Regioselective Acylation of Octyl β-D-Glucopyranoside by Chiral 4-Pyrrolidinopyridine Analogues

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Dedicated to the memory of the late Professor Yoshihiko Ito

Abstract: Chiral 4-pyrrolidinopyridine (PPY) analogues with dual functional side chains consisting of indole units have been prepared from *trans*-4-hydroxy-L-proline. Treatment of octyl β-D-glucopyranoside with isobutyric anhydride in the presence of the catalysts gave the 6-*O*-acylate as the major product via acylation of a primary hydroxyl group. On the other hand, the 4-*O*-acylate was obtained as the major product in 66% regioselectivity via acylation of the secondary hydroxyl group at C-4 on treatment of octyl β-D-glucopyranoside with isobutyric anhydride in the presence of a PPY catalyst. Use of isobutyryl chloride instead of isobutyric anhydride in the presence of the catalyst gave the 6-*O*-acylate in 87% regioselectivity.

Key words: regioselective acylation, nucleophilic catalyst, glucopyranoside, chiral pyrrolidinopyridine, organocatalyst

We previously developed the chiral 4-pyrrolidinopyridine (PPY) analogue **1**, which could effectively catalyze acylative kinetic resolution of racemic diol and amino alcohol derivatives with high enantioselectivity (Figure 1).[1,2] We further developed chiral PPY analogues **2**[3] and **3**.[4] Although chiral elements are not present in the catalytically active pyridine ring in these nucleophilic catalysts, they could promote enantioselective acylation via remote asymmetric induction. We then investigated the chemoselectivity of acylation of *meso*-1,3-cyclohexanediol with PPY and **1**–**3** (Table 1).[4] Treatment of *meso*-1,3-cyclohexanediol with isobutyric anhydride in the presence of PPY gave the monoacylate and the diacylate in 35% and 39% yield, respectively, together with 4% recovery (entry 1). A similar tendency for mono- and diacylation was observed in acylation with **1** (entry 2). On the other hand, the yield for monoacylation was slightly improved to 44% with **2**, and further improved to 60% with **3** (entries 3 and 4). These observations might indicate that the indole units in **2** and **3** could participate in the recognition of the 1,3-diol substructure. This background prompted us to develop PPY analogues **4**–**7** with dual functional side chains consisting of indole units. Here, we describe the preparation of chiral PPYs **4**–**7** and their use in the regioselective acylation of octyl β-D-glucopyranoside.

While we assumed that two indole units in **3** could participate in the substrate recognition, the indole unit in the C-4 side chain of **3** was assumed to be located far from the catalytically active pyridine nitrogen. Catalysts **4**–**7** were designed with the expectation that the indole unit of the C-4 side chain of catalysts would be located in proximity to

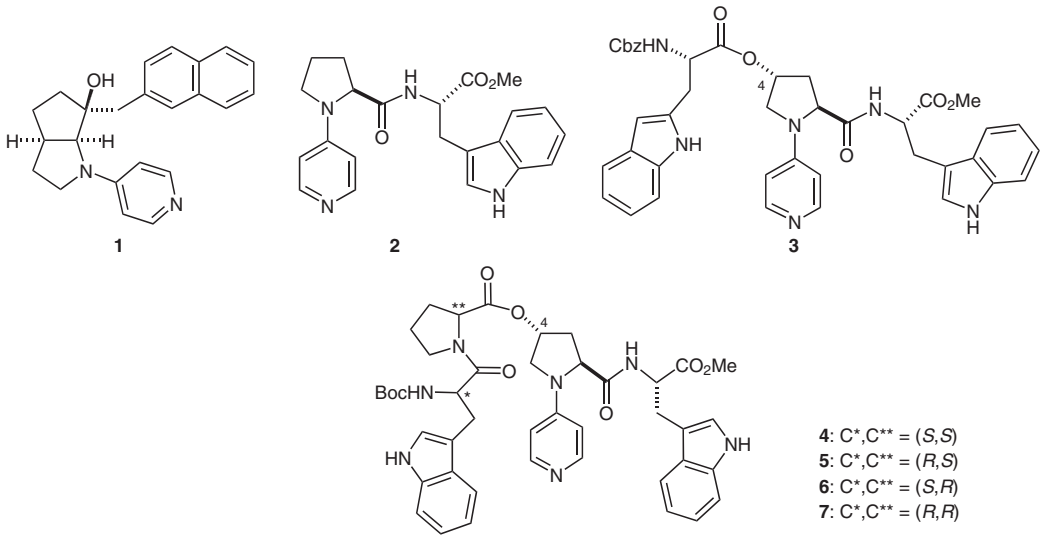

Figure 1

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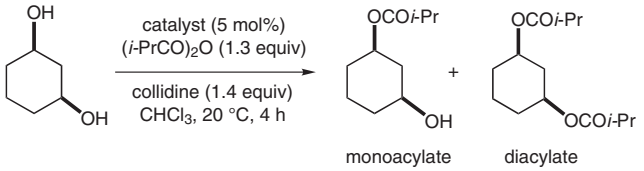
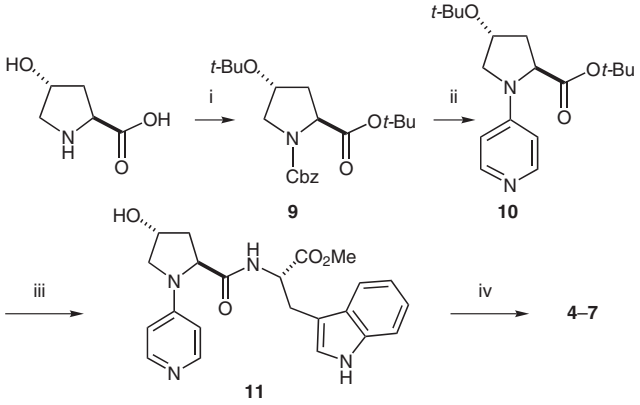
Table 1 Acylation of *meso*-1,3-Cyclohexanediol with PPY Analogues[a]



Entry	Catalyst	Monoacylate/diacylate/recovery (%)[b]
1	PPY	35:39:4
2	**1**	32:46:2
3	**2**	44:29:8
4	**3**	60:28:5

[a] Data quoted from Kawabata et al.[4]
[b] Yields determined by ^{1}H NMR with dibenzyl ether as an internal standard.



Scheme 1 *Reagents and conditions*: (i) (a) Z-Cl, NaOH, H_2O; (b) isobutene, conc. H_2SO_4, dioxane (53%); (ii) (a) H_2, 10% Pd/C, MeOH; (b) 4-bromopyridine hydrochloride, $Pd(OAc)_2$, dppp, Cs_2CO_3, toluene, 100 °C (65%); (iii) (a) SiO_2, toluene, reflux; (b) H-Trp-OMe, WSC·HCl, HOBt, NMM, DMSO–CH_2Cl_2 (70%); (c) TFA, ethanedithiol, CH_2Cl_2 (67%); (iv) Boc-Trp-Pro-OH, HOBt, DIC, DMF (47–92%).

the pyridine nitrogen due to the turn structure caused by proline. Since the relative orientation of two of the indole units was supposed to be linked to recognition of the substrate, all possible stereoisomers of the dipeptides consisting of proline and tryptophan were introduced at C-4 of the pyrrolidine ring. Molecular modeling of the acylpyridinium ion **8**,[5] generated from **4**, was performed by MacroModel (V. 9.0)/MCMM conformational searches with the AMBER* force field (Figure 2). The calculated structure indicated that the indole unit in the C-4 side chain of **8** was in close proximity to the reactive acyl group.

Catalysts **4**–**7**, with dual functional side chains consisting of two tryptophan substructures, were prepared (Scheme 1). Thus, *trans*-4-hydroxy-L-proline was transformed into the fully protected derivative **9** in 53% yield according to a standard procedure.[6] Hydrogenolysis of **9**, followed by coupling with 4-bromopyridine by Buchwald's procedure,[7] gave chiral PPY **10** in 65% yield. Selective removal of the *tert*-butyl ester protecting group of **10**, in the presence of *tert*-butyl ether, was achieved by treatment with SiO_2 in refluxing toluene. Condensation of the resulting acid [activated using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC·HCl)] with L-tryptophan methyl ester followed by removal of the *tert*-butyl ether protecting group with trifluoroacetic acid (TFA), gave **11** in 67% yield. Condensation of **11** with L,L-, D,L-, L,D-, D,D-Boc-Trp-Pro-OH, respectively, in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) gave **4**, **5**, **6** and **7**, respectively, in 47–92% yields. We then investigated the properties of catalysts **4**–**7** in the acylation of octyl β-D-glucopyranoside.

Regioselective protection of carbohydrates and polyol natural products is one of the major challenges in current organic synthesis.[8,9] Selective acylation of a primary hydroxyl group of alkyl β-D-glucopyranoside has been achieved in ~100% regioselectivity by enzymatic processes, however, concomitant diacylation was unavoidable.[10] Kattnig and Albert reported that acylation of octyl β-D-glucopyranoside with 4-dimethylaminopyridine (DMAP) and acetyl chloride proceeded selectively on the primary hydroxyl group to give the 6-*O*-acetate in 85% selectivity in 73% yield.[11] On the other hand, selective acylation of a secondary hydroxyl group in the presence of a free primary hydroxyl group has been known to be difficult.[12] Yoshida and coworkers reported regioselective acylation of a secondary hydroxyl group at C-4 of octyl α-D-glucopyranoside in 61% selectivity with an acetic anhydride–DMAP system.[13] Kattnig and Albert also reported that acylation of octyl β-D-glucopyranoside with acetic anhydride in the presence of DMAP and pyridine, gave

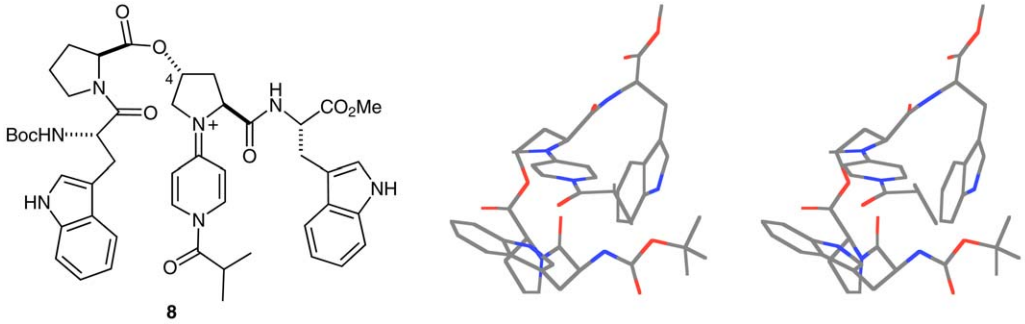
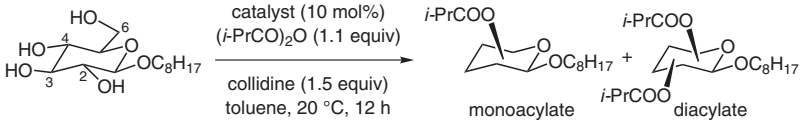


Figure 2 Acylpyridinium ion **8** and the most stable structure (stereo view) generated by Mocromodel (V. 9.0) with the AMBER* force field.

Table 2 Effects of Catalysts on the Regioselectivity of Acylation of Octyl β-D-Glucopyranoside[a]



Entry	Catalyst	Monoacylate (%)	Regioselectivity (%)[b] 6-*O*/4-*O*/3-*O*/2-*O*	Diacylate (%)	Recovery (%)
1	DMAP	47	36:26:26:12	22	31
2	**4**	66	30:60:10:0	16	16
3	**5**	65	46:40:11:3	20	12
4	**6**	67	56:33:10:1	19	14
5	**7**	62	49:39:11:1	24	10

[a] The reactions were carried out with a substrate concentration of 0.08 M.
[b] Regioselectivity among four monoacylates.

the 3-*O*-acetate in 57% regioselectivity.[11] Recently, Griswold and Miller reported an excellent approach for the selective introduction of an acetyl group at a secondary hydroxyl group of octyl β-D-glucopyranoside with peptide-based chiral catalysts;[14] moderately selective 4-*O*-acylation was achieved, giving 6-, 4-, 3- and 2-*O*-acylates in a ratio of 22:58:11:9. Recently, we found highly chemo- and regioselective acylation of monosaccharides catalyzed by C_2-symmetric chiral PPY derivatives.[15] In this report, we describe the regioselectivity profile for the acylation of octyl β-D-glucopyranoside with catalysts **4**–**7**.

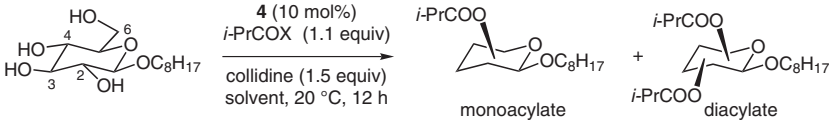
Isobutyric anhydride was employed as an acylating agent because it has been known to show high selectivity in acylative kinetic resolution of racemic alcohols[1b] due to the high k_{cat}/k_{uncat} ratio.[16] Acylation of octyl β-D-glucopyranoside was investigated with 10 mol% of catalysts and 1.1 mol equivalent of isobutyric anhydride (Table 2). Formation of the assigned products was unambiguously confirmed by comparison with authentic samples of 6-, 4-, 3- and 2-*O*-isobutyryl octyl β-D-glucopyranosides, which were independently prepared via conventional protection–deprotection sequences.[15] With DMAP as a catalyst, four monoacylates, 6-, 4-, 3- and 2-*O*-isobutyryl octyl β-D-glucopyranosides, were obtained in a ratio of 36:26:26:12, respectively, in a combined yield of 47% together with 22% of the diacylates and 31% recovery (entry 1). Thus, totally random acylation took place by DMAP-catalysis. With catalysts **5**–**7**, acylation took place with a regioselectivity similar to that obtained using DMAP, giving the 6-*O*-acylate as the major product. On the other hand, in the acylation with catalyst **4**, the secondary hydroxyl group at C-4 was predominantly acylated (60%), even in the presence of a free primary hydroxyl group at C-6 (entry 2). These observations indicate that the relative orientation of the two indole units of the catalyst is critically involved in the selective acylation of one out of the four hydroxyl groups of octyl β-D-glucopyranosides.

We then investigated the effects of solvents, acylating agents and temperature on the regioselectivity of acylation of octyl β-D-glucopyranoside with catalyst **4** (Table 3). Chloroform, tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were examined in addition to toluene. Acylation in chloroform gave slightly higher selectivity (61%) for 4-*O*-acylation and slightly improved yield (71%) for monoacylation than in toluene (entries 1 *vs.* 3). On the other hand, acylation in polar solvents such as THF and DMF gave the 6-*O*-acylate as the major product with low selectivity (entries 4 and 5). The observed solvent effects indicate that the driving force for 4-*O*-acylation may involve H-bonding between the substrate and the catalyst. Use of isobutyryl chloride instead of isobutyric anhydride gave the 6-*O*-acylate in high regioselectivity (87%) and in 77% yield for monoacylation (entry 6).[17] Acylation with *p*-nitrophenyl isobutyrate gave the 6-*O*-acylate as the major product in 65% regioselectivity (entry 7). Acylation of octyl β-D-glucopyranoside with isobutyric anhydride, in the presence of **4** in toluene at 0 °C, gave the highest regioselectivity (66%) for 4-*O*-acylation (entry 2).

It might be supposed that the acylation of C(4)-OH results from migration of the 6-*O*-acylate into the 4-*O*-acylate. This possibility was investigated through treatment of the 6-*O*-isobutyrate of octyl β-D-glucopyranoside with a C_2-symmetric chiral PPY derivative; in the presence of collidine and in the absence of isobutyric anhydride, the 6-*O*-isobutyrate was recovered in 99% yield and migration to the 4-*O*-isobutyrate was not detected at all.[15] This clearly indicates that acylation of a secondary hydroxyl group at C-4 took place directly under the influence of the catalyst.

In conclusion, we have developed chiral PPY analogues with dual functional side chains consisting of indole units. Among them, catalyst **4** was found to be effective for the regioselective acylation of the secondary hydroxyl group at C-4 of octyl β-D-glucopyranoside, in the presence of a free primary hydroxyl group at C-6.

Table 3 Effects of Solvents, Acylation Agents and Temperature on the Regioselectivity of Acylation of Octyl β-D-Glucopyranoside with **4**[a]



Entry	Solvent	*i*-PrCOX	Monoacylate (%)	Regioselectivity (%)[b] 6-*O*/4-*O*/3-*O*/2-*O*	Diacylate (%)	Recovery (%)
1	toluene	$(i\text{-PrCO})_2O$	66	30:60:10:0	16	16
2[c]	toluene	$(i\text{-PrCO})_2O$	69	25:66:9:0	20	10
3	$CHCl_3$	$(i\text{-PrCO})_2O$	71	22:61:17:0	18	10
4	THF	$(i\text{-PrCO})_2O$	69	37:22:34:7	18	13
5	DMF	$(i\text{-PrCO})_2O$	60	41:14:34:11	24	15
6	toluene	*i*-PrCOCl	77	87:9:4:0	11	10
7	toluene	$i\text{-PrCO}_2\text{Np}$[d]	48	65:20:13:2	6	41

[a] The reactions in entries 1, 2, 6 and 7 and those in entries 3–5 were carried out with a substrate concentration of 0.08 M and 0.1 M, respectively.
[b] Regioselectivity among four monoacylates.
[c] The reaction was run at 0 °C for 24 h.
[d] *p*-Nitrophenyl ester.

NMR spectra were obtained with a JEOL JMN 400 spectrometer, chemical shifts are given in ppm units (TMS or $CHCl_3$ as internal standards at 0 ppm or 7.24 ppm, respectively). IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Specific rotation was measured with a Horiba SEPA-200 automatic digital polarimeter. MS spectra were recorded with a JEOL JMS-DX300 mass spectrometer. TLC analysis and preparative TLC were performed on commercial glass plates bearing a 0.25 mm layer and 0.5 mm layer of Merck Kiesel-gel 60 F_{254}, respectively. Silica gel chromatography was carried out using Wakogel C-200, Fuji Silysia BW-1277H or Nacalai Tesque Silica gel 60 (150–325 mesh). Anhydrous solvents (THF, Et_2O, hexane, CH_2Cl_2 and toluene; <50 ppm H_2O content) were purchased from Kanto Chemical Co., Inc. and used without further treatment.

tert-Butyl (2*S*,4*R*)-4-*tert*-Butoxy-1-(pyridin-4-yl)pyrrolidine-2-carboxylate (10)

A mixture of **9** (31.9 g, 84.5 mmol)[6] and 10% Pd/C (3.19 g) in MeOH (300 mL) was stirred vigorously at r.t. under H_2 for 12 h. The mixture was filtered and washed with MeOH and the combined filtrate was evaporated in vacuo to give a colorless oil. A mixture of the oil, 4-bromopyridine hydrochloride (26.5 g, 136 mmol), $Pd(OAc)_2$ (3.80 g, 17.0 mmol), 1,3-bis(diphenylphosphino)propane (14.1 g, 34. 2 mmol) and Cs_2CO_3 (88.9 g, 273 mmol) in toluene (500 mL) was stirred with Ar bubbling for 15 min. The resulting mixture was heated at reflux under Ar for 48 h. After cooling to r.t., the mixture was filtered and washed with EtOAc. The combined filtrate was washed with sat. aq $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (SiO_2; EtOAc–hexane–Et_3N, 50:50:5) to give **10**.

Yield: 17.7 g (65%); $[\alpha]_D^{20}$ –69 (*c* 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ = 8.22 (d, *J* = 6.5 Hz, 2 H), 6.36 (d, *J* = 6.5 Hz, 2 H), 4.53 (quin, *J* = 7.2 Hz, 1 H), 4.23 (t, *J* = 5.9 Hz, 1 H), 3.70 (dd, *J* = 9.5, 7.2 Hz, 1 H), 3.19 (dd, *J* = 9.5, 6.0 Hz, 1 H), 2.25 (dd, *J* = 7.2, 5.9 Hz, 2 H), 1.44 (s, 9 H), 1.22 (s, 9 H).

MS (EI): *m*/*z* (%) = 320 (20) [M$^+$], 219 (100), 163 (100), 145 (50).

HRMS: *m*/*z* calcd for $C_{18}H_{28}N_2O_3$: 320. 2100; found: 320.2115.

Methyl (*S*)-2-[(2*S*,4*R*)-4-Hydroxy-1-(pyridin-4-yl)pyrrolidine-2-carboxamido]-3-(1*H*-indol-3-yl)propanoate (11)

A mixture of **10** (6.80 g, 21.2 mmol) and SiO_2 (67 g) in toluene (200 mL) was heated under reflux for 12 h. After cooling to r.t., the mixture was filtered, washed with NEt_3–MeOH (5:95, 50 mL) and the combined filtrate was evaporated in vacuo. To a solution of the residue in DMSO–CH_2Cl_2 (2:1, 200 mL) were added L-tryptophan methyl ester hydrochloride (11.8 g, 46.4 mmol), *N*-methylmorpholine (17.0 mL, 155 mmol), 1-hydroxybenzotriazole hydrate (5.00 g, 37.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.0 g, 61.9 mmol) at 0 °C. After stirring for 72 h at r.t., the mixture was diluted with EtOAc (300 mL) and washed with sat. aq $NaHCO_3$ (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (SiO_2; EtOAc–MeOH, 9:1→5:1) to give a pale-yellow foam (10.0 g). The foam was treated with 5% ethanedithiol in TFA (30 mL) at r.t. for 6 h. After evaporation of the solvent, the residue was diluted with CH_2Cl_2–EtOH (5:1, 200 mL) and washed with sat. aq $NaHCO_3$ (2 × 30 mL) and brine (1 × 30 mL), dried over Na_2SO_4, filtered and evaporated to give pale-yellow solids which were recrystallized (MeOH–Et_2O) to give pure **11**.

Yield: 5.80 g (67%); colorless prisms; mp 217–220 °C; $[\alpha]^D_{20}$ –62 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 7.92 (d, *J* = 6.8 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.18 (td, *J* = 8.1, 1.2 Hz, 1 H), 7.09 (td, *J* = 8.1, 1.0 Hz, 1 H), 6.89 (s, 1 H), 6.15 (d, *J* = 6.8 Hz, 1 H), 4.78 (dd, *J* = 7.3, 5.4 Hz, 1 H), 4.25 (quint, *J* = 5.1 Hz, 1 H), 4.12 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.71 (s, 1 H), 3.43–3.30 (m, 2 H), 3.22 (dd, *J* = 15.4, 7.3 Hz, 1 H), 3.10 (dd, *J* = 10.0, 4.4 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.11–2.03 (m, 1 H).

IR (KBr): 3294, 1741, 1667, 1601, 1520, 1227 cm^{-1}.

MS (EI): *m*/*z* (%) = 408 (20) [M$^+$], 279 (30), 256 (25), 163 (100), 145 (80), 130 (80).

HRMS: *m*/*z* calcd for $C_{22}H_{24}N_4O_4$: 408.1798; found: 408.1790.

(*S*)-{(3*R*,5*S*)-5-[(*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-ylcarbamoyl]-1-(pyridin-4-yl)pyrrolidin-3-yl}-1-[(*S*)-2-(*tert*-butoxycarbonylamino)-3-(1*H*-indol-3-yl)propanoyl]pyrrolidine-2-carboxylate (4)

To a solution of **11** (1.20 g, 2.94 mmol) and Boc-L-Trp-L-Pro-OH (2.93 g, 7.34 mmol) in DMF (30 mL), were added *N*-methylmorpholine (0.97 mL, 8.81 mmol), *N*,*N*′-diisopropylcarbodiimide (1.15 mL, 7.34 mmol) and DMAP (0.18 g, 1.47 mmol). The mixture was stirred at r.t. for 4 d then hexane was added and the resulting supernatant was decanted off. The remaining yellow oil was concentrated in vacuo and the residue was purified by column chromatography (SiO_2; EtOAc–hexane–NH_3 (25%), 84:16:2) to give **4**, which was further purified by recrystallization (2-propanol–Et_2O).

Yield: 1.29 g (55%); colorless crystals; mp 137–141 °C; $[\alpha]_D^{21}$ –40 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ (5:1 mixture of rotamers) = 11.0 (s, 1 H), 10.9 (s, 1 H), 8.80 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 5.6 Hz, 2 H), 7.55 (d, *J* = 7.9 Hz, 1 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.33 (d, *J* = 7.9 Hz, 1 H), 7.21 (s, 1 H), 7.18 (s, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 7.06 (t, *J* = 7.9 Hz, 1 H), 7.01–6.95 (m, 1 H), 6.99 (t, *J* = 7.9 Hz, 5/6H), 6.97 (t, *J* = 7.9 Hz, 5/6H), 6.92–6.86 (m, 2/6H), 6.53 (d, *J* = 5.6 Hz, 1/6H), 6.21 (d, *J* = 5.6 Hz, 11/6H), 5.35 (br s, 5/6H), 5.25 (br s, 1/6H), 4.57–4.50 (m, 1 H), 4.43–4.21 (m, 3 H), 3.77 (dd, *J* = 11.1, 5.1 Hz, 1 H), 3.72–3.55 (m, 1 H), 3.63 (s, 15/6H), 3.62 (s, 3/6H), 3.55–3.35 (m, 2 H), 3.24 (dd, *J* = 14.8, 4.6 Hz, 1 H), 3.08 (dd, *J* = 14.8, 9.7 Hz, 1 H), 2.98 (dd, *J* = 14.8, 4.6 Hz, 1 H), 2.86 (dd, *J* = 14.8, 9.7 Hz, 1 H), 2.40–2.30 (m, 1 H), 2.25–2.00 (m, 2 H), 2.00–1.82 (m, 3 H), 1.36 (s, 9/6H), 1.29 (s, 45/6H).

IR (KBr): 3277, 1740, 1637, 1601, 1174 cm^{-1}.

MS (FAB): *m*/*z* (%) = 792 (100) [MH$^+$], 692 (10), 662 (30), 504 (20), 391 (40).

HRMS: *m*/*z* calcd for $C_{43}H_{50}O_8N_7$: 792.3721; found: 792.3723.

(*S*)-{(3*R*,5*S*)-5-[(*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-ylcarbamoyl]-1-(pyridin-4-yl)-pyrrolidin-3-yl}-1-[(*R*)-2-(*tert*-butoxycarbonylamino)-3-(1*H*-indol-3-yl)propanoyl]pyrrolidine-2-carboxylate (5)

Prepared from **11** and and Boc-D-Trp-L-Pro-OH, according to the procedure for **4**.

Yield: 47%; colorless crystals; mp 143–146 °C; $[\alpha]_D^{21}$ –72 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ (5:1 mixture of rotamers) = 11.0 (s, 1 H), 10.8 (s, 1 H), 8.78 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 6.1 Hz, 10/6H), 7.85 (d, *J* = 6.1 Hz, 2/6H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.21 (s, 1 H), 7.16 (s, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 7.02–6.95 (m, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 6.97 (t, *J* = 8.0 Hz, 5/6H), 6.70 (m, 1/6H), 6.22 (d, *J* = 6.1 Hz, 10/6H), 5.95 (d, *J* = 6.1 Hz, 2/6H), 5.33 (br s, 1/6H), 5.27 (br s, 5/6H), 4.57–4.50 (m, 1 H), 4.43 (dd, *J* = 15.0, 7.0 Hz, 1 H), 4.32–4.20 (m, 1 H), 4.20–4.00 (m, 1 H), 3.77–3.72 (m, 1 H), 3.62 (s, 3 H), 3.57–2.80 (m, 7 H), 2.40–2.20 (m, 1 H), 2.20–2.00 (m, 1 H), 1.90–1.60 (m, 3 H), 1.60–1.40 (m, 1 H), 1.32 (s, 45/6H), 1.27 (s, 9/6H).

IR (KBr): 3280, 1740, 1637, 1601, 1174 cm^{-1}.

MS (FAB): *m*/*z* (%) = 792 (100) [MH$^+$], 692 (40), 662 (20), 504 (30), 391 (70).

HRMS: *m*/*z* calcd for $C_{43}H_{50}O_8N_7$: 792.3721; found: 792.3710.

(*R*)-{(3*R*,5*S*)-5-[(*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-ylcarbamoyl]-1-(pyridin-4-yl)pyrrolidin-3-yl}-1-[(*S*)-2-(*tert*-butoxycarbonylamino)-3-(1*H*-indol-3-yl)propanoyl]pyrrolidine-2-carboxylate (6)

Prepared from **11** and and Boc-L-Trp-D-Pro-OH, according to the procedure for **4**.

Yield: 92%; colorless crystals; 150–153 °C; $[\alpha]_D^{21}$ +34 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ (5:1 mixture of rotamers) = 11.0 (s, 1 H), 10.9 (s, 1 H), 8.90 (d, *J* = 8.2 Hz, 1/6H), 8.82 (d, *J* = 8.2 Hz, 5/6H), 7.95 (d, *J* = 6.1 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.21 (s, 1 H), 7.17 (s, 1 H), 7.10–6.90 (m, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 6.97 (t, *J* = 8.0 Hz, 5/6H), 6.70 (m, 1/6H), 6.30–6.10 (m, 2 H), 5.40–5.20 (m, 1 H), 4.60–4.50 (m, 1 H), 4.42 (dd, *J* = 15.0, 7.5 Hz, 1 H), 4.40–4.20 (m, 1 H), 4.20–4.00 (m, 1 H), 3.80–3.70 (m, 1 H), 3.63 (s, 3 H), 3.60–2.70 (m, 7 H), 2.45–2.20 (m, 1 H), 2.20–2.00 (m, 1 H), 1.90–1.40 (m, 4 H), 1.31 (s, 45/6H), 1.29 (s, 9/6H).

IR (KBr): 3280, 1740, 1637, 1601, 1174 cm^{-1}.

MS (FAB): *m*/*z* (%) = 792 (50) [MH$^+$], 692 (30), 662 (20), 504 (40), 391 (100).

HRMS: *m*/*z* calcd for $C_{43}H_{50}O_8N_7$: 792.3721; found: 792.3710.

(*R*)-{(3*R*,5*S*)-5-[(*S*)-3-(1*H*-Indol-3-yl)-1-methoxy-1-oxopropan-2-ylcarbamoyl]-1-(pyridin-4-yl)pyrrolidin-3-yl}-1-[(*R*)-2-(*tert*-butoxycarbonylamino)-3-(1*H*-indol-3-yl)propanoyl]pyrrolidine-2-carboxylate (7)

Prepared from **11** and and Boc-D-Trp-D-Pro-OH according to the procedure for **4**.

Yield: 83%; colorless crystals; mp 144–146 °C; $[\alpha]_D^{21}$ –16 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz, DMSO-d_6): δ (7:1 mixture of rotamers) = 10.93 (s, 1 H), 10.86 (s, 1 H), 8.82 (d, *J* = 8.0 Hz, 1/8H), 8.73 (d, *J* = 8.0 Hz, 7/8H), 7.94 (d, *J* = 6.1 Hz, 2/8H), 7.89 (d, *J* = 6.1 Hz, 14/8H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.20 (s, 1 H), 7.16 (s, 1 H), 7.10–7.02 (m, 2 H), 7.00–6.95 (m, 1 H), 6.98 (t, *J* = 8.0 Hz, 2 H), 6.51 (d, *J* = 6.1 Hz, 2/8H), 6.17 (d, *J* = 6.1 Hz, 14/8H), 5.35 (br s, 7/8H), 5.29 (br s, 1/8H), 4.60–4.50 (m, 1 H), 4.45–4.20 (m, 3 H), 3.90–3.60 (m, 1 H), 3.63 (s, 21/8H), 3.61 (s, 3/8H), 3.55–3.30 (m, 3 H), 3.24 (dd, *J* = 14.8, 4.6 Hz, 1 H), 3.07 (dd, *J* = 14.8, 10.2 Hz, 1 H), 2.95 (dd, *J* = 14.8, 4.6 Hz, 1 H), 2.82 (dd, *J* = 14.8, 10.2 Hz, 1 H), 2.45–2.30 (m, 1 H), 2.25–2.00 (m, 2 H), 2.00–1.75 (m, 3 H), 1.32 (s, 9/8H), 1.29 (s, 63/8H).

IR (KBr): 3277, 1740, 1637, 1601, 1174 cm^{-1}.

MS (FAB): *m*/*z* (%) = 792 (100) [MH$^+$], 692 (10), 662 (20), 504 (20), 391 (40).

HRMS: *m*/*z* calcd for $C_{43}H_{50}O_8N_7$: 792.3721; found: 792.3710.

Regioselective Acylation of Octyl β-D-Glucopyranoside (Table 3, entry 2); Typical Procedure

Octyl β-D-glucopyranoside (58.5 mg, 0.20 mmol), **4** (15.8 mg, 20 μmol) and 2,4,6-collidine (40 mL, 0.30 mmol) were dissolved in toluene (2.5 mL) at 20 °C. After cooling the solution to 0 °C, isobutyric anhydride (36 mL, 0.22 mmol) was added and the solution was stirred at 0 °C for 24 h. The reaction mixture was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2; EtOAc–hexane, 30:70→100:0) to give diacylates (17.7 mg, 20%), octyl 6-*O*-isobutyryl-β-D-glucopyranoside (12.3 mg, 17%) and a mixture of

octyl 4-*O*-isobutyryl- and 3-*O*-isobutyryl-β-D-glucopyranoside (88:12, 37.9 mg, 52%) and recovered starting material (5.6 mg, 10%). Identification of the regioisomeric products was unambiguously made by comparison with pure regioisomers prepared independently by a conventional protection–deprotection procedure.[15]

The preparation and characterization of octyl 2-, 3-, 4- and 6-*O*-isobutyryl-β-D-glucopyranosides has been previously described.[15] Selected data for these are as follows.

Octyl 2-*O*-Isobutyryl-β-D-glucopyranosides

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (dd, *J* = 9.3, 8.0 Hz, 1 H), 4.43 (d, *J* = 8.0 Hz, 1 H), 4.34 (br s, 1 H), 3.99 (br s, 1/2H), 3.90–3.80 (m, 2 H), 3.50 (dt, *J* = 9.7, 6.5 Hz, 1 H), 3.67 (br t, *J* = 9.2 Hz, 1 H), 3.59 (br t, *J* = 9.4 Hz, 1 H), 3.43 (dt, *J* = 9.7, 6.9 Hz, 1 H), 3.33 (dt, *J* = 9.2, 3.4 Hz, 1 H), 3.19 (br s, 1/2H), 2.60 (hept, *J* = 7.0 Hz, 1 H), 2.25 (br s, 1 H), 1.60–1.50 (m, 2 H), 1.30–1.22 (m, 10 H), 1.18 (d, *J* = 7.0 Hz, 6 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.09, 100.98, 77.23, 75.38, 73.73, 70.49, 70.18, 61.76, 34.09, 31.83, 29.56, 29.38, 29.24, 25.93, 22.65, 19.04, 18.81, 14.08.

Octyl 3-*O*-Isobutyryl-β-D-glucopyranosides

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (t, *J* = 9.3 Hz, 1 H), 4.37 (d, *J* = 7.8 Hz, 1 H), 3.94–3.80 (m, 2 H), 3.90 (dt, *J* = 9.4, 6.8 Hz, 1 H), 3.67 (br t, *J* = 9.3 Hz, 1 H), 3.56 (dt, *J* = 9.4, 6.8 Hz, 1 H), 3.49 (br t, *J* = 8.7 Hz, 1 H) 3.42 (ddd, *J* = 9.7, 4.6, 3.6 Hz, 1 H) 3.12 (br s, 1 H), 2.67 (hept, *J* = 7.0 Hz, 1 H), 2.52 (br s, 1 H), 1.81 (br s, 1 H), 1.65–1.59 (m, 2 H), 1.38–1.18 (m, 10 H), 1.22 (d, *J* = 7.0 Hz, 3 H), 1.21 (d, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.96, 102.81, 78.03, 75.72, 72.20, 70.53, 69.79, 62.34, 34.15, 31.80, 29.61, 29.36, 29.22, 25.93, 22.64, 18.95, 18.92, 14.09.

Octyl 4-*O*-Isobutyryl-β-D-glucopyranosides

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (t, *J* = 9.7 Hz, 1 H), 4.32 (d, *J* = 7.8 Hz, 1 H), 3.89 (dt, *J* = 9.4, 7.0 Hz, 1 H), 3.69 (t, *J* = 8.8 Hz, 2 H), 3.53 (dt, *J* = 9.4, 7.0 Hz, 1 H), 3.48–3.40 (m, 3 H), 2.65 (br s, 1 H), 2.62 (hept, *J* = 7.0 Hz, 1 H), 1.63 (quin, 7.0 Hz, 2 H), 1.40–1.20 (m, 10 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.52, 102.59, 74.41, 74.23, 74.16, 70.60, 70.42, 61.46, 34.05, 31.83, 29.60, 29.41, 29.26, 25.93, 22.66, 19.00, 18.85, 14.10.

Octyl 6-*O*-Isobutyryl-β-D-glucopyranosides

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61 (br s, 1 H), 4.37 (dd, *J* = 12.1, 2.5 Hz, 1 H), 4.32 (dd, *J* = 12.1, 5.8 Hz, 1 H), 4.26 (d, *J* = 7.8 Hz, 1 H), 4.19 (m, 1 H), 3.84 (dt, *J* = 9.4, 7.0 Hz, 1 H), 3.76 (br s, 1 H), 3.57–3.48 (m, 1 H), 3.51 (dt, *J* = 9.4, 7.3 Hz, 1 H), 3.46 (dd, *J* = 5.8, 2.7 Hz, 1 H), 3.36 (t, *J* = 8.7 Hz, 2 H), 2.60 (hept, *J* = 7.0 Hz, 1 H), 1.64–1.58 (m, 2 H), 1.29–1.26 (m, 10 H), 1.18 (d, *J* = 7.0 Hz, 3 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.69, 102.59, 76.16, 73.89, 73.53, 70.37, 70.31, 63.52, 33.95, 31.84, 29.62, 29.41, 29.28, 25.92, 22.65, 19.03, 18.95, 14.09.

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