using excess methylamine- or benzylamine-trimethylaluminum complex.[6]

The unmasked hydroxyl group at the C-3 position was then subjected to either acylation or alkylation. Using a DIC−DMAP coupling procedure, smooth acylation was achieved with several carboxylic acids. Resin **3** (where R_1 = *n*-propyl) was also alkylated at the C-3 position with benzyl bromide or methyl iodide in the presence of NaH. 15-Crown-5 ether was added to speed up this reaction, which was otherwise quite slow. To ensure complete alkylation, this procedure was repeated three times. Subsequent cleavage of resins **4** or **6** with TFA−CH_2Cl_2−H_2O (9:9:2) and brief

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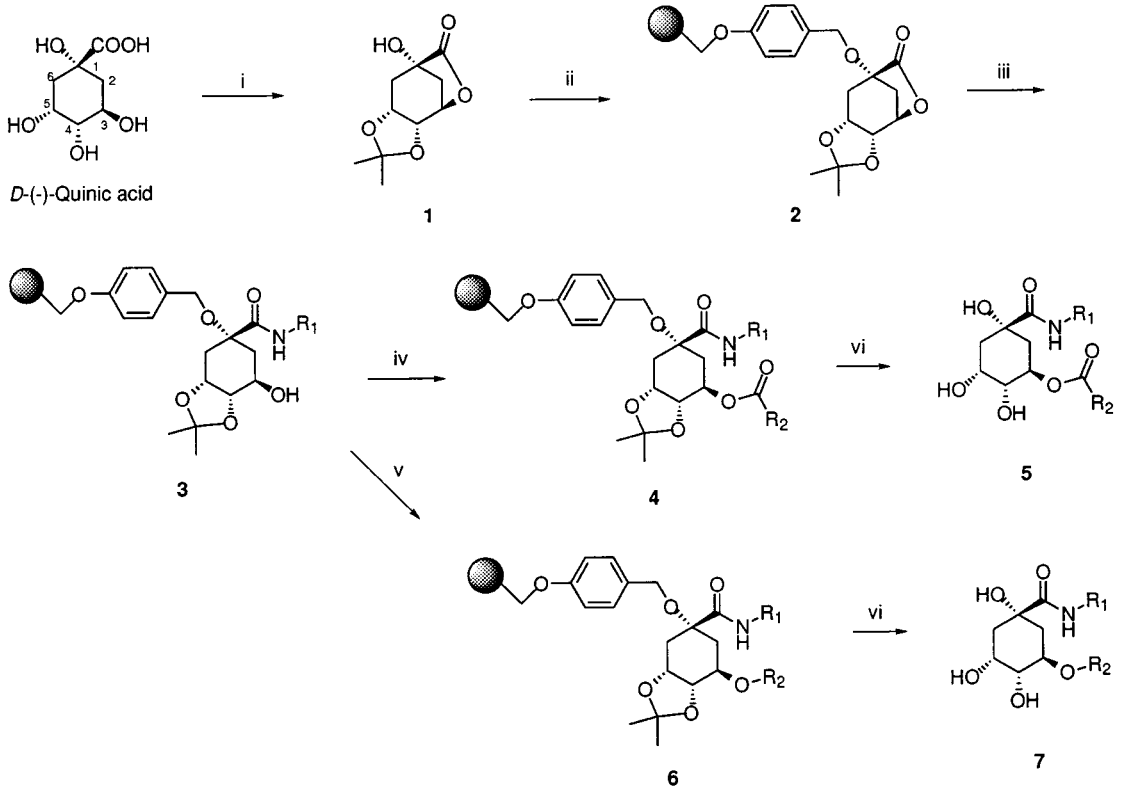
Scheme 1[a]



[a] Reagents and conditions: (i) 2,2-dimethoxypropane (1.8 equiv), *p*-TsOH (cat.), acetone, reflux, 18 h (78%); (ii) NaH (3 equiv), DMA, 23 °C, 1 h, then bromo-Wang resin, *n*-Bu_4NI (0.6 equiv), 23 °C, 8 h (90%, determined by the cleave and weigh method); (iii) R_1NH_2 (11 equiv), 2-hydroxypyridine (0.6 equiv), THF, 23 °C, 2−18 h; (iv) R_2COOH (11 equiv), DIC (11 equiv), DMAP (0.6 equiv), CH_2Cl_2, 23 °C, 18 h; (v) NaH (3.3 equiv), 15-crown-5 ether (0.6 equiv), DMF, 23 °C, 18 h, then BnBr (8.9 equiv) and *n*-Bu_4NI (0.6 equiv), or MeI (8.9 equiv), 23 °C, 8 h, 3 cycles; (vi) TFA−CH_2Cl_2−H_2O (9:9:2), 23 °C, 18 h.

washes with saturated aqueous sodium bicarbonate gave the C-1,3 quinate analogues **5** or **7** in excellent purities and high yields (Table 1).[9] ^{1}H NMR spectra of two representative cleaved products are shown in Figure 2.

The synthesis of C-1,3,4,5 substituted analogues **10** was carried out first by removal of the ketal protecting group (Scheme 2) and then by derivatization at the free hydroxyl sites. It was found that the ketal group could be completely removed by repeated treatments with *p*-toluenesulfonic acid in THF−H_2O (3:1) at room temperature. The concentration of *p*-toluenesulfonic acid was kept between 0.4 and 0.5 M. These mild conditions were necessary to avoid any cleavage of the acid-sensitive Wang linker. The progress of deprotection could be followed by gradual disappearance of the ketal peaks in the gel-phase ^{13}C NMR spectrum (Figure 1). The rate of deprotection varied depending on the type of substituents at the C-3 position. It was slower for the benzoylated series (required five cycles of treatment) than for the acetylated compounds (required three cycles of treatment). It was subsequently found that the deprotection rate was significantly accelerated for both series by heating at 50 °C for 6 h using 1,2-dimethoxyethane (DME)−H_2O (3:1) as the solvent system. At this higher temperature, the optimum concentration of *p*-toluenesulfonic acid was found to be 0.35 M. Higher concentrations (e.g., 0.45 M) led to a small amount of premature cleavage, while at lower concentrations (e.g., 0.2 M) the ketal group was not completely removed. Under these conditions, all the C-3 acetylated resins required only one treatment and the C-3 benzoylated resins needed treatment twice for complete ketal removal.

Both batches of deprotected resins **8** (where R_2 = Ac and R_2 = Bz) were then acylated at the C-4,5 hydroxyl groups. DIC−DMAP mediated acylation was achieved smoothly, giving resins **9**. The C-1,3,4,5 quinate substituted analogues **10** were obtained in moderate to good isolated yields after cleavage (Table 2).[9] ^{1}H NMR spectroscopy revealed the presence of tribenzoylated products in the cleaved mixtures from resins **9a**, **9c**, **9e**. The ratio of tribenzoylated to the desired products was 13:87, 29:71, 26:74 in mixtures cleaved from resins **9a**, **9c**, **9e** which had been subjected to the deprotection protocol at room temperature previously. In the case where the resins were deprotected more quickly at the elevated temperature, improved ratios of 11:89, 10:90, 7:93 were observed. These mixtures could be separated by column chromatography. Formation of tribenzoylated product was due to partial cleavage of the acetyl group upon treatment with *p*-toluenesulfonic acid, which revealed the C-3 position for benzoylation. All of the C-3 benzoylated resins **4**, whether deprotected at room temperatue or 50 °C, tolerated the ketal deprotection step, and no triacetylated products were detected. The diacetylated analogues **10b**, **10d**, **10f** were consequently obtained in higher purities than the dibenzoylated series (**10a**, **10c**, **10e**).

Conclusion

Our results illustrate that quinate-based libraries can be generated in a straightforward manner. The yields and

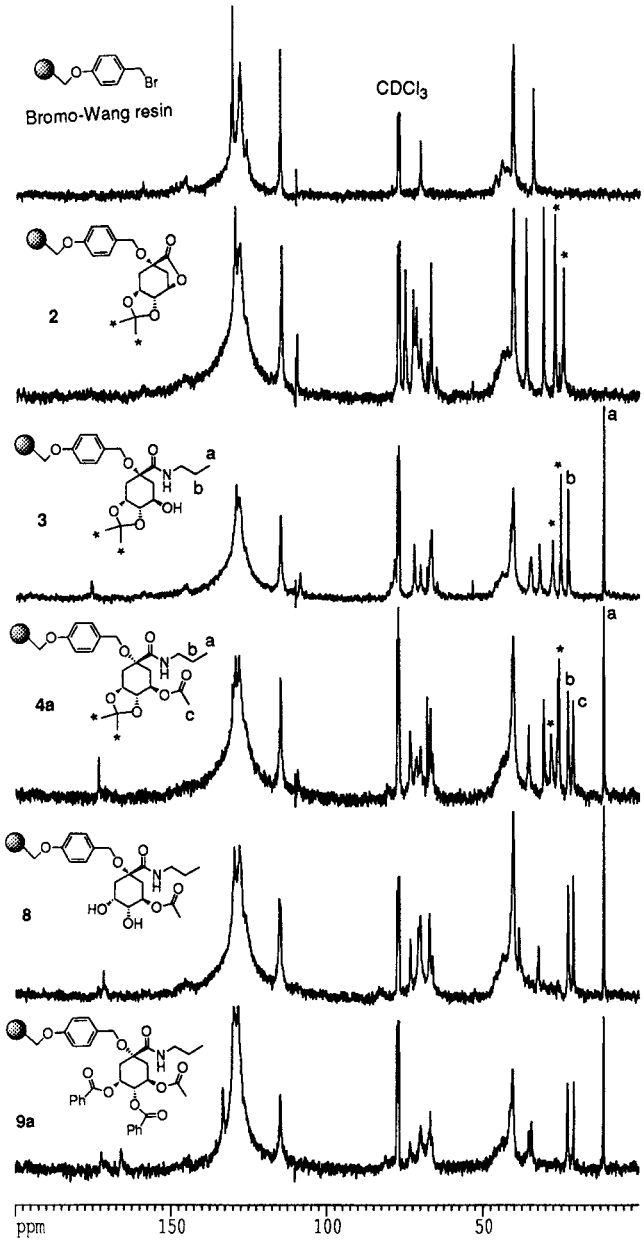


Figure 1. Gel-phase ^{13}C NMR spectra of the resin intermediates.

purities of the products are high, particularly in the C-1,3 substituted series. This general procedure, coupled with the ease of reaction monitoring by gel-phase ^{13}C NMR and FTIR spectroscopies, validates this system for the preparation of expanded libraries. Studies on the synthesis of other differentially substituted analogues are currently being undertaken.

Experimental Section

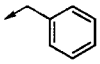
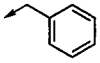
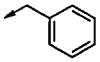
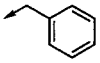
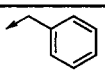
Materials and General Procedures. Reagents and resins were purchased from Aldrich, Lancaster, or Polymer Laboratories. All solvents were freshly distilled before use. Experiments involving moisture- and/or air-sensitive components were performed under a positive pressure of argon in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by syringes or cannulae. The number of equivalents of reagents added is calculated based on the loading of the ketal lactone **1**. Resins were dried in a vacuum evaporative system after washing. Analytical thin-layer chromatography was performed using Merck 60 F254 precoated silica gel plates (0.2 mm thickness). Spots were visualized by ultraviolet illumination at 254 nm, staining with iodine vapor or a solution of potassium permanganate. Column chromatography was performed using Merck silica gel (230−400 mesh silica kieselgel) under low positive pressure or gravity. All HPLC analyses were carried out on a Kromasil KR100-5C18-150A C18 reverse-phase column (4.6 mm × 15 cm); gradient elution with 0.1% TFA/CH_3CN and 0.1% TFA/H_2O starting at 5:95 and ending at 95:5, flow rate 1.2 mL/min over 20 min. Detection was by UV at 254 nm and by SEDEX, an evaporative light scattering detector. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at the frequencies indicated. Signals were quoted as δ values (in ppm) and described as follows: s (singlet), d (doublet), t (triplet), q (quartet), sx (sextet), multiplets (m), and broad (br). Gel-phase ^{13}C NMR spectra were obtained in 20−30 min of experimentation time (AQ = 0.1 s, zero delay). The dried resins (75−100 mg) were packed into NMR sample tubes (5 mm o.d.) and then swelled with chloroform-*d*. Only the diagnostic peaks are listed. Infrared spectra were recorded on a FTIR spectrometer. Bands were characterized as follows: br (broad), s (strong), and m (medium). Absorbance wavenumbers were quoted in cm^{-1}. High-resolution mass spectra were recorded on the FTICR or Q-TOF spectrometers. Melting points determined were uncorrected.

Preparation of Bromo-Wang Resin.[10] Bromine (2.1 mL, 40.8 mmol) was introduced dropwise to a solution of triphenylphosphine (10.7 g, 40.8 mmol) in anhydrous dichloromethane (80 mL) at 0 °C. After the mixture was stirred for 30 min at 0 °C, Wang resin (Polymer Laboratories; 1.7 mequiv/g; 150−300 mm; 8 g) was added. The suspension was gently stirred at 23 °C for 24 h and then filtered. The resin was washed with CH_2Cl_2 (8 × 20 mL) and dried in vacuo for 48 h. The above procedure was repeated, giving the product as a white resin. ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.0 (CH_2Br), 70.2 ($-CH_2O-$).

Preparation of Resin-Bound Lactone 2. To a solution of ketal lactone **1** (2.96 g, 13.8 mmol) in anhydrous DMA (30 mL) was added NaH (60% suspension in oil; 552 mg, 13.8 mmol). After the mixture was vigorously stirred at 23 °C for 1 h, the resulting dark green solution, together with tetra-*n*-butylammonium iodide (1.02 g, 2.77 mmol), was added to bromo-Wang resin (3 g). The suspension was gently stirred at 23 °C for 8 h and then filtered. The resin was washed successively with THF−H_2O 3:2 (3 × 15 mL), H_2O (3 × 15 mL), THF (3 × 15 mL), and CH_2Cl_2 (3 × 15 mL) and dried in vacuo for 48 h. ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 27.1, 30.7, 36.2, 66.8, 70.1, 72.4, 75.0, 109.6; FTIR (CH_2Cl_2) 1789 (s, C═O); 90% loading, determined by the cleave and weigh method as mentioned earlier.

General Procedure for the Preparation of Resin 3. To a suspension of resin **2** (200 mg) containing 2-hydroxypyridine (0.6 equiv) in anhydrous THF (3 mL) was added the amine (11 equiv). The suspension was gently stirred at 23 °C for 2−18 h and then filtered. The resin was washed successively with THF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL),

Table 1

Product	R_1	R_2	Yield[a]	Purity %[b]
5a			62%	99[ii]
5b			92%	98[i]
5c			83%	99[ii]
5d			74%	89[ii]
5e			81%	98[i]
5f			80%	99[i]
5g			91%	84[i]
5h			77%	95[ii]
5i			83%	98[i]
5j			80%	98[ii]
7a			73%	97[ii]
7b			67%	91[ii]

[a] Overall yields based on the initial loading of the ketal lactone. [b] Purity as assessed by HPLC, monitored (i) at 254 nm by a UV detector or (ii) by an evaporative light scattering detector.

THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuo for 48 h.

General Procedure for the Preparation of Resin 4. To a suspension of resin **3** containing DMAP (0.6 equiv) in anhydrous CH_2Cl_2 (3 mL) was added DIC (11 equiv), followed by the carboxylic acid (11 equiv). The suspension was gently stirred at 23 °C for 18 h and then filtered. The resin was washed successively with THF−H_2O 3:2 (3 × 5 mL), H_2O (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuo for 48 h.

General Procedure for the Preparation of Resin 6. To a suspension of resin **3** containing NaH (3.3 equiv) in anhydrous DMF (3 mL) was added 15-crown-5 ether (0.6 equiv). After gentle stirring at 23 °C for 18 h, the alkyl halide (8.9 equiv) was introduced. *n*-Tetrabutylammonium iodide (0.6 equiv) was added in the case of benzyl bromide. The suspension was stirred further for 8 h at 23 °C and then filtered. The resin was washed successively with THF−H_2O 3:2 (3 × 5 mL), H_2O (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuo for 24 h. This procedure was performed three times.

General Procedure for Removal of the Ketal Group. A solution of *p*-toluenesulfonic acid (0.4−0.5 M) in THF−H_2O 3:1 was added to resin **4**. The suspension was gently stirred at 23 °C for 6 h and then filtered. The procedure was carried out three times for the C-3 acetylated resins, five times for the C-3 benzoylated resins. Following this, the resins were washed with THF−H_2O 3:2 (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuo for 48 h.

General Procedure for Removal of the Ketal Group at 50 °C. A solution of *p*-toluenesulfonic acid (0.35 M) in DME−H_2O 3:1 was added to resin **4**. The suspension was gently stirred at 50 °C for 6 h and then filtered. The procedure was carried out once for the C-3 acetylated resins, twice for the C-3 benzoylated resins. Following this, the resin was washed with THF−H_2O 3:2 (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuo for 48 h.

General Procedure for the Preparation of Resin 9. To a suspension of resin **8** containing DMAP (0.6 equiv) in anhydrous CH_2Cl_2 (3 mL) was added DIC (11 equiv), followed by the carboxylic acid (11 equiv). The suspension was gently stirred at 23 °C for 18 h and then filtered. The resin was washed successively with THF−H_2O (3 × 5 mL), H_2O (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuo for 48 h.

General Cleavage Procedure. A solution of TFA−CH_2Cl_2−H_2O (9:9:2) was added to the dried resin. After

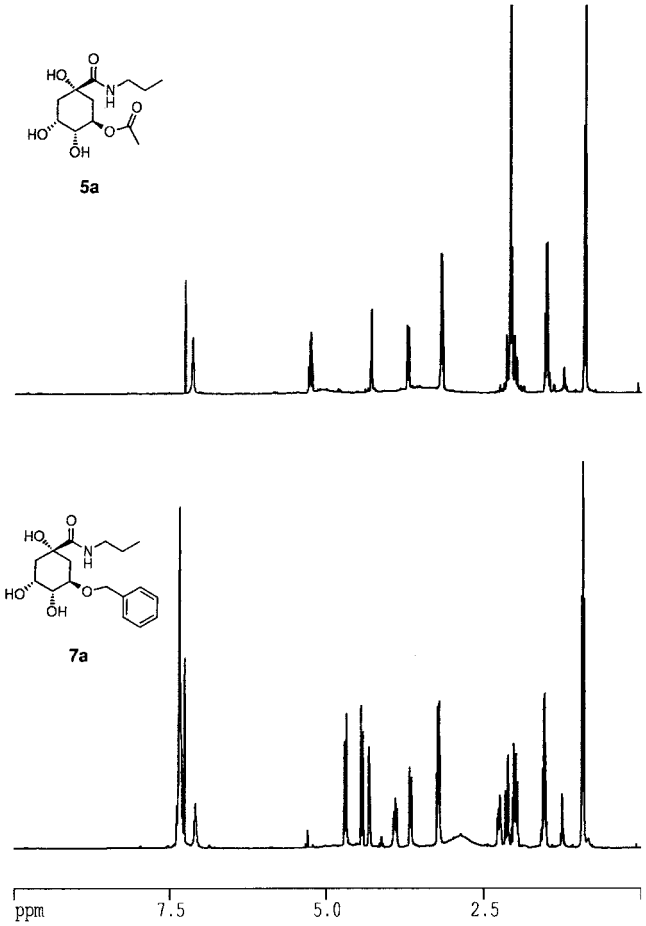


Figure 2. Representative ^{1}H NMR spectra of the crude cleavage products.

being stirred gently at 23 °C for 18 h, the suspension was filtered, and the resin was washed with CH_2Cl_2 (3 × 5 mL). Most of the solvents and TFA were removed under reduced pressure from the filtrate and washings. To the remaining residue was added saturated aqueous $NaHCO_3$ (5 mL). The mixture was then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure to give the cleaved product.

Resin 4a: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 21.3, 22.9, 26.0, 28.2, 30.5, 35.4, 109.3, 173.2; FTIR (CH_2Cl_2) 1671 (s, C═O amide), 1736 (s, C═O ester), 3410 (s, NH).

Resin 4b: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 22.9, 26.1, 28.3, 30.4, 35.8, 109.3, 173.2; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 1714 (s, C═O ester), 3415 (s, NH).

Resin 4c: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 18.0, 22.9, 26.1, 28.3, 30.7, 35.5, 109.2, 173.2; FTIR (CH_2Cl_2) 1660 (s, C═O amide), 1712 (s, C═O ester), 3415 (s, NH).

Resin 4d: ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 26.0, 28.2, 30.6, 35.3, 109.3, 173.2; FTIR (CH_2Cl_2) 1674 (s, C═O amide), 1730 (s, C═O ester), 3411 (s, NH).

Resin 4e: ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 28.3, 30.5, 35.7, 109.3, 173.1; FTIR (CH_2Cl_2) 1674 (s, C═O amide), 1712 (s, C═O ester), 3413 (s, NH).

Resin 4f: ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 26.0, 28.3, 30.7, 35.4, 109.3, 173.2; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 1712 (s, C═O ester), 3413 (s, NH).

Resin 4g: ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 28.3, 30.2, 35.7, 109.5, 150.6, 172.9; FTIR (CH_2Cl_2) 1665 (s, C═O amide), 1730 (s, C═O ester), 3417 (s, NH).

Resin 4h: ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 24.7, 25.4, 26.0, 28.3, 30.6, 33.0, 35.3, 109.2, 172.1; FTIR (CH_2Cl_2) 1666 (s, C═O amide), 1730 (s, C═O ester), 3402 (s, NH).

Resin 4i: ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.4, 26.1, 28.3, 30.5, 33.0, 35.7, 109.3, 172.1; FTIR (CH_2Cl_2) 1666 (s, C═O amide), 1712 (s, C═O ester), 3404 (s, NH).

Resin 4j: ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 24.7, 25.4, 26.1, 28.3, 30.7, 33.0, 35.3, 109.3, 172.2; FTIR (CH_2Cl_2) 1666 (s, C═O amide), 1712 (s, C═O ester), 3404 (s, NH).

Resin 6a: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 22.9, 26.1, 28.4, 29.4, 37.2, 110.1, 173.5; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 3419 (m, NH).

Resin 6b: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 22.9, 26.0, 28.4, 29.2, 37.4, 57.7, 108.7, 173.6; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 3419 (m, NH).

Resin 9a: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 21.0, 22.9, 34.4, 35.2, 165.9, 172.2; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 1730 (s, C═O ester), 3419 (m, NH).

Resin 9b: ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 20.8, 22.9, 33.6, 35.7, 170.1, 172.1; FTIR (CH_2Cl_2) 1680 (s, C═O amide), 1730 (s, C═O ester), 3419 (s, NH).

Resin 9c: ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 34.5, 35.0, 165.8, 172.2; FTIR (CH_2Cl_2) 1682 (s, C═O amide), 1730 (s, C═O ester), 3415 (s, NH).

Resin 9d: ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 33.7, 35.4, 170.1, 172.1; FTIR (CH_2Cl_2) 1682 (s, C═O amide), 1730 (s, C═O ester), 3415 (s, NH).

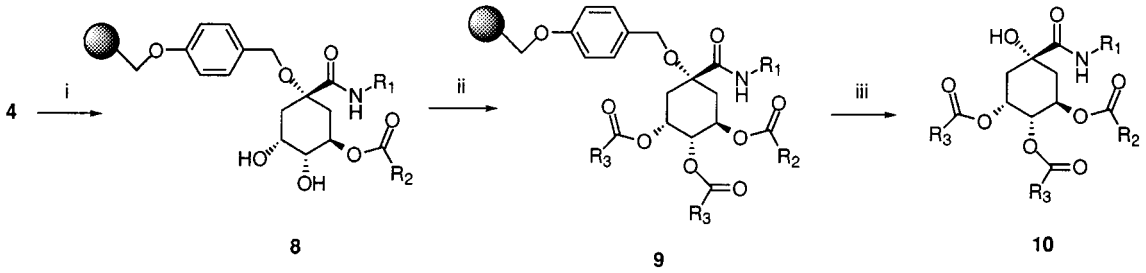
Resin 9e: ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.7, 25.4, 33.0, 34.4, 35.1, 165.9, 171.2; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 1730 (s, C═O ester), 3406 (s, NH).

Resin 9f: ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 24.7, 25.4, 33.0, 33.6, 35.6, 170.1, 171.1; FTIR (CH_2Cl_2) 1668 (s, C═O amide), 1730 (s, C═O ester), 3406 (m, NH).

(1*R*,3*R*,4*R*,5*R*)-Propyl-3-acetyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5a): pale yellow oil; R_f 0.13 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_3$), 1.50 (2H, sx, J = 7.3 Hz, $CH_2CH_2CH_3$), 1.99−2.16 (4H, m, 2-H, 6-H), 2.09 (3H, s, $-O_2CCH_3$), 3.18 (2H, q, J = 7.3 Hz, $CH_2CH_2CH_3$), 3.71 (1H, dd, J = 9.7, 3.1 Hz, 4-H), 4.29 (1H, dd, J = 5.9, 3.1 Hz, 5-H), 5.26 (1H, q, J = 9.7 Hz, 3-H), 7.14 (1H, br, N*H*); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 21.2, 22.7, 36.6, 38.6, 40.9, 71.5, 71.8, 73.8, 76.4, 172.3, 173.7; FTIR ($CHCl_3$) 1677 (s), 1730 (s), 2936 (s), 3417 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{12}H_{22}O_6N$ (MH^+) requires 276.1447, found 276.1457.

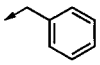
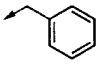
(1*R*,3*R*,4*R*,5*R*)-Propyl-3-benzoyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5b): pale yellow oil; R_f 0.18 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_3$), 1.51 (2H, sx, J = 7.3 Hz, $CH_2CH_2CH_3$), 2.03−2.29 (4H, m, 2-H, 6-H), 3.18 (2H, q, J = 7.3 Hz, $CH_2CH_2CH_3$), 3.86 (1H, dd, J = 9.6, 3.0 Hz, 4-H), 4.32 (1H, br d, J = 3.0 Hz, 5-H), 5.52 (1H, ddd, J = 11.3, 9.6, 5.5 Hz, 3-H), 7.15 (1H, br, N*H*), 7.40 (2H, t, J = 7.4 Hz, *m*-H), 7.54 (1H, tt, J = 7.4, 1.2 Hz, *p*-H), 7.99 (2H, dd, J = 7.1, 1.2 Hz, *o*-H); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 22.7, 36.7, 38.8, 40.9, 71.6, 72.3, 74.0, 76.5, 128.4, 129.6,

Scheme 2[a]



[a] Reagents and conditions: (i) *p*-TsOH (0.4−0.5 M), THF−H_2O (3:1), 23 °C, 18 h, 3−5 times, or *p*-TsOH (0.35 M), DME−H_2O (3:1), 50 °C, 6 h, 1 or 2 times; (ii) R_3COOH (11 equiv), DIC (11 equiv), DMAP (0.6 equiv), CH_2Cl_2, 23 °C, 18 h; (iii) TFA−CH_2Cl_2−H_2O (9:9:2), 23 °C, 18 h.

Table 2

Product	R_1	R_2	R_3	Yield %[a]
10a		$-CH_3$		84, 80
10b			$-CH_3$	78, 74
10c		$-CH_3$		63, 71
10d			$-CH_3$	64, 69
10e		$-CH_3$		69, 77
10f			$-CH_3$	84, 80

[a] Overall yields after purification by column chromatography, based on the initial loading of the ketal lactone. The first yield quoted is that when the acetal deprotection was carried out at room temperature, the second when the deprotection was perfomed at 50 °C.

129.8, 133.4, 167.6, 173.8; FTIR ($CHCl_3$) 1660 (s), 1708 (s), 2935 (s), 3417 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{17}H_{24}O_6N$ (MH^+) requires 338.1604, found 338.1621.

(1*R*,3*R*,4*R*,5*R*)-Propyl-3-*trans*-crotonyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5c): white foam; R_f 0.15 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.52 (2H, sx, J = 7.4 Hz, CH_2CH_2-CH_3), 1.89 (3H, dd, J = 6.9, 1.7 Hz, CH=CHCH_3), 2.02−2.19 (4H, m, 2-H, 6-H), 3.19 (2H, q, J = 7.4 Hz, $CH_2CH_2CH_3$), 3.75 (1H, dd, J = 9.5, 3.1 Hz, 4-H), 4.30 (1H, dd, J = 5.8, 3.1 Hz, 5-H), 5.01 (1H, br s, OH), 5.30 (1H, ddd, J = 11.3, 9.5, 5.6 Hz, 3-H), 5.86 (1H, dd, J = 15.5, 1.7 Hz, CH=CHCH$_3$), 7.02 (1H, qd, J = 15.5, 6.9 Hz, CH=C*H*CH$_3$), 7.11 (1H, br t, J = 5.6 Hz, N*H*); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 18.1, 22.8, 36.5, 38.7, 40.9, 71.5, 71.8, 74.1, 76.4, 122.2, 146.6, 167.8, 173.6; FTIR ($CHCl_3$) 1660 (s), 1709 (s), 2936 (s), 3418 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{14}H_{24}O_6N$ (MH^+) requires 302.1603, found 302.1601.

(1*R*,3*R*,4*R*,5*R*)-Benzyl-3-acetyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5d): colorless oil; R_f 0.13 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02−2.17 (4H, m, 2-H, 6-H), 2.10 (3H, s, $-O_2CCH_3$), 3.69 (1H, br s, OH), 3.72 (1H, dd, J = 9.6, 3.1 Hz, 4-H), 4.29 (1H, br d, J = 3.1 Hz, 5-H), 4.42 (2H, d, J = 6.0 Hz, CH_2Ph), 5.00 (1H, br s, OH), 5.26 (1H, q, J = 9.6 Hz, 3-H), 7.23−7.34 (5H, m), 7.43 (1H, br t, J = 6.0 Hz); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 21.2, 36.6, 38.6, 43.2, 71.5, 71.8, 73.8, 76.5, 127.5, 128.7, 138.0, 172.5, 173.6; FTIR ($CHCl_3$) 1668 (s), 1734 (s), 2936 (s), 3416 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{16}H_{22}O_6N$ (MH^+) requires 324.1447, found 324.1457.

(1*R*,3*R*,4*R*,5*R*)-Benzyl-3-benzoyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5e): white foam; R_f 0.22 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05−2.32 (4H, m, 2-H, 6-H), 3.86 (1H, br s, OH), 3.87 (1H, dd, J = 9.5, 3.1 Hz, 4-H), 4.33 (1H, br d, J = 3.1 Hz, 5-H), 4.42 (2H, d, J = 6.0 Hz, CH_2Ph), 5.09 (1H, br s, OH), 5.52 (1H, ddd, J = 11.5, 9.5, 5.4 Hz, 3-H), 7.23−7.55 (9H, m, Ph, N*H*), 7.99 (2H, d, J = 7.1 Hz, Ph); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 36.6, 38.7, 43.2, 71.5, 72.5, 74.0, 76.5, 127.49, 127.53, 128.48, 128.71, 129.48, 129.83, 133.5, 138.0, 167.8, 173.7; FTIR ($CHCl_3$) 1670 (s), 1711 (s), 2933 (s), 3415 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{21}H_{24}O_6N$ (MH^+) requires 386.1604, found 386.1625.

(1*R*,3*R*,4*R*,5*R*)-Benzyl-3-*trans*-crotonyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5f): colorless oil; R_f 0.18 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, dd, J = 6.9, 1.6 Hz, CH=CHCH_3), 2.05−2.24 (4H, m, 2-H, 6-H), 3.59 (1H, br s, OH), 3.76 (1H, dd, J = 9.5, 3.1 Hz, 4-H), 3.77 (1H, br s, OH), 4.31 (1H, br d, J = 3.1 Hz, 5-H), 4.43 (2H, d, J = 6.0 Hz, CH_2Ph), 4.99 (1H, br s, OH), 5.30 (1H, m, 3-H), 5.87 (1H, dd, J = 15.5, 1.6 Hz, C*H*=CHCH$_3$), 7.03 (1H, qd, J = 15.5, 6.9 Hz, CH=C*H*CH$_3$), 7.24−7.35 (5H,

m), 7.42 (1H, br t, $J = 5.8$ Hz); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 18.1, 36.4, 38.7, 43.2, 71.4, 71.9, 74.1, 76.4, 122.1, 127.47, 127.55, 128.7, 138.1, 146.8, 167.9, 173.6; FTIR ($CHCl_3$) 1662 (s), 1708 (s), 2935 (s), 3416 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{18}H_{24}O_6N$ (MH^+) requires 350.1604, found 350.1608.

(1*R*,3*R*,4*R*,5*R*)-Benzyl-3-isonicotinyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5g): colorless oil; R_f 0.09 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09−2.34 (4H, m, 2-H, 6-H), 3.90 (1H, dd, $J = 9.5$, 3.1 Hz, 4-H), 4.38 (1H, q, $J = 3.1$ Hz, 5-H), 4.43 (2H, d, $J = 6.0$ Hz, C*H*$_2$Ph), 5.60 (1H, ddd, $J = 11.2$, 9.5, 5.7 Hz, 3-H), 7.23−7.34 (5H, m), 7.45 (1H, br t, $J = 5.9$ Hz), 7.73 (2H, dd, $J = 4.5$, 1.5 Hz, 3-H of py), 8.67 (2H, dd, $J = 4.5$, 1.5 Hz, 2-H of py); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 36.8, 38.7, 43.2, 71.8, 73.4, 73.5, 76.5, 123.0, 127.5, 128.7, 137.3, 137.9, 150.3, 165.3, 173.5; FTIR ($CHCl_3$) 1670 (s), 1730 (s), 2981 (s), 3415 (m), 3300−3600 (br); *m*/*z* (ESI) $C_{20}H_{22}O_6N_2Na$ (MNa^+) requires 409.1376, found 409.1351.

(1*R*,3*R*,4*R*,5*R*)-Cyclohexyl-3-acetyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5h): colorless oil; R_f 0.12 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.40 (6H, m, cyclohexyl), 1.59−1.72 (3H, m, cyclohexyl), 1.84−2.16 (5H, m, cyclohexyl, 2-H, 6-H), 2.10 (3H, s, $-O_2CCH_3$), 3.66 (2H, br, OH, NC*H*), 3.72 (1H, dd, $J = 9.6$, 2.9 Hz, 4-H), 3.79 (1H, br s, OH), 4.30 (1H, br d, $J = 2.9$ Hz, 5-H), 4.99 (1H, br s, OH), 5.25 (1H, m, 3-H), 6.97 (1H, br, N*H*); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 21.2, 24.8, 25.5, 32.9, 36.6, 38.6, 47.9, 71.5, 71.8, 73.8, 76.3, 172.44, 172.61; FTIR ($CHCl_3$) 1656 (s), 1731 (s), 2935 (s), 3409 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{15}H_{26}O_6N$ (MH^+) requires 316.1760, found 316.1752.

(1*R*,3*R*,4*R*,5*R*)-Cyclohexyl-3-benzoyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5i): white solid; mp 176−178 °C; R_f 0.27 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.40 (6H, m, cyclohexyl), 1.58−1.87 (4H, m, cyclohexyl), 2.04−2.29 (4H, m, 2-H, 6-H), 3.60 (1H, br s, OH), 3.71 (2H, br, OH, NC*H*), 3.89 (1H, dd, $J = 9.5$, 3.1 Hz, 4-H), 4.35 (1H, br d, $J = 3.1$ Hz, 5-H), 4.98 (1H, br s, OH), 5.50 (1H, ddd, $J = 11.6$, 9.5, 5.4 Hz, 3-H), 6.99 (1H, br, N*H*), 7.43 (2H, t, $J = 7.5$ Hz, *m*-H), 7.58 (1H, tt, $J = 7.5$, 1.3 Hz, *p*-H), 8.02 (2H, dd, $J = 7.5$, 1.3 Hz, *o*-H); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 24.8, 25.5, 33.0, 36.4, 38.7, 47.9, 71.6, 72.9, 74.1, 76.3, 128.5, 129.5, 129.9, 133.5, 167.9, 172.6; FTIR ($CHCl_3$) 1662 (s), 1716 (s), 2935 (s), 3407 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{20}H_{28}O_6N$ (MH^+) requires 378.1917, found 378.1946.

(1*R*,3*R*,4*R*,5*R*)-Cyclohexyl-3-*trans*-crotonyloxy-1,4,5-trihydroxycyclohexanecarboxamide (5j): white foam; R_f 0.21 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.40 (6H, m, cyclohexyl), 1.59−1.72 (3H, m, cyclohexyl), 1.87 (1H, m, cyclohexyl), 1.89 (3H, dd, $J = 6.9$, 1.7 Hz, CH=CHC*H*$_3$), 2.01−2.15 (4H, m, 2-H, 6-H), 3.64−3.76 (2H, br m, OH, NC*H*), 3.75 (1H, dd, $J = 9.5$, 3.1 Hz, 4-H), 3.82 (1H, br s, OH), 4.30 (1H, br d, $J = 3.1$ Hz, 5-H), 4.98 (1H, br s, OH), 5.29 (1H, m, 3-H), 5.86 (1H, dd, $J = 15.5$, 1.7 Hz, C*H*=CHCH$_3$), 6.97 (1H, br, N*H*), 7.03 (1H, qd, $J = 15.5$, 6.9 Hz, CH=C*H*CH$_3$); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 18.1, 24.8, 25.5, 32.9, 36.4, 38.6, 47.9, 71.5, 71.9, 74.1, 76.3, 122.2, 146.6, 167.9, 172.6; FTIR ($CHCl_3$) 1658 (s), 1709 (s), 2936 (s), 3408 (m), 3300−3600 (br); *m*/*z* (ESI) $C_{17}H_{28}O_6N$ (MH^+) requires 342.1917, found 342.1932.

(1*R*,3*R*,4*R*,5*R*)-Propyl-3-benzyloxy-1,4,5-trihydroxycyclohexanecarboxamide (7a): pale yellow oil; R_f 0.18 (Hex−EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.4$ Hz, $CH_2CH_2CH_3$), 1.55 (2H, sx, $J = 7.4$ Hz, $CH_2CH_2CH_3$), 1.96−2.06 (2H, m, 2-H, 6-H), 2.14 (1H, dd, $J = 15.1$, 2.9 Hz, 6-H), 2.26 (1H, ddd, $J = 13.2$, 4.6, 2.9 Hz, 2-H), 3.22 (2H, q, $J = 7.4$ Hz, C*H*$_2$CH$_2$CH$_3$), 3.66 (1H, dd, $J = 9.3$, 2.9 Hz, 4-H), 3.90 (1H, ddd, $J = 11.7$, 9.3, 4.6 Hz, 3-H), 4.32 (1H, q, $J = 2.9$ Hz, 5-H), 4.43 (1H, d, $J = 11.4$ Hz, C*H*HPh), 4.69 (1H, d, $J = 11.4$ Hz, CH*H*Ph), 7.08 (1H, br, N*H*), 7.29−7.38 (5H, m, Ph); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 22.8, 36.6, 37.8, 40.8, 70.9, 71.1, 74.4, 75.4, 76.7, 127.89, 127.96, 128.6, 138.1, 173.9; FTIR ($CHCl_3$) 1667 (s), 3421 (m), 3250−3600 (br); *m*/*z* (ESI) $C_{17}H_{25}O_5NNa$ (MNa^+) requires 346.1630, found 346.1636.

(1*R*,3*R*,4*R*,5*R*)-Propyl-3-methoxy-1,4,5-trihydroxycyclohexanecarboxamide (7b): pale yellow oil; R_f 0.11 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.4$ Hz, $CH_2CH_2CH_3$), 1.54 (2H, sx, $J = 7.4$ Hz, CH_2CH_2-CH_3), 1.86 (1H, dd, $J = 12.9$, 11.6 Hz, 2-H), 2.01 (1H, dt, $J = 15.0$, 3.0 Hz, 6-H), 2.11−2.23 (2H, m, 2-H, 6-H), 3.22 (2H, q, $J = 7.4$ Hz, C*H*$_2$CH$_2$CH$_3$), 3.40 (3H, s, OMe), 3.59−3.70 (2H, m, 4-H, 3-H), 4.33 (1H, q, $J = 2.9$ Hz, 5-H), 7.08 (1H, br, N*H*); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 22.8, 36.47, 36.94, 40.8, 56.5, 70.8, 74.3, 76.65, 76.76, 173.9; FTIR ($CHCl_3$) 1658 (s), 3421 (m), 3250−3600 (br); *m*/*z* (ESI) $C_{11}H_{21}O_5NNa$ (MNa^+) requires 270.1317, found 270.1317.

(1*R*,3*R*,4*S*,5*R*)-Propyl-3-acetyloxy-4,5-dibenzoyloxy-1-hydroxycyclohexanecarboxamide (10a): white solid; mp 187−189 °C; R_f 0.20 (Hex−EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, $J = 7.5$ Hz, $CH_2CH_2CH_3$), 1.53 (2H, sx, $J = 7.5$ Hz, $CH_2CH_2CH_3$), 1.96 (3H, s, $-O_2CCH_3$), 2.16 (1H, br d, $J = 15.9$ Hz, 6-H), 2.35 (2H, m, 2-H), 2.66 (1H, dd, $J = 15.9$, 3.3 Hz, 6-H), 3.22 (2H, m, C*H*$_2$CH$_2$-CH$_3$), 3.51 (1H, s, OH), 5.38 (1H, dd, $J = 10.4$, 3.3 Hz, 4-H), 5.82 (1H, td, $J = 10.4$, 7.1 Hz, 3-H), 6.04 (1H, q, $J = 3.3$ Hz, 5-H), 7.03 (1H, br, NH), 7.32 (2H, t, $J = 7.6$ Hz, Ph), 7.49 (3H, br t, $J = 7.6$ Hz, Ph), 7.62 (1H, tt, $J = 7.5$, 1.3 Hz, Ph), 7.86 (2H, dd, $J = 8.3$, 1.3 Hz, Ph), 7.98 (2H, dd, $J = 8.3$, 1.3 Hz, Ph); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 21.0, 22.8, 36.5, 39.1, 41.0, 67.0, 71.1, 73.2, 76.3, 128.40, 128.87, 129.24, 129.26, 129.56, 129.69, 133.25, 133.71, 164.9, 165.5, 170.4, 172.4; FTIR ($CHCl_3$) 1677 (s), 1728 (s), 2895 (s), 2977 (s), 3424 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{26}H_{29}O_8NNa$ (MNa^+) requires 506.1791, found 506.1730.

(1*S*,3*R*,4*R*,5*R*)-Propyl-3-benzoyloxy-4,5-diacetyloxy-1-hydroxycyclohexanecarboxamide (10b): colorless oil; R_f 0.15 (Hex−EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, $J = 7.5$ Hz, $CH_2CH_2CH_3$), 1.52 (2H, sx, $J = 7.5$ Hz, $CH_2CH_2CH_3$), 1.92 (3H, s, $-O_2CCH_3$), 1.99 (1H, dt, $J = 15.9$, 3.3 Hz, 6-H), 2.18 (3H, s, $-O_2CCH_3$), 2.33 (1H, q, $J = 13.5$ Hz, 2-H), 2.38 (1H, ddd, $J = 13.5$, 5.4, 2.9 Hz, 2-H), 2.55 (1H, dd, $J = 15.9$, 3.3 Hz, 6-H), 3.20 (2H, q, $J = 7.5$ Hz, C*H*$_2$CH$_2$CH$_3$), 3.61 (1H, s, OH), 5.25 (1H, dd, $J = 10.4$,

3.3 Hz, 4-H), 5.66 (1H, td, J = 10.4, 5.4 Hz, 3-H), 5.73 (1H, q, J = 3.3 Hz, 5-H), 7.02 (1H, br, NH), 7.43 (2H, br t, J = 7.4 Hz, *m*-H), 7.56 (1H, tt, J = 7.4, 1.3 Hz, *p*-H), 7.98 (2H, dd, J = 7.4, 1.3 Hz, *o*-H); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 11.3, 20.6, 21.1, 22.8, 36.4, 39.2, 41.0, 67.7, 70.5, 72.3, 76.2, 128.5, 129.57, 129.66, 133.3, 165.8, 168.9, 170.1, 172.6; FTIR ($CHCl_3$) 1670 (s), 1723 (s), 1747 (s), 2938 (s), 2977 (s), 3431 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{21}H_{28}O_8N$ (MH^+) requires 422.1815, found 422.1834.

(1*R*,3*R*,4*S*,5*R*)-Benzyl-3-acetyloxy-4,5-dibenzoyloxy-1-hydroxycyclohexanecarboxamide (10c): white solid; mp 119−121 °C; R_f 0.26 (Hex−EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s, $-O_2CCH_3$), 2.20 (1H, br d, J = 15.8 Hz, 6-H), 2.39 (2H, br d, J = 7.9 Hz, 2-H), 2.70 (1H, dd, J = 15.8, 3.1 Hz, 6-H), 3.52 (1H, s, OH), 4.44 (2H, d, J = 5.9 Hz, CH_2Ph), 5.40 (1H, dd, J = 10.4, 3.1 Hz, 4-H), 5.83 (1H, q, J = 10.4 Hz, 3-H), 6.06 (1H, q, J = 3.1 Hz, 5-H), 7.24−7.35 (8H, m, Ph, N*H*), 7.46−7.50 (3H, m, Ph), 7.61 (1H, tt, J = 7.5, 1.3 Hz, Ph), 7.86 (2H, dd, J = 8.4, 1.3 Hz, Ph), 7.96 (2H, dd, J = 8.4, 1.3 Hz, Ph); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 21.0, 36.5, 39.1, 43.4, 67.0, 71.0, 73.1, 76.3, 127.7, 128.40, 128.80, 128.87, 129.19, 129.22, 129.53, 129.69, 133.27, 133.73, 137.8, 164.9, 165.5, 170.4, 172.7; FTIR ($CHCl_3$) 1673 (s), 1728 (s), 2895 (s), 2977 (s), 3421 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{30}H_{29}O_8$-NNa (MNa^+) requires 554.1791, found 554.1777.

(1*S*,3*R*,4*R*,5*R*)-Benzyl-3-benzoyloxy-4,5-diacetyloxy-1-hydroxycyclohexanecarboxamide (10d): colorless oil; R_f 0.16 (Hex−EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (3H, s, $-O_2CCH_3$), 2.04 (1H, dt, J = 15.8, 3.1 Hz, 6-H), 2.17 (3H, s, $-O_2CCH_3$), 2.37 (1H, q, J = 13.5 Hz, 2-H), 2.43 (1H, ddd, J = 13.5, 5.3, 2.9 Hz, 2-H), 2.58 (1H, dd, J = 15.8, 3.1 Hz, 6-H), 3.62 (1H, s, OH), 4.41 (1H, dd, J = 14.8, 5.9 Hz, C*H*HPh), 4.46 (1H, dd, J = 14.8, 5.9 Hz, CH*H*Ph), 5.27 (1H, dd, J = 10.4, 3.1 Hz, 4-H), 5.67 (1H, td, J = 10.4, 5.3 Hz, 3-H), 5.75 (1H, q, J = 3.1 Hz, 5-H), 7.24−7.35 (6H, m, Ph, N*H*), 7.44 (2H, t, J = 7.5 Hz, *m*-H), 7.57 (1H, tt, J = 7.5, 1.3 Hz, *p*-H), 7.99 (2H, dd, J = 7.5, 1.3 Hz, *o*-H); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 20.6, 21.0, 36.5, 39.2, 43.4, 67.6, 70.5, 72.3, 76.2, 127.6, 128.52, 128.78, 129.55, 129.68, 133.4, 137.8, 165.8, 168.8, 170.1, 172.6; FTIR ($CHCl_3$) 1673 (s), 1726 (s), 1746 (s), 2895 (s), 2977 (s), 3421 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{25}H_{27}O_8$-NNa (MNa^+) requires 492.1634, found 492.1618.

(1*R*,3*R*,4*S*,5*R*)-Cyclohexyl-3-acetyloxy-4,5-dibenzoyloxy-1-hydroxycyclohexanecarboxamide (10e): colorless oil; R_f 0.31 (Hex−EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.43 (5H, m, cyclohexyl), 1.59−1.72 (3H, m, cyclohexyl), 1.87 (2H, m, cyclohexyl), 1.96 (3H, s, $-O_2CCH_3$), 2.15 (1H, br d, J = 15.9 Hz, 6-H), 2.33 (2H, d, J = 10.2 Hz, 2-H), 2.66 (1H, dd, J = 15.9, 3.2 Hz, 6-H), 3.46 (1H, s, OH), 3.71 (1H, m, NC*H*), 5.39 (1H, dd, J = 10.2, 3.2 Hz, 4-H), 5.82 (1H, br q, J = 10.2 Hz, 3-H), 6.04 (1H, q, J = 3.2 Hz, 5-H), 6.90 (1H, br, N*H*), 7.32 (2H, t, J = 8.0 Hz, Ph), 7.49 (3H, m, Ph), 7.62 (1H, tt, J = 7.4, 1.2 Hz, Ph), 7.86 (2H, dd, J = 8.3, 1.3 Hz, Ph), 7.98 (2H, dd, J = 8.2, 1.4 Hz, Ph); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 21.0, 24.7, 25.5, 33.0, 36.4, 39.1, 48.0, 67.1, 71.1, 73.2, 76.2, 128.39, 128.87, 129.25, 129.27, 129.56, 129.69, 133.24, 133.70, 164.9, 165.5, 170.4, 171.8; FTIR ($CHCl_3$) 1666 (s), 1728 (s), 2937 (s), 3412 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{29}H_{33}O_8$-NNa (MNa^+) requires 546.2104, found 546.2055.

(1*S*,3*R*,4*R*,5*R*)-Cyclohexyl-3-benzoyloxy-4,5-diacetyloxy-1-hydroxycyclohexanecarboxamide (10f): colorless oil; R_f 0.21 (Hex−EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.42 (5H, m, cyclohexyl), 1.59−1.74 (3H, m, cyclohexyl), 1.86 (2H, m, cyclohexyl), 1.93 (3H, s, $-O_2CCH_3$), 1.98 (1H, dt, J = 15.8, 3.1 Hz, 6-H), 2.01 (3H, s, $-O_2CCH_3$), 2.32 (1H, q, J = 13.5 Hz, 2-H), 2.38 (1H, ddd, J = 13.5, 5.3, 2.9 Hz, 2-H), 2.54 (1H, dd, J = 15.8, 3.1 Hz, 6-H), 3.57 (1H, s, OH), 3.69 (1H, m, NC*H*), 5.26 (1H, dd, J = 11.0, 3.1 Hz, 4-H), 5.66 (1H, td, J = 11.0, 5.3 Hz, 3-H), 5.73 (1H, q, J = 3.1 Hz, 5-H), 6.89 (1H, br, N*H*), 7.43 (2H, t, J = 7.4 Hz, *m*-H), 7.56 (1H, tt, J = 7.4, 1.3 Hz, *p*-H), 7.98 (2H, dd, J = 7.4, 1.3 Hz, *o*-H); ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 20.13, 20.64, 24.7, 25.5, 32.9, 36.3, 39.2, 48.0, 67.8, 70.6, 72.3, 76.0, 128.5, 129.58, 129.66, 133.3, 165.8, 168.9, 170.1, 171.6; FTIR ($CHCl_3$) 1666 (s), 1722 (s), 1747 (s), 2937 (s), 3412 (m), 3300−3500 (br); *m*/*z* (ESI) $C_{24}H_{31}O_8NNa$ (MNa^+) requires 484.1947, found 484.1929.

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