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Regioselective synthesis and characterization of naphthylethylcarbamoyl-β-cyclodextrins

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ABSTRACT

Regioselective reactions of 1-(1-naphthyl)ethyl isocyanate (NEIC) with β-cyclodextrin (β-CD) were studied with and without NaH activation of β-CD in *N*,*N*-dimethylformamide (DMF) and pyridine. All six possible monosubstituted CD products were separated and characterized by proton NMR. Primary substitution product predominates when the reaction was carried out under reflux condition in pyridine without NaH activation. The C-2 substitution product predominates when the reaction was carried out in DMF. Conversion of 2-*O*-(1-(1-naphthyl)ethylcarbamoyl)-β-CD to 6-*O*-(1-(1-naphthyl)ethylcarbamoyl)-β-CD was observed when NaH was used to activate hydroxyl groups of CD.

INTRODUCTION

Derivatized cyclodextrins[1] (CDs) have been extensively studied to obtain better enzyme models[2], molecular recognition models[3], and chiral selectivities in chromatography[4]. Among the derivatized CD based chiral stationary phases (CSPs), the naphthylethylcarbamoylated CD (NEC-CD) CSPs are used either in the reversed or normal phase mode because of their stability and unique chiral resolution capability in either mode[5]. The introduction of a $\pi-\pi$ donor and additional hydrogen bonding sites by the aromatic and carbamate substituents as well as residual CD hydroxyls are all thought to contribute to their uncommon enantioselectivity[6]. The average degree of substitution of naphthylethylcarbamate was found to vary from 3 to 7 although the sites of substitution were unclear.

Regioselective derivatization of the various hydroxyl groups of CDs is not an easy task. Selective derivatization of primary or secondary hydroxyl groups of CDs such as acylation, sulfonylation, or silylation have been reported[7]. A convenient method of derivatizing C-2 hydroxyl groups of CD was demonstrated using NaH to selectively deprotonate those hydroxyl groups, resulting in alkoxides which could undergo various nucleophilic substitutions[8]. The regioselectivity of this process is

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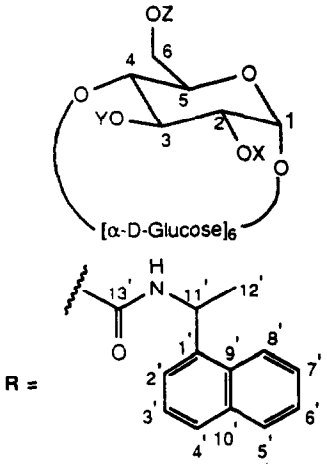

Scheme 1.

thought to arise in the deprotonation step of the most acidic hydroxyl group at C-2 and controlled by limiting the amount of NaH consumed. The relative reactivities toward methylation of the three different alkoxides produced by excess NaH were reported[9]. Recently, greater preference for the C-3 substitution over C-2 substitution was observed in the electrophilic substitution to β-CD of carbenes formed from aromatic diazo compounds upon pyrolysis[10].

Complete understanding of chiral recognition of NEC-CD CSPs requires information regarding the sites of substitution. The purpose of our study is to support on-going investigations of the chiral selectivity of NEC-CD CSPs. We now report the synthesis of monosubstituted NEC-CDs which can serve as model compounds for the study of chiral resolution mechanisms of the NEC-CD CSPs. Monocarbamoylation of the native CD was accomplished under a variety of conditions. Quite different regioselectivity was observed with each of the two solvents used in this study.

RESULTS

Identification of the regioisomers.—(*S*)-(+)- or (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (S-NEIC or R-NEIC) were reacted with β-CD and all six possible monosubstituted products as well as minor amounts of disubstituted products were isolated by HPLC. The numbering system of protons and carbon atoms of the products is given in Scheme 1 and Table I.

The proton NMR spectra of **I** to **VI** were obtained in CD_3OD. NMR results are given in the Experimental section. A large downfield shift was observed for the protons α to the site of carbamoylation, and can be attributed to the anisotropic deshielding of the carbonyl group of the carbamate linkage. This shift of adjacent proton resonances away from the main carbohydrate envelope allowed for unam-

TABLE I

The numbering system of proton and carbon atoms of I–VI

Compound				Configuration at C′-11
I	X=–R	Y=–H	Z=–H	*S*
II	X=–H	Y=–R	Z=–H	*S*
III	X=–H	Y=–H	Z=–R	*S*
IV	X=–R	Y=–H	Z=–H	*R*
V	X=–H	Y=–R	Z=–H	*R*
VI	X=–H	Y=–H	Z=–R	*R*

biguous determination of the substitution site. For instance, the resonance at δ 4.604 ppm is a doublet of a doublet with an observed splitting of 3.1 and 10.8 Hz, as a result of coupling to the anomeric and H-3 protons of **I**, respectively. Therefore, this peak is unambiguously assigned to H-2 attached to the C-2 derivatized site. The chemical shift of this proton is almost 1.10 ppm downfield compared to those of the underivatized glucose units. Through a ^1H–^1H COSY spectrum, the resonances at δ 5.009 and at δ 4.098 ppm are assigned to H-1 and H-3 of the derivatized glucose unit, respectively.

Substitution at the O-3 site causes a downfield shift of the C-3 proton of **II** which appears as a triplet at δ 5.090 ppm. The same deshielding phenomena are observed for the H-6 protons of derivatized glucose units of **III**. Multiplets at δ 4.407 and δ 4.296 ppm show the typical AB pattern of the H-6 protons. In addition, H-6b couples to H-5 at δ 3.934 ppm, which shows a small β downfield shift. Analogously, peak assignments for **IV** to **VI** could be done as in the case of their epimers, **I** to **III**, respectively.

Role of solvent.—Product distributions obtained under reflux conditions in either pyridine (Expt. 1) or DMF (Expt. 2) are listed in Table II. When pyridine was used as a solvent, substitution occurred predominantly at the primary site (ca. 85%). The combined product yield and the distribution of products was fairly independent of reaction time. However, in DMF, initial substitution occurred primarily on the C-2 site (ca. 83% at 0.5 h reaction time). In addition, the combined yield decreased and the product distribution changed with reaction time.

Role of NaH.—Product distributions after activation of the C-2 hydroxyl with stoichiometric amounts of NaH in DMF (Expt. 3) or in pyridine (Expt. 4) with subsequent S-NEIC addition are listed in Table II. After 4 or 5 h reaction, there seemed to be no significant increase in the intensity of **I** in both reactions. After stirring the mixture for 5 h, the relative percentage of **I** was 88 and 87% in Expts. 3 and 4, respectively. Further stirring of the reaction mixture at room temperature resulted in loss of **I** with concomitant increase in **III**, as shown in Fig. 1 in the DMF case. After stirring the mixture for 307 h, the relative percentage of **I** and **III** in DMF was 9.7 and 86.7%, respectively. In addition, the combined intensity of all three products was fairly constant over the reaction period.

TABLE II

Distribution of regioisomers under various reaction conditions

Experiment No.	Solvent	Reaction conditions	Site of Substitution	Relative percent
1	pyridine	4 h	O-2	11.3
		Reflux	O-6	84.9
			O-3	4.8
2	DMF	0.5 h	O-2	83
		Reflux	O-6	< 1
			O-3	16
		4 h	O-2	56.6
		Reflux	O-6	9.6
			O-3	33.8
3	DMF	5 h	O-2	88.2
		Room temperature	O-6	5.3
		with NaH	O-3	6.5
		307 h	O-2	9.7
			O-6	86.7
			O-3	3.6
4	pyridine	5 h	O-2	86.9
		Room temperature	O-6	6.5
		with NaH	O-3	6.5
		162 h	O-2	46.5
			O-6	37.0
			O-3	15.5
5	DMF	0 h	O-2	96.8
		Room temperature	O-6	< 1
		with NaOH	O-3	3.2
		1 h	O-2	52.7
			O-6	34.9
			O-3	12.4
		3 h	O-2	42.6
			O-6	46.0
			O-3	11.4
		7 h	O-2	< 1
			O-6	> 98
			O-3	< 1

Role of base.—When pure **I** was treated with NaOH in DMF, almost all of **I** converted to **III** (see Expt. 5 in Table II).

DISCUSSION

NMR.—The large downfield shifts of protons at the substitution site in the carbamoylation reaction made the identification of the point of derivatization

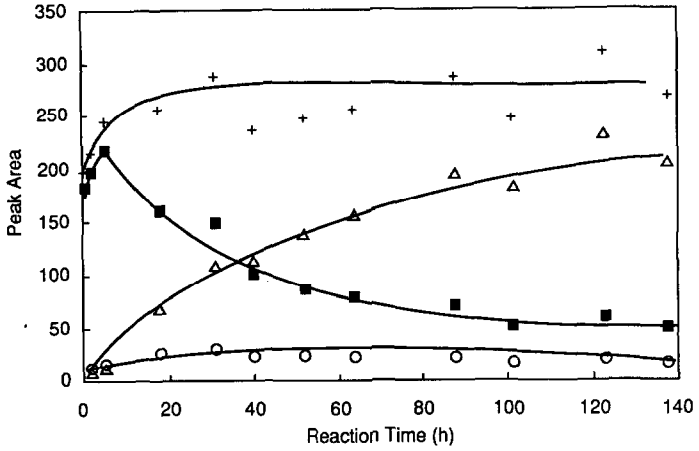

Fig. 1. Product distribution for the reaction between S-NEIC and β-CD in DMF (NaH activation, ambient temperature): ■, 2-*O*-S-NEC-β-CD (**I**); ○, 3-O-S-NEC-β-CD (**II**); △ 6-*O*-S-NEC-β-CD (**III**); and + all three monosubstituted products. Peak area pertains to HPLC integration (arbitrary unit).

possible using proton NMR spectra. In the case of primary substitution, the extent of deshielding of C-6 protons is less than those of H-2 and H-3 protons suggesting less conformational rigidity for the primary sites and the deshielding effect of carbonyl group is minimized. Of the three, H-3 shows the largest deshielding effect (ca. 1.30 ppm), which suggests that the motion of the NEC group is more restricted in this molecule. Not much difference in the extent of deshielding of the α protons was observed between the *R* and *S* epimers. However, a large difference (0.141 ppm) in the deshielding of the anomeric proton in the case of the C-2 substituted epimers (**I** and **IV**) was observed. This suggests that the configuration of the substituent affects the geometry around the anomeric proton of the derivatized glucose unit even though the magnitude of the inductive effect of the carbamoyl group upon the β protons is the same. The configurational effect of these epimers requires further NMR studies (e.g., NOE). The large downfield shift of protons in the derivatized residue from the broad envelope from the protons of the nonsubstituted glucose units of the CD should facilitate the study of the degrees and sites of substitution of multiply substituted products which may be more representative of the chiral selector of the NEC-CD CSPs and is the subject of future work.

Synthesis.—In pyridine, under reflux conditions, the regioselectivity of the isocyanate-alcohol reaction seems to be controlled by steric factors (e.g., primary more reactive than secondary alcohols) and may explain why the C-6 substitution product predominates. Similar results were reported in the synthesis of monotosylated CDs[7(e),11]. Reaction of CDs with *p*-toluenesulfonyl chloride in pyridine at room temperature resulted in the attachment of a tosyl group at the primary site. Also, in pyridine, there seems to be no significant increase in the concentration of products after 2 h reaction time.

In contrast to the pyridine case, the predominant product is the C-2 substituted

isomer in DMF. The decline in overall product concentration compared to pyridine may be attributed to thermal degradation due to the high temperature of the DMF reflux. The extent of decomposition of the C-2 substituted product, under DMF reflux, is higher than that of the primary product.

Modification of the secondary hydroxyl side of CDs is thought to be more important for chiral distinction than the primary site because the more open rigid secondary side can more easily accommodate chiral guest molecules[7(c)]. Pyridine was used as a solvent for the preparation of NEC-CD CSPs. The usual method for the preparation of NEC-CD CSPs involves refluxing NEIC and CD bonded silica sorbent in pyridine for 4 h[6]. The present results suggest that substitution might occur mostly at the primary sites under these reaction conditions, although this effect might be mitigated because of steric hinderance imposed by the linkages through which primary sites of CDs are thought to be connected to the silica[12].

Product distribution changed with reaction time when stoichiometric amounts of NaH was used to activate the hydroxyl groups of CD either in DMF or pyridine. Despite the fact that the C-2 hydroxyl group is activated and, therefore, the initial site of substitution, substitution on the primary site yields a product which is more thermodynamically stable. Whether inter- or intra-molecular rearrangement processes are resposible for conversion is subject to further study. Since NaH activation was performed at ambient temperature, the higher rate of conversion in DMF over that in pyridine is probably due to the difference in polarity of the solvents with the more polar DMF perhaps providing better solvation of intermediates thereby hastening the reaction. The probable role of the base in the conversion of secondary to primary is supported by the results obtained upon addition of NaOH to the solution of compound **I** in DMF at ambient temperature.

EXPERIMENTAL

Chemicals.—β-CD was obtained from Pfanstiehl Laboratories, Inc., (Waukegan, IL). (*R*)- or (*S*)-1-(1-naphthyl)ethyl isocyanate, anhyd pyridine, DMF, NaH, and deuterated solvents were obtained from Aldrich (Milwaukee, WI).

General methods.—To quench the reaction, 500 or 100 μL of the mixture was taken and added to 100 or 20 mL of 50:50 MeOH–water, respectively. Product distribution was monitored using a Shimadzu LC-600 liquid chromatograph system, an SPD-6A UV detector (282 nm), and a Rheodyne model 7161 injection valve with a 100-μL sample loop for the HPLC separation. Compounds **I** to **VI** were successfully separated on an Axxiom ODS 5-μm silica column (4.8 × 150 mm). The mobile phase consisted of 75:12.5:12.5 or 70:15:15 water–MeOH–MeCN, which had been degassed before use. A flow rate of 2, 1.5, or 1 mL/min at 18°C was employed. Elemental analyses were performed by Galbraith Laboratories, Inc., (Knoxville, TN).

Spectral analysis.—NMR measurements of all compounds except **II** were carried out in CD_3OD at ambient temperature (297 K) on a GE NMR spectrometer

at 500.11 MHz for ^1H NMR and 125.76 MHz for ^{13}C NMR. Because of poor solubility of **II** in MeOH, 10 drops of $(CD_3)_2SO$ was added to 0.5 mL of CD_3OD. Proton and carbon chemical shifts were determined relative to the residual MeOH peak (3.30 ppm for ^1H; 49.0 ppm for ^{13}C). Mass spectra were determined in the positive ion FAB mode.

Role of solvent.—S-NEIC (0.20 g; 1.0 mmol) was added to a solution of 1.60 g (1.4 mmol) of dried CD in 100 mL of anhyd pyridine (Expt. 1) or DMF (Expt. 2) and subsequently refluxed under N_2. An aliquot of the mixture was taken, quenched, and analyzed by HPLC.

Role of NaH.—Anhydrous DMF (95 ml) (Expt. 3) or pyridine (95 ml) (Expt. 4) was added to 2.30 g (2 mmol) of dried CD and 0.046 g (2 mmol) of NaH. The mixture was stirred for 4 h at room temperature under a vacuum. After 4 h, S-NEIC (0.40 g, 2 mmol), dissolved in 5 mL of DMF or pyridine, was added to the mixture. The mixture was stirred continuously at room temperature. Aliquots taken at specific time intervals were quenched and analyzed as mentioned previously.

Role of base (Expt. 5).—Compound **I** (100 mg) and NaOH (70 mg) were added to 100 mL of anhyd DMF and the mixture was stirred continuously at room temperature. Aliquots of the mixture were taken and analyzed by HPLC.

Synthesis of 2-O[(S)-1-(1-naphthyl)ethylcarbamoyl]-β-CD (**I**).—Anhydrous pyridine (95 mL) was added to 2.30 g (2 mmol) of CD dried in a vacuum at 110°C overnight. Residual water was removed through a Dean Stark trap and NaH (0.046 g, 2 mmol) was added to the mixture. The mixture was stirred for 4 h at room temperature under a vacuum. After 4 h stirring, S-NEIC (0.40 g, 2 mmol) dissolved in 5 mL of pyridine, was added to the mixture, and the mixture was continuously stirred at room temperature for 4 h. After stirring, the mixture was acidified by adding concd HCl. Chloroform (200 mL) and acetone (600 mL) were added to the mixture, and the resulting precipitate was obtained by filtration, and subjected to column chromatography (SiO_2, 10:1 → 2:1 $CHCl_3$–MeOH, stepwise) (0.929 g, 34% yield). ^1H NMR data: δ 8.116 (d, 1 H, $J_{8',7'}$ 8.5 Hz, H-8'), 7.862 (d, 1 H, $J_{5,'6'}$ 8.0 Hz, H-5'), 7.752 (d, 1 H, $J_{4',3'}$ 8.5 Hz, H-4'), 7.691 (d, 1 H, $J_{2',3'}$ 7.0 Hz, H-2'), 7.543 (bt, 1 H, $J_{7',6'} = J_{7',8'} = 7.5$ Hz, H-7'), 7.490–7.443 (m, 2 H, H-6',3'), 5.577 (q, 1 H, $J_{11',12'}$ 7.0 Hz, H-11'), 5.009 (bs, 1 H, H-1), 4.604 (dd, 1 H, $J_{2,1}$ 3.1, $J_{2,3}$ 10.8 Hz, H-2), 4.098 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz), 1.574 (d, 3 H, $J_{12',11'}$ 6.5 Hz, H-12'); ^{13}C NMR data: δ 157.06, 141.09, 135.39, 131.96, 129.86, 128.63, 127.24, 126.63, 126.56, 124.02, 123.41, 103.92, 103.85, 103.81, 103.62, 101.26, 83.30, 83.14, 83.10, 83.03, 82.94, 75.28, 74.78, 74.23, 74.15, 74.09, 74.03, 73.85, 73.70, 73.36, 71.85, 61.98, 61.84, 61.69, 48.34, 22.53; FABMS (*m/z*) 1332 ($M + H^+$), 1354 ($M + Na^+$), 1370 ($M + K^+$). Anal. Calcd for $C_{55}H_{81}NO_{36} \cdot 3H_2O$: C, 47.65; H, 6.33; N, 1.01 Found: C, 47.79; H, 6.64; N, 2.40.

Synthesis of 3-O-[(S)-1-(1-naphthyl)ethylcarbamoyl]-β-CD (**II**).—S-NEIC (0.20 g; 1.0 mmol) was added to a solution (1.60 g, 1.4 mmol) of dried CD in 100 mL of anhyd DMF and the mixture was refluxed under N_2. After 3 h of reaction, the

mixture was treated as described for the preparation of **I**. The resulting precipitate was extracted twice with 200 mL of MeOH. The MeOH extract was concentrated and the residue was dissolved in 70:15:15 water–MeOH–MeCN. An aliquot of this solution was subjected to C_{18} preparative column clean-up (14% carbon loading, 40 g of total packing material, prepared according to Stalcup et al.[13] and 50 mg of product was collected. ^{1}H NMR data: δ 8.221 (d, 1 H, $J_{8',7'}$ 8.5 Hz, H-8'), 7.969 (d, 1 H, $J_{5',6'}$ 7.0 Hz, H-5'), 7.854 (d, 1 H, $J_{4',3'}$ 8.5 Hz, H-4'), 7.706 (d, 1 H, $J_{2',3'}$ 6.5 Hz, H-2'), 7.637–7.529 (m, 3 H, H-7',6',3'), 5.558 (q, 1 H, $J_{11',12'}$ 6.5 Hz, H-11'), 5.090 (t, 1 H, $J_{3,2} = J_{3,4} = 9.3$ Hz, H-3), 1.591 (d, 3 H, $J_{12',11'}$ 7.0 Hz, H-12'); ^{13}C NMR data: δ 157.99, 141.48, 135.31, 131.90, 130.08, 128.57, 127.28, 126.69, 124.19, 123.72, 103.85, 103.72, 103.34, 103.02, 83.26, 82.97, 82.83, 82.78, 82.52, 79.30, 76.62, 74.77, 74.72, 74.47, 74.25, 74.19, 74.06, 73.72, 73.61, 73.57, 73.48, 61.80, 61.70, 61.63, 48.35, 22.64; FABMS (*m/z*) 1332 ($M + H^+$), 1338 ($M + Li^+$) 1354 ($M + Na^+$), 1370 ($M + K^+$). Anal. Calcd for $C_{55}H_{81}NO_{36} \cdot 5H_2O$: C, 46.45; H, 6.45; N, 0.98 Found: C, 46.15; H, 6.40; N, 0.99.

Synthesis of 6-O-[(S)-1-(1-naphthyl)ethylcarbamoyl]-β-CD (**III**).—The same conditions as Expt. 3 were used. After 20 days stirring the mixture was treated as described for the preparation of **I** to give a pure product (0.436 g, 16%). The low yield compared to the synthesis of **I** resulted from nonoptimal chromatographic conditions. ^{1}H NMR data: δ 8.162 (d, 1 H, $J_{8',7'}$ 8.5 Hz, H-8'), 7.904 (d, 1 H, $J_{5',6'}$ 8.0 Hz, H-5'), 7.799 (d, 1 H, $J_{4',3'}$ 8.0 Hz, H-4'), 7.580–7.468 (m, 4 H, H-2',7',6',3',), 5.596 (q, 1 H, $J_{11',12'}$ 7.0 Hz, H-11'), 4.407 (d, 1 H, J_{gem} 11.0 Hz, H-6a), 4.296 (dd, 1 H, J_{gem} 11.5, $J_{6b,5}$ 5.3 Hz, H-6b), 1.611 (d, 3 H, $J_{12',11'}$ 7.0 Hz, H-12'); ^{13}C NMR data: δ 157.99, 141.10, 135.41, 132.07, 129.86, 128.74, 127.16, 126.62, 126.47, 124.12, 123.27, 104.13, 103.86, 103.72, 83.53, 83.42, 82.93, 74.77, 74.22, 73.85, 73.65, 71.45, 65.04, 62.08, 61.80, 48.04, 22.29; FABMS (*m/z*) 1332 ($M + H^+$), 1354 ($M + Na^+$), 1370 ($M + K^+$). Anal. Calcd for $C_{55}H_{81}NO_{36} \cdot 2H_2O$: C, 48.28; H, 6.26; N, 1.02 Found: C, 48.59; H, 6.27; N, 1.36.

Synthesis of 2-O-[(R)-1-(1-naphthyl)ethylcarbamoyl]-β-CD (**IV**).—Anhydrous pyridine (95 mL) was added to 5.76 g (5 mmol) of CD dried in vacuum at 110°C overnight. Sodium hydride (0.122 g, 5 mmol) was added and the mixture was stirred for 4 h at room temperature under a vacuum. R-NEIC (1 g, 5 mmol) dissolved in 5 mL of pyridine, was added to the mixture and the mixture was continuously stirred at room temperature for 4 h. The mixture was then acidified by adding concd HCl. The mixture was partitioned between 400 mL of water and 400 mL of $CHCl_3$. The aqueous layer was separated and concentrated. Addition of acetone yielded a powder which was subjected to column chromatography (SiO_2, 10:1 → 2:1 $CHCl_3$–MeOH, stepwise) to obtain a pure product (1.094 g, 18% yield). ^{1}H NMR data: δ 8.120 (d, 1 H, $J_{8',7'}$ 8.3 Hz, H-8'), 7.869 (d, 1 H, $J_{5',6'}$ 8.3 Hz, H-5'), 7.768 (d, 1 H, $J_{4',3'}$ 8.3 Hz, H-4'), 7.592 (d, 1 H, $J_{2',3'}$ 7.2 Hz, H-2'), 7.524 (bt, 1 H, $J_{7',6'} = J_{7',8'} = 7.3$ Hz, H-7'), 7.486–7.434 (m, 2 H, H-6',3'), 5.561 (q, 1 H, $J_{11',12'}$ 6.7 Hz, H-11'), 5.150 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.538 (dd, 1 H, $J_{2,1}$ 3.5, $J_{2,3}$ 10.2 Hz, H-2), 4.048 (bt, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz), 1.594 (d, 3 H, $J_{12',11'}$ 7.2 Hz,

H-12′); ^{13}C NMR data: δ 157.22, 140.84, 135.40, 132.05, 129.85, 128.78, 127.21, 126.63, 126.50, 124.18, 123.38, 103.87, 103.64, 101.59, 83.49, 83.08, 83.02, 82.96, 82.88, 75.32, 74.77, 74.49, 74.34, 74.15, 73.88, 73.68, 73.47, 73.31, 71.67, 62.19, 62.14, 61.84, 61.79, 61.62, 48.19, 22.27; FABMS (*m/z*) 1354 ($M + Na^+$), 1370 ($M + K^+$). Anal. Calcd for $C_{55}H_{81}ON_{36} \cdot 4H_2O$: C, 47.04; H, 6.39; N, 1.00 Found: C, 46.83; H, 6.19; N, 1.49.

Synthesis of 3-O-[(R)-1-(1-naphthyl)ethylcarbamoyl]-β-CD (**V**).—The same procedure as described for the preparation of II was used except R-NEIC was substituted for S-NEIC. ^{1}H NMR data: δ 8.164 (d, 1 H, $J_{8',7'}$ 9.0 Hz, H-8′), 7.859 (d, 1 H, $J_{5',6'}$ 8.5 Hz, H-5′), 7.747 (d, 1 H, $J_{4',3'}$ 8.0 Hz, H-4′), 7.589 (d, 1 H, $J_{2',3'}$ 7.0 Hz, H-2′), 7.553 (t, 1 H, $J_{7',8'} = J_{7',6'} = 7.5$ Hz, H-7′) 7.470 (t, 1 H, $J_{3',2'} = J_{3',4'} = 7.5$ Hz, H-3′), 7.435 (t, 1 H, $J_{6',7'} = J_{6',5'} = 7.5$ Hz, H-6′), 5.591 (q, 1 H, $J_{11',12'}$ 6.5 Hz, H-11′), 5.085 (t, 1 H, $J_{3,2} = J_{3,4} = 9.5$ Hz, H-3), 1.597 (d, 3 H, $J_{12',11'}$ 7.0 Hz, H-12′); ^{13}C NMR data: δ 158.58, 141.41, 135.40, 132.06, 129.76, 128.57, 127.20, 126.55, 124.24, 123.30, 103.86, 103.78, 103.45, 103.33, 83.12, 83.07, 82.96, 82.88, 82.82, 82.33, 80.14, 76.97, 74.83, 74.79, 74.73, 74.45, 74.29, 74.18, 73.71, 73.49, 73.04, 62.02, 61.90, 61.83, 61.74, 48.40, 22.42; FABMS (*m/z*) 1332 ($M + H^+$), 1354 ($M + Na^+$), 1370 ($M + K^+$). Anal. Calcd for $C_{55}H_{81}NO_{36} \cdot 4H_2O$: C, 47.04; H, 6.39; N, 1.00 Found: C, 47.25; H, 6.29; N, 1.18.

Synthesis of 6-O-[(R)-1-(1-naphthyl)ethylcarbamoyl)-β-CD (**VI**).—The same procedure as described for the preparation of **V** was used. ^{1}H NMR data: δ 8.145 (d, 1 H, $J_{8',7'}$ 8.5 Hz, H-8′), 7.869 (d, 1 H, $J_{5',6'}$ 8.0 Hz, H-5′), 7.767 (d, 1 H, $J_{4',3'}$ 8.5 Hz, H-4′), 7.549–7.524 (m, 2 H, H-2′,7′), 7.480 (t, 1 H, $J_{3',2'} = J_{3',4'} = 7.5$ Hz, H-3′) 7.451 (t, 1 H, $J_{6,7} = J_{6,5} = 7.5$ Hz, H-6) 5.545 (q, 1 H, $J_{11',12'}$ 7.0 Hz, H-11′), 4.370 (d, 1 H, J_{gem} 12.0 Hz, H-6a), 4.229 (dd, 1 H, J_{gem} 11.8, $J_{6b,5}$ 5.5 Hz, H-6b), 1.570 (d, 3 H, $J_{12',11'}$ 7.0 Hz, H-12′); ^{13}C NMR data: δ 158.09, 141.03, 135.45, 132.15, 129.87, 128.77, 127.24, 126.63, 126.49, 124.25, 123.62, 104.12, 103.86, 103.73, 83.47, 83.31, 83.02, 82.88, 74.79, 74.26, 74.04, 73.95, 73.90, 73.70, 73.60, 71.37, 65.19, 62.15, 61.87, 61.83, 61.71, 48.18, 22.21; FABMS (*m/z*) 1332 ($M + H^+$), 1354 ($M + Na^+$), 1370 ($M + K^+$). Anal. Calcd for $C_{55}H_{81}NO_{36} \cdot 3H_2O$: C, 47.65; H, 6.33; N, 1.01 Found: C, 47.83; H, 6.47; N, 0.99.

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