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Note

Fine tuning of β-glucosidase inhibitory activity in the 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) system

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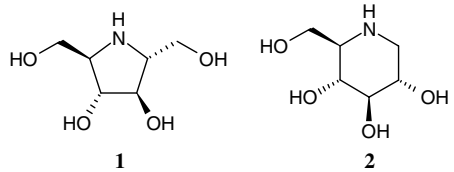
Abstract—Based on our extensive studies of D-glucosidase inhibiting 2,5-dideoxy-2,5-imino-D-mannitol derivatives, we have been trying to create a series of fluorescent derivatives with a view to an 'inhibitory activity ruler' based on competitive displacement reactions of non-fluorescent inhibitors by fluorescent ones and vice versa, which can be performed and followed in microtiter plates or on-chips. Thus, a set of compounds was assembled with K_i values between 2 nM and 1 μM against *Agrobacterium* sp. β-glucosidase.

Keywords: Glucosidase inhibitor; 2,5-Dideoxy-2,5-imino-D-mannitol; Fluorescent tag; Synthesis

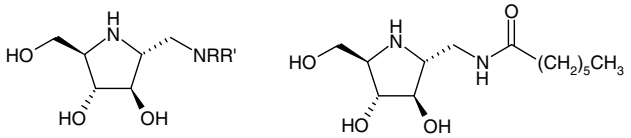
Iminosugars including iminoalditols such as compounds **1** and **2** (Fig. 1) are well-known (usually) competitive, glycosidase inhibitors.[1] Representatives of this class of compounds have found important roles as biological probes, for example, in the investigation of glycoprotein trimming glycosidases[2] or as pharmaceutical substances such as in the treatment of diabetes type II symptoms.[3] Other biological activities associated with their glycosidase inhibitory properties are anti-viral, anti-cancer and anti-metastatic, anti-infective as well as insect anti-feedant and plant growth regulating effects.[4]

It was demonstrated that N-alkylation of iminoalditol inhibitors also results in active compounds but this structural modification has frequently been associated with a loss of inhibitory activity of around one to two orders of magnitude.[5] Recently, we have found that some fluorescently labeled derivatives of the glucosidase inhibitor 2,5-dideoxy-2,5-imino-D-mannitol, **1** (DMDP), for example, compound **3** (Fig. 2), are very powerful inhibitors exceeding the parent compound's activity by two orders of magnitude.[6] Such compounds may generally prove useful for the identification and quantification of glycosidase activities by fluorescence spectrometric methods in biological specimens as well as for the discovery of glycosidase inhibitory activities in chemical compound collections, both in solution as well as, ideally, on-chips. As a prerequisite to such applications, fluorescent inhibitors need to be tuned to define appropriate activities covering



1 **2**

Figure 1. Iminoalditols **1** and **2**.



3: R = H, R' = dansyl
4: R = R' = H

5

Figure 2. DMDP derivatives **3**–**5**.

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0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
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the respective analytically interesting range. As a first step toward such a test case for a particular β-glucosidase, the enzyme from *Agrobacterium* sp., we were attempting to design a set of fluorescent DMDP derivatives providing K_i values suitably distributed over a range of three orders of magnitude. Based on our extensive work[7] on structure–inhibitory activity relationships of the DMDP system, we have tried to exploit information suggesting trends for inhibitory activities obtained by specific structural modifications at C-1 as well as the ring nitrogen of the iminoalditol including parameters such as chain length, polarity, and bulkiness of substituents employed (Table 1).

Previous studies[6] revealed that simple dansylation at *N*-1 in 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol **4** (K_i 25 μM) gives a powerful inhibitor, **3**, with a K_i of 2 nM for the β-glucosidase under consideration. It was also known[8] that a basic nitrogen at C-1 (**4**) could be expected to reduce the biological activity by two orders of magnitude compared to the parent compound **1**. The same is true for an acylated nitrogen such as in compound **5**. Several contributions[5] have shown that N-alkylation of the ring nitrogen would reduce activity by around one order of magnitude. Additional increase of steric crowding in the aglycon binding site by functionalization of both, N-1 and the ring nitrogen, was expected to further reduce inhibitory power by a factor ranging between 10 and 100.

For rapid diagnosis, we were seeking a set of derivatives with larger steps of K_i value differences between the single figure nanomolar and the 100 nM range. For more accurate and telling future competition experiments, inhibitors with smaller differences, for example, between 0.1 and 1 μM, were also required. The latter range of K_i values is where most of the non-fluorescent derivatives previously prepared[7] inhibit the same enzyme. Consequently, we concluded to prepare the four labeled compounds: **7**, **9**, **10**, **11**. Conventional[9] N-alkylation of compound **1** gave known compound **6**. Saponification of the methyl ester followed by reaction with mono-*N*-dansylethylenediamine in the presence of HBTU furnished labeled inhibitor **7** (Scheme 1). Gratifyingly, this compound had a K_i of 0.04 μM, perfectly positioned between the activity of parent **1** and our most potent compound in this study, **3**. A reduction of around 200-fold relative to **7** was achieved by introducing the dansyl group into the C-1 side chain but rendering N-1 a (basic) secondary amine. Thus, the known[8] free triamine **8** was chemo- and regioselectively N-dansylated at the terminal primary amine to provide inhibitor **9** (Scheme 2). This compound exhibited a K_i of 0.14, nicely matching the potency of non-fluorescent DMDP (K_i 0.2 μM) itself. Based on compound **3**, the increased steric crowding arising from a medium length ring nitrogen substituent previously employed by us[9] and others[5] gave a compound, **10**, with a K_i 0.35 (Scheme 3). Extending the chain length led to compound **11**, which was found to inhibit with a K_i value of 0.9. This particular set of fluorescent inhibitors now covers an activity range of 5×10^2 (Fig. 3), starting at 0.002 μM (**3**), with steps at 0.04 μM (factor of 20, **7**), 0.14 μM (factor of 3–4, **9**), 0.35 μM (factor of 2–3, **10**), and, finally, 0.9 μM (factor of 3, **11**). These values are conveniently positioned along the scale of activities of related non-fluorescent analogues and should provide a quick-screen 'fluorescent K_i-value ruler' for fluorescence spectrometric evaluation of glycosidase activities as well as potential inhibitory potencies of natural products or synthetic chemical compounds also applicable to compound collections and 'libraries'.

1. Experimental

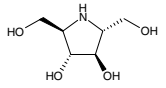
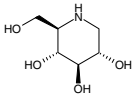
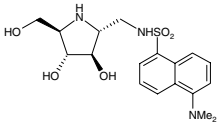
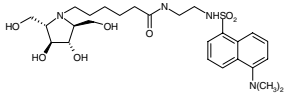
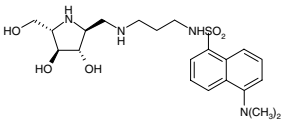
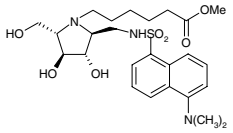
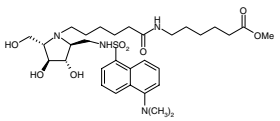
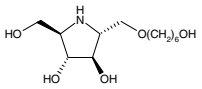
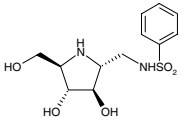
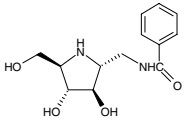
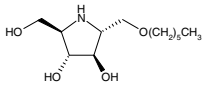
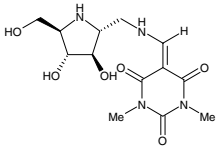
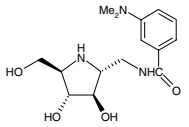
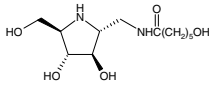
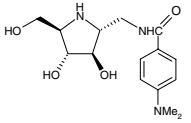
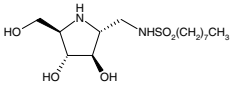
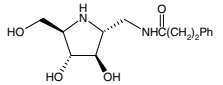
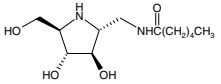
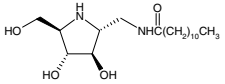
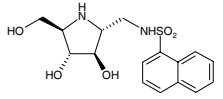
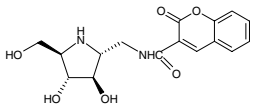
1.1. General methods

Optical rotations were measured on a JASCO Digital polarimeter or with a Perkin Elmer 341 polarimeter with a path length of 10 cm. Electrospray mass spectra were recorded with a HP 1100 series MSD, Hewlett Packard. Samples were dissolved in acetonitrile/CH_3OH mixtures. The scan mode for negative ions (mass range 100–1000 D) was employed, varying the fragmentation voltage from 30 to 130 V. NMR spectra were recorded at 499.778 MHz (^1H), and at 125.682 MHz (^{13}C). $CDCl_3$ was employed for protected compounds and D_2O as well as CD_3OD for deprotected sugars. Chemical shifts are listed in δ employing residual, not deuterated, solvent as the internal standard. The signals of the aromatic groups were found in the expected regions and are not listed explicitly. TLC was performed on precoated aluminum sheets (E. Merck 5554). Compounds were detected by staining with concd H_2SO_4 containing 5% vanillin. TLC of iminoalditols was performed employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v). For column chromatography Silica Gel 60 (E. Merck, 0.040–0.036 mm) was used.

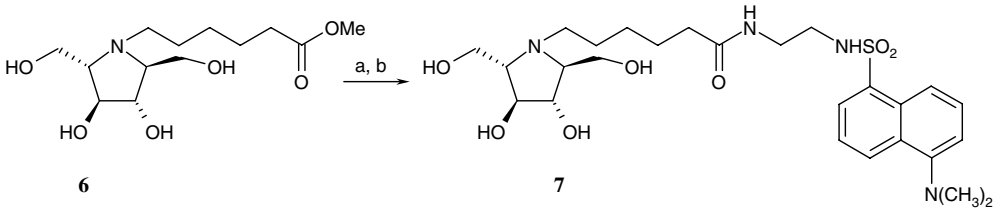
1.2. *N*-[(*N*′-Dansylaminoethyl)]aminocarbonylpentyl-2,5-dideoxy-2,5-imino-D-mannitol (7)

To a solution of compound **6** (56.5 mg, 0.19 mmol) in H_2O/dioxane (1:1.5 mL v:v), NaOH (0.5 M) was added drop-wise until the solution was pH ~9 and the reaction mixture was stirred at rt for 1 h, then neutralized (ion exchange resin Amberlite IR 120-H^+) and concentrated under reduced pressure to give an oily residue (44.2 mg, 82%). This was dissolved in CH_3OH (3 mL) and *N*-dansylethylenediamine (80 mg, 0.27 mmol), HBTU (98 mg, 0.25 mmol), Et_3N (40 μL, 0.29 mmol), and DMF (1 mL) were added consecutively. The mixture was

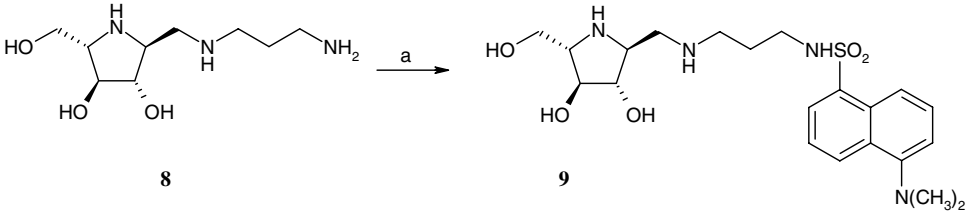
Table 1. Activities (K_i, μM, pH = 7.0) of derivatives of DMDP against *Agrobacterium* sp. β-glucosidase (see also Refs. 1d, 7a, and 7b)

 **1** K_i = 0.2 (Ref. 1d)	 **2** K_i = 12 (Ref. 1d)	 **3** K_i = 0.0024 (Ref. 6)	 **7** K_i = 0.04 [+]	 **8** K_i = 0.14 [+]
 **9** K_i = 0.35 [+]	 **10** K_i = 0.90 [+]	 **11** K_i = 1.2 (Ref. 8)	 **12** K_i = 1.0 (Ref. 7a)	 **13** K_i = 0.88 (Ref. 7a)
 **14** K_i = 0.74 (Ref. 8)	 **15** K_i = 0.44 (Ref. 7a)	 **16** K_i = 0.39 (Ref. 7a)	 **17** K_i = 0.3 (Ref. 8)	 **18** K_i = 0.27 (Ref. 7a)
 **19** K_i = 0.2 (Ref. 7a)	 **20** K_i = 0.15 (Ref. 7b)	 **21** K_i = 0.1 (Ref. 8)	 **22** K_i = 0.1 (Ref. 7b)	 **23** K_i = 0.10 (Ref. 7b)
 **24** K_i = 0.037 (Ref. 7a)				

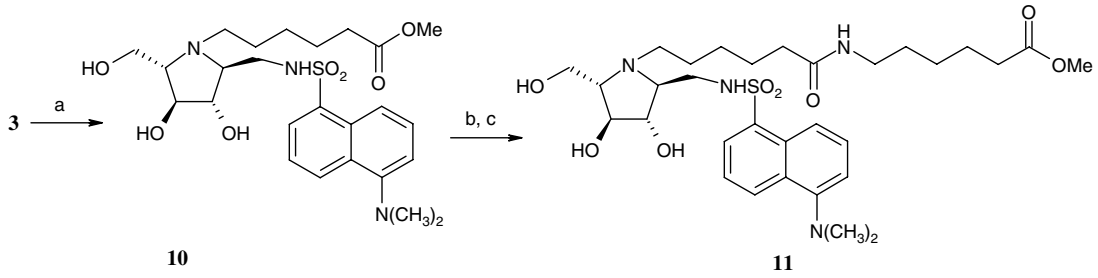
[+] This work.



Scheme 1. Reagents and conditions: (a) NaOH, dioxane/H_2O (v/v 1.5/1), (b) HBTU, 1-amino-3-*N*-dansylaminoethane, Et_3N, CH_3OH.



Scheme 2. Reagents and conditions: (a) dansylchloride, Et_3N, CH_3OH.



Scheme 3. Reagents and conditions: (a) methyl 6-oxohexanoate, $NaBH_3CN$, CH_3OH, (b) NaOH, dioxane/H_2O (v/v 1.5/1), (c) methyl 6-aminohexanoate hydrochloride, TBTU, Et_3N, DMF.

stirred at rt for 4 h until TLC (5:1, $CHCl_3/CH_3OH$ containing 1% NH_4OH) showed completed conversion of the starting material. The reaction mixture was concentrated under reduced pressure. Chromatography (10:1, $CHCl_3/CH_3OH$ containing 1% NH_4OH) gave **7** as a green oil (46.3 mg, 45%); $[\alpha]_D$ −7.8 (*c* 1.2, CH_3OH); δ_H (CD_3OD): 4.00 (m, 2H, H-3, H-4), 3.84 (dd, 2H, $J_{1a,1b=6a,6b}$ 12.2 Hz, $J_{1a,2}$ 4.4 Hz, $J_{5,6a}$ 3.9 Hz, H-1a, H-6a), 3.78 (dd, 2H, H-1b, H-6b), 3.66–3.56 (m, 1H, H-8′), 3.18 (m, 4H, H-2, H-5, H-7′), 3.06–2.99 (m, 1H, H-8′), 2.92 (t, 2H, H-1′), 2.88 (s, 6H, 2 × NCH_3-dansyl), 2.04 (t, 2H, H-5′), 1.67–1.54 (m, 4H, H-2′, H-4′), 1.34 (m, 2H, H-3′); δ_C (CD_3OD): 175.2 (C=O), 152.1, 135.5, 130.1, 130.1, 129.7, 129.1, 128.2, 123.2, 119.2, 115.3 (dansyl), 77.7 (2C, C-3, C-4), 70.6 (2C, C-2, C-5), 58.6 (2C, C-1, C-6), 47.3 (C-1′), 44.6 (2C, NCH_3dansyl), 42.1, 39.1 (C-7′, C-8′), 35.5 (C-5′), 27.6, 26.4, 25.2 (C-2′, C-3′, C-4′); ESIMS *m/z* calcd for $C_{26}H_{40}O_7SN_4$: 552.68. Found: 551.65 (M−H). Anal. Calcd for $C_{26}H_{40}O_7SN_4$: C, 56.50; H, 7.29. Found: C, 56.39; H, 7.40.

1.3. 1-(*N*-Dansylaminopropyl)amino-1,2,5-trideoxy-2,5-imino-D-mannitol (9)

To a solution of compound **8** (63.5 mg, 0.3 mmol) in CH_3OH (3 mL), Et_3N (80 μL, 0.6 mmol) and dansyl chloride (90 mg, 0.3 mmol) were added and the reaction mixture was stirred at rt for 3 h, then concentrated under reduced pressure. Preparative TLC purification (7:1, $CHCl_3/CH_3OH$ containing 1% NH_4OH) gave **9** as a green syrup (115.3 mg, 88%); $[\alpha]_D$ +5.4 (*c* 1.1, CH_3OH); δ_H (CD_3OD): 3.84 (dd, 1H, $J_{3,4}$ 6.9 Hz, $J_{4,5}$ 7.2 Hz, H-4), 3.76 (dd, 1H, $J_{2,3}$ 6.9 Hz, H-3), 3.71 (dd, 1H, $J_{6a,5}$ 3.6 Hz, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.65 (dd, 1H, $J_{1a,2}$ 2.3 Hz, $J_{1a,1b}$ 14.9 Hz, H-1a), 3.59 (dd, 1H, H-6b), 3.50 (dd, 1H, $J_{1b,2}$ 7.5 Hz, H-1b), 3.40 (ddd, 1H, H-2), 3.31 (m, 1H, H-5), 3.29–3.22 (m, 2H, H-3′), 3.02 (ddd, 1H, $J_{1,1}$ 10 Hz, H-1′), 2.89–2.86 (m, 1H, H-1′), 2.87 (s, 6H, 2 × NCH_3-dansyl), 1.82–1.91 (m, 1H, H-2′), 1.73–1.66 (m, 1H, H-2′); δ_C (CD_3OD): 152.9, 135.3, 130.2 (2C), 129.1, 128.0, 123.2, 119.6, 115.4 (dansyl), 78.0, 76.1 (2C, C-3, C-4), 68.0,

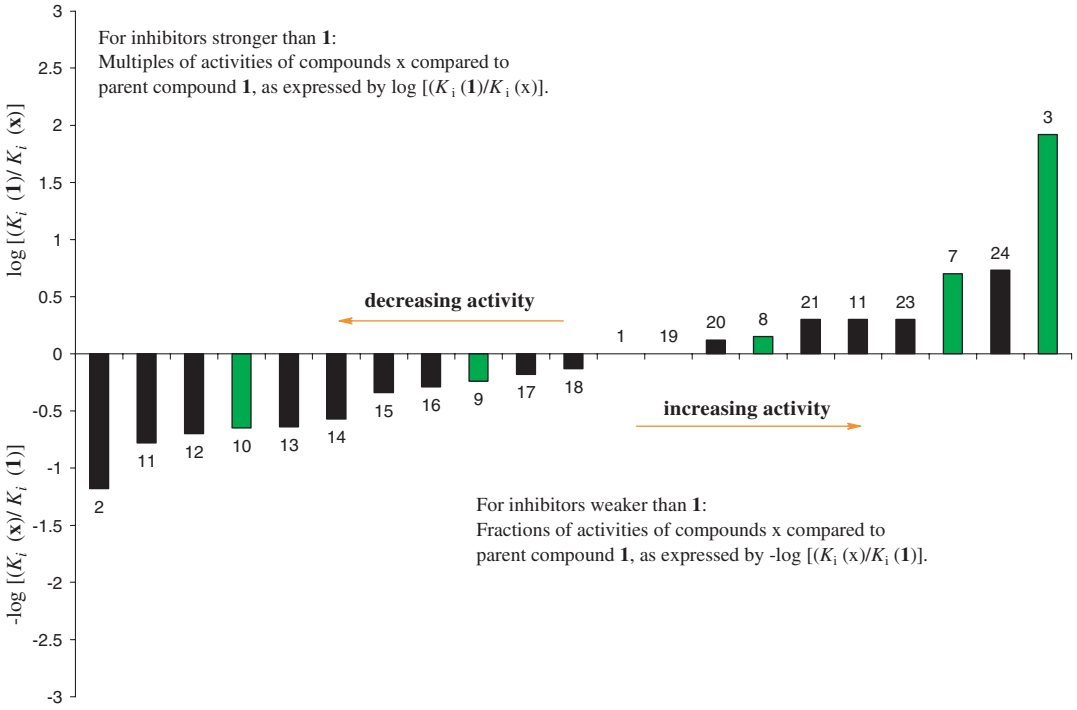


Figure 3. Comparison of K_i values of compounds as multiples, or fractions, respectively, of K_i (**1**).

67.5 (C-2, C-5), 59.4 (C-6), 49.7, 49.4 (C-1, C-1′), 47.2 (C-3′), 27.4 (C-3′); ESIMS *m*/*z* calcd for $C_{21}H_{32}O_5SN_4$: 452.59. Found: 451.58 (M−H). Anal. Calcd for $C_{21}H_{32}O_5SN_4$: C, 55.73; H, 7.13. Found: C, 55.50; H, 7.35.

1.4. 1-*N*-Dansyl-2-*N*-methoxycarbonylpentyl-1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol (10)

To a solution of compound **3** (650.2 mg, 1.6 mmol) in CH_3OH (6 mL), methyl 6-oxohexanoate (290 μL, 2.0 mmol), and $NaBH_3CN$ (260 mg, 4.1 mmol) were added and the reaction mixture was stirred at room temperature for 12 h, then concentrated under reduced pressure. Column chromatography (15:1, $CHCl_3$/CH_3OH containing 1% NH_4OH) gave **10** as a pale green syrup (740.5 mg, 86%); $[\alpha]_D$ −49.3 (*c* 1.5, CH_3OH); δ_H (CD_3OD): 3.91 (m, 1H, H-4), 3.89 (m, 1H, H-3), 3.65 (s, 3H, OCH_3), 3.63 (dd, 1H, $J_{6a,5}$ 4.9 Hz, $J_{6a,6b}$ 11.2 Hz, H-6a), 3.57 (dd, 1H, $J_{5,6b}$ 3.4 Hz, H-6b), 3.01 (dd, 1H, $J_{1a,2}$ 2.9 Hz, $J_{1a,1b}$ 12.5 Hz, H-1a), 2.93–2.89 (m, 2H, H-1b, H-5), 2.88 (s, 6H, 2 × NCH_3-dansyl), 2.84 (m, 1H, H-2), 2.38 (m, 1H, H-1′), 2.23 (t, 2H, H-5′), 2.15 (m, 1H, H-1′), 1.44 (m, 2H, H-4′), 1.29 (m, 1H, H-2′), 1.10 (m, 1H, H-2′), 0.99 (m, 2H, H-3′); δ_C (CD_3OD): 174.7 (C=O), 152.0, 135.0, 130.2, 129.8, 129.5, 128.2, 123.2, 119.3, 115.3 (dansyl), 79.6 (2C, C-3, C-4), 69.0 (C-5). 68.2 (C-2), 59.4 (C-6), 51.0 (OCH_3), 46.3 (C-1′), 44.7 (2C, NCH_3dansyl), 41.3 (C-1), 33.6 (C-5′), 27.6 (C-2′), 26.9 (C-4′), 24.6 (C-3′); ESIMS *m*/*z* calcd for $C_{25}H_{37}O_7SN_3$: 523.64. Found: 522.61 (M−H). Anal. Calcd for $C_{25}H_{37}O_7SN_3$: C, 57.34; H, 7.12. Found: C, 57.19; H, 7.22.

1.5. 1-*N*-Dansyl-2-*N*-(methoxycarbonylpentyl)amino-carbonylpentyl-1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol (11)

To a solution of compound **10** (325.8 mg, 0.7 mmol) in DMF (15 mL), methyl 6-aminohexanoate hydrochloride (300 mg, 1.7 mmol), TBTU (350 mg, 1.1 mmol), and Et_3N (300 μL, 2.2 mmol) were added and the reaction mixture was stirred at rt for 24 h, then quenched by addition of CH_3OH (10 mL) and concentrated under reduced pressure. Column chromatography (15:1, $CHCl_3$/CH_3OH containing 1% NH_4OH) gave **11** as a pale green glass (290 mg, 71%); $[\alpha]_D$ −37.2 (*c* 1.7, CH_3OH); δ_H (CD_3OD): 3.91 (m, 1H, $J_{3,4}$ 2.0 Hz, H-4), 3.85 (m, 1H, H-3), 3.63 (s, 1H, OCH_3), 3.63 (dd, 1H, $J_{6a,5}$ 4.9 Hz, H-6a), 3.57 (dd, 1H, $J_{5,6b}$ 3.4 Hz, $J_{6a,6b}$ 11.2 Hz, H-6b), 3.14 (t, 2H, H-7′), 3.01 (dd, 1H, $J_{1a,2}$ 2.4 Hz, $J_{1a,1b}$ 12.2 Hz, H-1a), 2.94–2.90 (m, 2H, H-1b, H-5), 2.87 (s, 6H, 2 × NCH_3dansyl), 2.88–2.86 (m, 1H, H-2), 2.42 (m, 1H, H-1′), 2.30 (t, 2H, H-5′), 2.21 (m, 1H, H-1′), 2.10 (t, 2H, H-11′), 1.60 (m, 2H, H-4′), 1.48 (m, 4H, H-8′, H-10′), 1.32 (m, 3H, H-9′, H-2′), 1.17 (m, 1H, H-2′), 1.05 (m, 2H, m, H-3′); δ_C (CD_3OD): 174.9, 174.7 (2C, C=O), 152.1, 135.1, 130.2, 130.0, 129.8, 129.3, 128.1, 123.1, 119.3, 115.3 (dansyl), 79.6 (2C, C-3, C-4), 69.1, 68.2 (C-2, C-5), 59.4 (C-6), 50.8 (OCH_3),

46.3 (C-1′), 44.7 (2C, NCH_3dansyl), 41.3 (C-1), 39.0 (C-7′), 35.9 (C-5′), 33.5 (C-11′), 28.9 (C-8′), 27.5 (C-2′), 26.7 (C-3′), 25.3 (C-9′), 25.6 (C-4′), 24.5 (C-10′); ESIMS m/z calcd for $C_{31}H_{48}O_8SN_4$: 636.80. Found: 635.79 (M−H). Anal. Calcd for $C_{31}H_{48}O_8SN_4$: C, 58.47; H, 7.60. Found: C, 58.35; H, 7.55.

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