β-Cyclodextrin as a Scaffold for Supramolecular Chemistry, To Reverse the Regioselectivity of Nitrile Oxide Cycloadditions

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β-Cyclodextrin has been used as a molecular scaffold, whereby tethering dipolarophiles to the cyclodextrin and then allowing preassociation of the modified cyclodextrins with aromatic nitrile oxides, as host−guest complexes, controls the relative orientations of the dipoles and the dipolarophiles in their cycloadditions. In this manner it has been possible to reverse the usual regioselectivity of cycloadditions of nitrile oxides, as illustrated by reactions with a terminal alkene, a terminal alkyne, and a 1,2-disubstituted alkene. For example, in aqueous solution, 4-*tert*-butylbenzonitrile oxide reacted with 6^A-deoxy-6^A-propynamido-β-cyclodextrin to give the corresponding 4- and 5-substituted isoxazoles, in a 15:1 ratio. With DMF as the solvent, to reduce the extent of host−guest complexation, the product ratio was 1:1.5. The role of complexation in these reactions is also demonstrated by contrasting these results with that of the reaction of the nitrile oxide with methyl propynoate, which afforded only the 5-substituted cycloaddition product. Molecular recognition by the cyclodextrin scaffolds was demonstrated through treatment of 4-*tert*-butylbenzonitrile oxide with an equimolar mixture of 6^A-deoxy-6^A-propynamido-β-cyclodextrin and methyl propynoate, in aqueous solution, which gave only the cycloadducts from reaction of the cyclodextrin dipolarophile.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of α-1,4-linked D-(+)-glucopyranose units. They are well-known to form host−guest or inclusion complexes with a wide variety of hydrophobic species in aqueous solutions[1,2] and have shown potential for use in areas such as drug delivery[2,3] and chromatographic separations.[4] Furthermore, they have been found to enhance the rates of organic transformations and control the distribution of products. In this context, the CD annulus serves as a reaction vessel and has been used in various processes, including the saponification of esters[5,6] and the electrophilic substitution of arenes.[7] Pericyclic processes such as Diels−Alder reactions[8] and [2 + 2] photochemical cycloadditions[9] are also facilitated by CDs, by virtue of aggregation of the starting materials within the CD annuli, but suggestions that CDs control the regiochemical outcome of nitrile oxide cycloadditions[10] have been discounted.[11] Whereas the reactions reported to date have involved the self-assembly of reagents, our interest in modified CDs is toward the controlled assembly of starting materials to manipulate the outcome of chemical reactions.[12]

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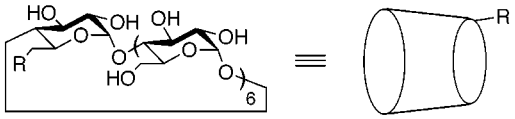
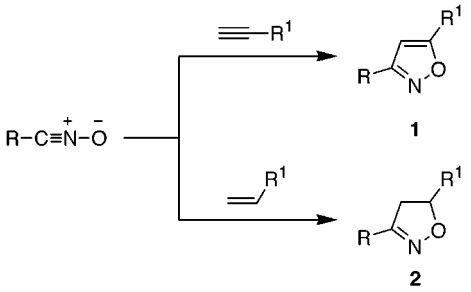


3 R = OH

Figure 1. Structure of β-CD and its representation as a truncated cone.

Scheme 1



Nitrile oxides (1,3-dipoles) undergo efficient [3 + 2] cycloadditions with alkynes and alkenes (dipolarophiles), to generate isoxazoles and 4,5-dihydroisoxazoles, respectively.[13] With unsymmetrical dipolarophiles there exists the possibility of regioisomeric mixtures of products; however, it is generally found that the regioselectivity is determined by steric effects and the more encumbered end of the dipolarophile becomes attached to the oxygen of the nitrile oxide. For example, terminal alkynes and alkenes afford almost exclusively 5-substituted isoxazoles **1** and dihydroisoxazoles **2**, respectively (Scheme 1).

We envisaged that CDs could be used as molecular scaffolds to control the assembly of reactants in nitrile oxide cycloadditions.[14] With the dipolarophile tethered to β-cyclodextrin (β-CD) (**3**) (Figure 1), the host−guest complex formed between the modified CD and an aromatic nitrile oxide was expected to predetermine the relative orientation of reaction of those species (Figure 2). With terminal dipolarophiles it was anticipated that this would result in a reversal of the usual regioselectivity, with alkynes and alkenes giving 4-substituted isoxazoles. Similarly, we aimed to control the regioselectivity of cycloadditions involving 1,2-disubstituted alkenes.

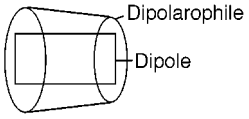
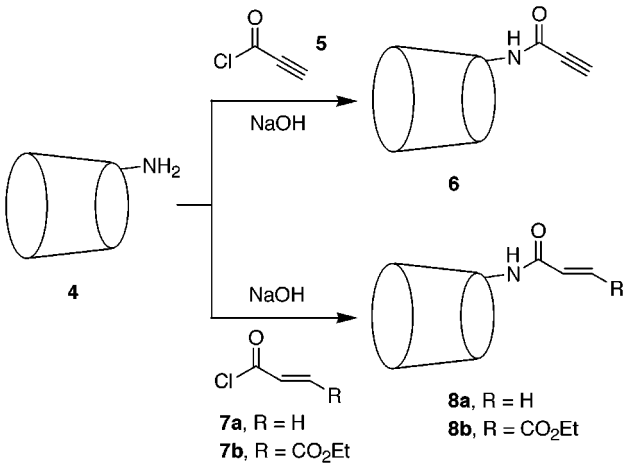


Figure 2. The relative orientation of the dipole and dipolarophile in the host−guest complex.

Scheme 2



Results

The means used to tether dipolarophiles to β-CD (**3**) are shown in Scheme 2 and involved treatment of the amino-substituted β-CD **4**[15] with the acid chlorides **5**[16] and **7a**,**b**, under basic aqueous conditions, to give the corresponding amides **6** and **8a**,**b**, in yields of 71, 79, and 77%, respectively. 4-*tert*-Butylbenzonitrile oxide (**11a**), 4-phenylbenzonitrile oxide (**11b**), and benzonitrile oxide (**11c**) were selected as the dipoles, since benzene derivatives are known to form thermodynamically stable inclusion complexes with CDs.[1] In particular, the nitrile oxide **11a** was chosen because *tert*-butylbenzene derivatives are known to form very stable CD inclusion complexes.[17] However, it is not feasible to determine the equilibrium constants for formation of the inclusion complexes of the nitrile oxides **11a**−**c** with the CDs **6** and **8a**,**b** since the contributing species react with each other in the complex. The nitrile oxides **11a**−**c** were generated for the cycloadditions in situ, through reaction of triethylamine with the hydroximinoyl chlorides **10a**−**c**, which were prepared from the appropriate aldehydes **9a**−**c** by treatment with

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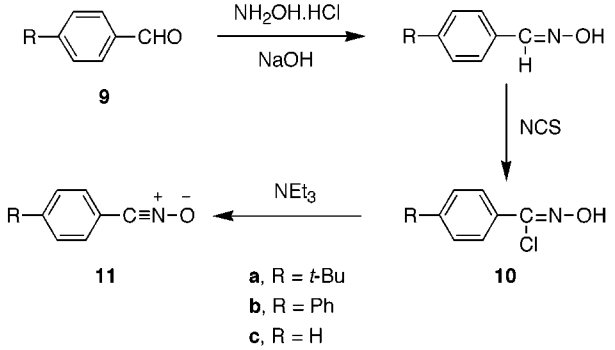
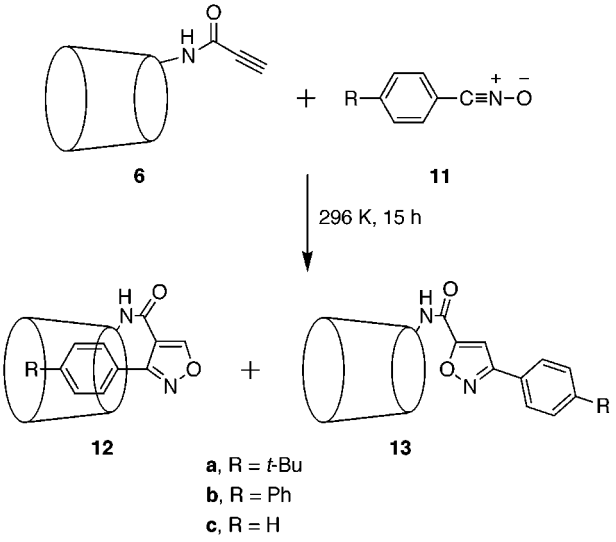
Scheme 3



Scheme 4



hydroxylamine hydrochloride and *N*-chlorosuccinimide (Scheme 3).[18] Cycloaddition reactions were conducted in aqueous solution to allow host−guest dipolarophile−dipole complexes to form. The role of the CD cavity was investigated by repeating the cycloadditions in DMF instead of water, since DMF generally reduces the thermodynamic stability of CD host−guest complexes,[19] and by comparing reactions of the CD dipolarophiles **6** and **8a**,**b** with those of methyl propynoate (**16**) and propenamide (**18**).

The results of the cycloaddition reactions of the CD derivatives **6** and **8a**,**b** (Schemes 4 and 5) are summarized in Table 1.[14] The reactions of methyl propynoate (**16**) and propenamide (**18**) with the nitrile oxide **11a**, in either water or DMF, gave the 5-substituted isoxazoles **17** and **19**, respectively (Scheme 6). Each of the cycloaddition products **12a**−**c**, **13a**−**c**, **14a**,**c**, **15a**−**c**, **17**, and **19** was isolated as an individual component and fully characterized. The isoxazoles **12a**−**c** and **13a**−**c** were most readily distinguished on the basis of their ^{1}H NMR spectra. The 4-substituted isoxazoles **12a**−**c** showed resonances for their C-5 protons at δ 9.27, 9.30, and 9.29, respectively, while the 5-substituted regioisomers **13a**−**c** exhibited resonances for their C-4 protons at δ 7.58, 7.66, and 7.61, respectively. These data are in good agreement

Scheme 5

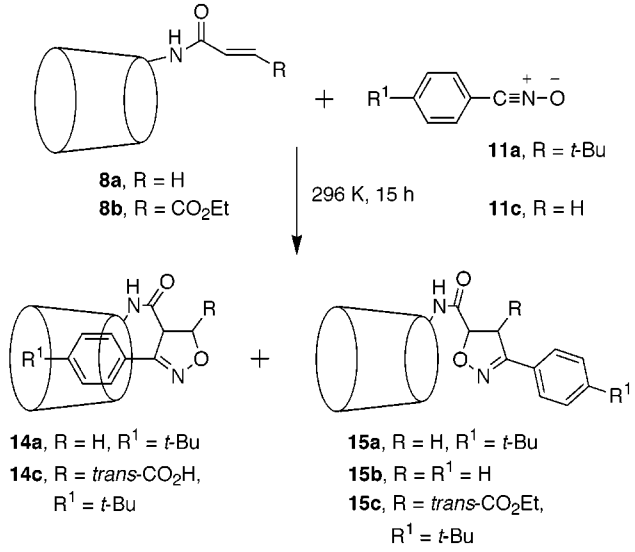
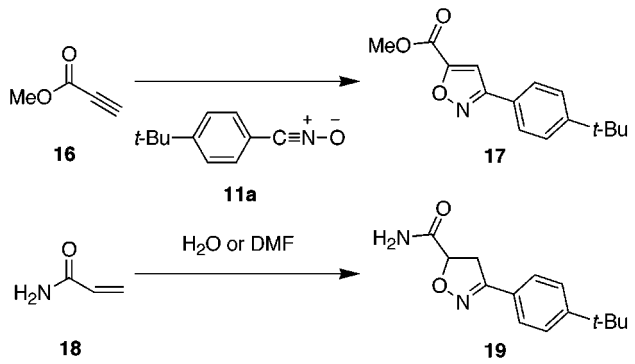


Table 1. Results of Reactions of the CDs 6 and 8a,b with the Nitrile Oxides 11a−c

dipolarophile	nitrile oxide	solvent	ratio of regioisomers[a]	yield (%)[b]
6	**11a**	H_2O	**12a**:**13a**, 15:1	71
6	**11a**	DMF	**12a**:**13a**, 1:1.5	86
6	**11b**	H_2O	**12b**:**13b**, 5:1	100
6	**11b**	DMF	**12b**:**13b**, 1:5	93
6	**11c**	H_2O	**12c**:**13c**, 1:2	100
6	**11c**	DMF	**12c**:**13c**, 1:10	87
8a	**11a**	H_2O	**14a**:**15a**, 2.3:1[c]	100
8a	**11a**	DMF	**14a**:**15a**, 1:4[c]	87
8a	**11c**	H_2O	**15b**	97
8a	**11c**	DMF	**15b**	82
8b	**11a**	H_2O	**14c**:**15c**, 3:1	100
8b	**11a**	DMF	**14c**:**15c**, 1:15	64

[a] Determined through ^{1}H NMR analysis (500 MHz, [$^2H_6$]DMSO) of the crude reaction mixtures. [b] Total isolated yield of regioisomers. [c] Reference 14.

Scheme 6



with typical literature values.[20] The phenyl proton resonances for the 4-substituted isoxazole **12a**, at δ 7.58 and 7.47, were upfield relative to those of the regioisomer **13a**, at δ 7.82 and 7.54. This relative shielding of the phenyl protons of the 4-substituted isoxazole **12a** is consistent with the inclusion of that aromatic group within the β-CD cavity, as depicted in Scheme 4.[21] The substitution pattern of the isoxazoles **14a**,**c** and **15a**−**c** was also determined on the basis of their ^{1}H NMR

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spectra. The isoxazoles **15a**−**c** showed resonances for their C-5 protons at δ 5.09, 5.10, and 5.14, respectively, while the regioisomer **14a** displayed a resonance for its C-4 proton at ca. δ 4.40. Although the latter resonance was masked by CD proton resonances in the 1D spectrum, it was readily identified using a 2D COSY experiment, through a ^{1}H−^{1}H correlation with the resonances of the C-5 protons at δ 4.66 and 4.60. The chemical shift values for the C-4 and C-5 protons of the isoxazoles **14a** and **15a**−**c**, respectively, agree with those reported for analogous compounds.[20] The acid **14c** is probably produced through hydrolysis of the corresponding ester, due to the proximity of CD hydroxyl groups.[5] The C-4 proton resonance of the isoxazole **14c** is also masked by CD proton resonances but there is no resonance in the range δ 5.3−4.9 which would be expected for the C-5 proton of the regioisomeric cycloadduct. The isoxazoles **14a**,**c** and **15a**−**c** appear to be single compounds, on the basis of their physical and spectroscopic properties, but they probably exist as diastereomers. Presumably, there is insufficient interaction between the chiral centers of the substituents and those of the CD annuli for the diastereomers to be distinguished. The 4-substituted isoxazoles **12a**−**c** and **14a** were readily soluble in water whereas the 5-substituted regioisomers **13a**−**c** and **15a** dissolved only sparingly. This difference is consistent with intramolecular complexation of the phenyl substituent within the annuli of the CDs **12a**−**c** and **14a**. The isoxazoles **17** and **19** were also identified as 5-substituted regioisomers on the basis of their ^{1}H NMR spectra.

Discussion

The results shown in Table 1 establish that β-CD (**3**) is an effective template to control the regioselectivity of nitrile oxide cycloaddition reactions, as illustrated in Figure 2. The effect is most clearly demonstrated in the reactions of the propynamido-β-CD **6** with 4-*tert*-butylbenzonitrile oxide (**11a**). In aqueous solution, the 4- and 5-substituted isoxazoles **12a** and **13a** formed in a 15:1 ratio. The predominance of the 4-substituted regioisomer **12a** can be attributed to the reaction of a preassociated complex of the dipole **11a** and the dipolarophile **6** because, when DMF was used instead of water as the solvent, to reduce the extent of host−guest complexation, the product ratio decreased to 1:1.5. It follows that the small amount of the isoxazole **13a** formed in the reaction in water most probably results from noncomplexed nitrile oxide **11a**. The effect of the host−guest complex in these reactions is also demonstrated by contrasting these results with that of the reaction of the nitrile oxide **11a** with methyl propynoate (**16**), which afforded only the 5-substituted cycloaddition product **17**.

Cycloaddition of the propynamido-β-CD **6** with 4-phenylbenzonitrile oxide (**11b**) in aqueous solution furnished a 5:1 ratio of the 4- and 5-substituted isoxazoles **12b** and **13b**. This preference for the 4-substituted regioisomer **12b** is less pronounced than that observed in the corresponding reaction of the nitrile oxide **11a**; however, it is still an obvious effect of host−guest complexation. This conclusion is supported by the observation that changing the solvent to DMF altered the product ratio by a factor of 25, in favor of the 5-substituted isoxazole **13b**. In water, the effect of the CD annulus of the propynamide **6** is even less pronounced in the reaction with benzonitrile oxide (**11c**), which afforded the 4- and 5-substituted regioisomers **12c** and **13c** in a ratio of 1:2. This indicates a lower thermodynamic stability of the complex of the nitrile oxide **11c** with the CD **6**, as would be expected.[17] Even so, preassociation of the dipole **11c** and the dipolarophile **6** must be a contributing factor in this reaction, since the corresponding reaction in DMF shows an even greater preference for production of the 5-substituted regioisomer **13c**.

The effect of the CD **6**, to reverse the usual regioselectivity of reactions of nitrile oxides with terminal alkynes, is substantially greater than that observed in our preliminary work[14] with the propenamido-β-CD **8a**, which serves as an example of a terminal alkene. Whereas the cycloaddition of the nitrile oxide **11a** and propenamide (**18**) in either water or DMF gave the 5-substituted isoxazoline **19**, reaction of the CD **8a** with the nitrile oxide **11a** gave mainly the 4-substituted isoxazole **14a** in water and mainly the 5-substituted isoxazole **15a** in DMF. Furthermore, benzonitrile oxide (**11c**) reacted with the CD **8a** to give only the 5-substituted isoxazole **15b** in both water and DMF. Again, this indicates the relatively low thermodynamic stability of CD complexes of the dipole **11c**.

The CD moiety differentiates the reactive centers of the fumaric acid derivative **8b**. In the reaction of the dipolarophile **8b** with 4-*tert*-butylbenzonitrile oxide (**11a**), in water it functions as a binding site to favor production of the isoxazole **14c**. By contrast, in the corresponding reaction in DMF, it disfavors the formation of the isoxazole **14c**, presumably through a steric effect. The regioisomer **15c** is by far the predominant product in that case. Similar steric effects would also be expected in the reactions of the propynamide **6** and the propenamide **8a**, where the bulk of the CD would disfavor formation of the 4-substituted isoxazoles **12a**−**c** and **14a**. Therefore, the extent to which these products form in the reactions of the CDs **6** and **8a** with the nitrile oxides **11a**−**c** in water is even more remarkable.

Overall, the results shown in Table 1 demonstrate the effect of the CD annulus, to control the regioselectivity of nitrile oxide cycloadditions, through host−guest complex formation as illustrated in Figure 2. It follows that molecular recognition should occur between dipoles and dipolarophiles by virtue of their ability to form host−guest complexes. Accordingly, treatment of the nitrile oxide **11a**, in aqueous solution, with equimolar amounts of the dipolarophiles **6** and **16**, afforded only the cycloadducts **12a** and **13a**, from reaction of the CD **6**.

Conclusions

Earlier studies have demonstrated the use of CDs in the self-assembly of reactants for cycloaddition reactions.[8,9] The results described above constitute controlled-assembly of reactants through the use of β-CD (**3**) as a molecular scaffold. They show it is possible to manipulate the regioselectivity of nitrile oxide cycloadditions with terminal alkynes and alkenes, and 1,2-disubstituted alkenes. This has been achieved by predetermining the orientation of reaction of the dipoles and dipolarophiles,

(21) (a) Lehmann, J.; Kleinpeter, E.; Krechl, J. *J. Inclusion Phenom.* **1991**, *10*, 233−239. (b) For a review, see: Inoue, Y. *Annu. Rep. NMR Spectrosc.* **1993**, *27*, 59−101. (b) Ndou, T. T.; Mukundan, S., Jr.; Warner, I. M. *J. Inclusion Phenom.* **1993**, *15*, 9−25. (c) Chen, Z.; Bradshaw, J. S.; Yi, G.; Pyo, D.; Black, D. R.; Zimmerman, S. S.; Lee, M. L.; Tong, W.; D'Souza, V. T. *J. Org. Chem.* **1996**, *61*, 8949−8955.

through appropriate design of their host−guest complexes, and exemplifies the utility of CDs in the construction of templates to control the geometry of organic transformations.

Experimental Section

General Methods. Proton nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 75 MHz, using [$^2H_6$]DMSO as the solvent and the internal reference. ^{13}C NMR spectra were assigned with the aid of attached proton test NMR experiments. Electrospray ionization mass spectra (ESI-MS) were measured at 120 eV unless otherwise specified. Microanalyses were performed by the Australian National University Microanalytical Service. High-performance liquid chromatography (HPLC) involved analysis with a differential refractometer operating at 254 nm. Preparative HPLC was conducted using a YMC ODS-AQ 250 × 10 mm column. Analytical HPLC was performed on an Alltima C18 250 × 4.6 mm column, eluting at 0.9 cm^3 min^{-1} with acetonitrile/water (10% v/v). The t_R of a CD derivative indicates its retention time relative to that of β-CD (**3**). Compounds were recrystallized from water. Thin-layer chromatography was performed on alumina plates coated with Merck silica gel 60 F_{254}. Flash column chromatography[22] was carried out on Merck silica gel 60 (230−440 mesh). Melting points were performed on a hot-stage apparatus and are uncorrected. Water was purified using a Waters Millipore filtration system. Petroleum ether refers to that fraction boiling between 40 and 60 °C. DMF was dried over CaH_2 and then distilled and stored over 4 Å molecular sieves prior to use. Commercially available compounds were used as received. (*E*)-3-Ethoxycarbonylpropenoyl chloride (**7b**) was prepared from fumaric acid monoethyl ester using $SOCl_2$. 6^A-Amino-6^A-deoxy-β-cyclodextrin (**4**)[15] and propynoyl chloride (**5**)[16] were prepared as reported.

General Procedure for Preparation of the CD Derivatives 6 and 8a,b. Aqueous NaOH (0.24 cm^3, 1 mol dm^{-3}, 0.24 mmol) was added to an ice-cooled solution of 6^A-amino-6^A-deoxy-β-cyclodextrin (**4**) (250 mg, 0.22 mmol) in water (10 cm^3). The relevant acid chloride **5** or **7a**,**b** (0.24 mmol) was then added, and the mixture was stirred vigorously for 2 h at 0 °C. It was then allowed to warm to ambient temperature and stirred at that temperature overnight. The mixture was then poured into acetone (75 cm^3), and the precipitate which formed was collected by centrifugation (4000 rpm, 5 min). This material was dissolved in water (5 cm^3) and the solution was passed through a column of Bio-Rex 70 ion-exchange resin (H^+ form) by eluting with water (300 cm^3). The eluant was recycled through the column a further eight times in order to remove 6^A-amino-6^A-deoxy-β-cyclodextrin (**4**). The column was then rinsed with water (300 cm^3), and the combined eluants were concentrated in vacuo, to give the amide **6** or **8a**,**b**, as a fine colorless powder.

6^A-Deoxy-6^A-propynamido-β-cyclodextrin (6): yield 184 mg (71%); HPLC t_R = 1.1; ^{1}H NMR δ 8.56 (m, 1H, NH), 5.83−5.64 (m, 14H), 4.88−4.78 (m, 7H), 4.50−4.38 (m, 6H), 3.68−3.15 (m, 43H); ^{13}C NMR δ 151.9 (C═O), 102.2−101.6 (C-1), 83.8 and 81.7−81.2 (C-4), 78.2 and 75.6 (C≡C), 73.0−72.0 and 69.5 (C-2, C-3, and C-5), 59.9−59.5 (C-6); ESI-MS (50 eV) *m*/*z* 1185 (M^+). Anal. Calcd for $C_{45}H_{71}NO_{35}$·8H_2O: C, 40.63; H, 6.59; N, 1.05. Found: C, 40.82; H, 6.29; N, 1.38.

6^A-Deoxy-6^A-propenamido-β-cyclodextrin (8a): yield 207 mg (79%); HPLC t_R = 1.2; ^{1}H NMR δ 7.95 (m, 1H, NH), 6.26 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.03 (d, *J* = 17.5 Hz, 1H), 5.83−5.64 (m, 14H), 5.55 (d, *J* = 11.0 Hz, 1H), 4.87−4.81 (m, 7H), 4.50−4.44 (m, 6H), 3.78−3.15 (m, 42H); ^{13}C NMR δ 164.8 (C═O), 131.6 (═CH_2), 125.1 (═CH), 102.2−101.5 (C-1), 83.8 and 81.7−81.1 (C-4), 73.2−71.9 and 69.6 (C-2, C-3, and C-5), 59.9−59.5 (C-6); ESI-MS *m*/*z* 1187 (M^+). Anal. Calcd for $C_{45}H_{73}NO_{35}$·6H_2O: C, 41.70; H, 6.61; N, 1.08. Found: C, 41.59; H, 6.30; N, 1.19.

(*E*)-6^A-Deoxy-6^A-(3-ethoxycarbonylpropenamido)-β-cyclodextrin (8b): yield 214 mg (77%); ^{1}H NMR δ 8.43 (br s, 1H, NH), 7.09 (d, *J* = 15.0 Hz, 1H), 6.53 (d, *J* = 15.0 Hz, 1H), 5.81−5.68 (m, 14H), 4.87−4.81 (m, 7H), 4.54−4.44 (m, 6H), 4.17 (q, *J* = 5.5 Hz, 2H, OCH_2CH_3), 3.72−3.28 (m, 42H), 1.23 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 165.2 and 163.1 (C═O), 137.5 (═CH), 128.4 (═CH), 102.2−101.7 (C-1), 83.4 and 81.6−81.4 (C-4), 73.0−72.0 and 69.3 (C-2, C-3, and C-5), 60.7 (OCH_2CH_3), 59.9−59.6 (C-6), 14.1 (OCH_2CH_3); ESI-MS *m*/*z* 1259 (M^+). Anal. Calcd for $C_{48}H_{77}NO_{37}$·5H_2O: C, 42.70; H, 6.49; N, 1.04. Found: C, 42.73; H, 6.76; N, 0.74.

General Procedure for Reactions of the CD Derivatives 6 and 8a,b with the Nitrile Oxides 11a−c in Aqueous Solution. To a rapidly stirred solution of the CD derivative **6** or **8a**,**b** (0.04 mmol) in water (3 cm^3) was added the appropriate hydroximinoyl chloride **10a**,**b**, or **c** (0.16 mmol), and the mixture was allowed to stir at ambient temperature for 1 h. NEt_3 (0.17 mmol) was then added, and the mixture was stirred for a further 15 h. It was then diluted with aqueous EtOH (20% v/v, 10 cm^3) and washed with EtOAc (3 × 15 cm^3). The solvent was removed in vacuo to give a fine colorless powder.

General Procedure for Reactions of the CD Derivatives 6 and 8a,b with the Nitrile Oxides 11a−c in DMF. To a solution of the CD derivative **6** or **8a**,**b** (0.04 mmol) in DMF (1.5 cm^3) was added the appropriate hydroximinoyl chloride **10a**,**b**, or **c** (0.045 mmol) and NEt_3 (0.045 mmol), and the solution was allowed to stir at ambient temperature for 15 h. It was then poured into acetone (50 cm^3), and the precipitate which formed was collected by centrifugation (4000 rpm, 5 min) and isolated as a fine colorless powder.

***N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-4-(aminocarbonyl)-3-(4-*tert*-butylphenyl)isoxazole (12a).** The title compound was prepared as a 15:1 mixture with the regioisomer **13a**, in 71% yield, as described above from reaction of the CD **6** with the nitrile oxide **11a** in aqueous solution. It was isolated by HPLC (acetonitrile/water, 10% v/v) and had the following: HPLC t_R = 2.7; ^{1}H NMR δ 9.27 [s, 1H, isoxazole C(5)−H], 7.98 (m, 1H, NH), 7.58 (d, 2H, *J* = 8.0 Hz, PhH), 7.47 (d, 2H, *J* = 8.0 Hz, PhH), 5.86−5.66 (m, 14H), 4.90−4.80 (m, 7H), 4.57−4.13 (m, 6H), 3.68−3.26 (m, 42H), 1.32 (s, 9H, *t*-Bu); ^{13}C NMR δ 160.7 (quaternary), 160.6 (isoxazole C-5), 159.4 and 152.7 (quaternary), 128.1 and 125.3 (methine, Ph), 124.8 (quaternary, Ph), 116.1 (isoxazole C-4), 102.2−101.8 (CD C-1), 83.7 and 81.7−81.3 (CD C-4), 73.1−72.0 and 70.2 (CD C-2, C-3, and C-5), 60.0−59.8 (CD C-6), 34.6 (quaternary, *t*-Bu), 31.1 (methyl, *t*-Bu); ESI-MS (50 eV) *m*/*z* 1360 (M^+). Anal. Calcd for $C_{56}H_{84}N_2O_{36}$·8H_2O: C, 44.68; H, 6.70; N, 1.86. Found: C, 44.40; H, 6.98; N, 1.81.

***N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-4-(aminocarbonyl)-3-(4-biphenyl)isoxazole (12b).** The title compound was prepared as a 5:1 mixture with the regioisomer **13b**, in 100% yield, as described above from reaction of the CD **6** with the nitrile oxide **11b** in aqueous solution. It was isolated by HPLC (acetonitrile/water, 12% v/v) and had the following: HPLC t_R = 2.8; ^{1}H NMR δ 9.30 [s, 1H, isoxazole C(5)], 8.42 (m, 1H, NH), 7.83 (d, *J* = 8.5 Hz, 2H, PhH), 7.76 (d, *J* = 8.5 Hz, 2H, PhH), 7.72 (d, *J* = 7.0 Hz, 2H, PhH), 7.49 (t, *J* = 7.5 Hz, 2H, PhH), 7.40 (m, 1H, PhH), 5.89−5.69 (m, 14H), 4.92−4.80 (m, 7H), 4.63−4.45 (m, 6H), 3.75−3.29 (m, 42H); ^{13}C NMR δ 161.0 (isoxazole C-5), 160.9, 159.4, 141.8 and 139.4 (quaternary), 129.2, 129.1, 128.0 and 126.9 (methine, Ph), 126.9 (quaternary, Ph), 115.9 (isoxazole C-4), 102.5−101.8 (CD C-1), 83.6 and 81.9−81.4 (CD C-4), 73.1−72.1 and 69.8 (CD C-2, C-3, and C-5), 60.2−59.8 (CD C-6); ESI-MS *m*/*z* 1403 ($M + Na^+$). Anal. Calcd for $C_{58}H_{80}N_2O_{36}$·4H_2O: C, 47.93; H, 6.10; N, 1.93. Found: C, 47.83; H, 5.99; N, 1.93.

***N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-4-(aminocarbonyl)-3-phenylisoxazole (12c).** The title compound was prepared as a 1:2 mixture with the regioisomer **13c**, in 100% yield, as described above from reaction of the CD **6** with the nitrile oxide **11c** in aqueous solution. It was isolated by HPLC (acetonitrile/water, 10% v/v) and had the following: HPLC t_R = 5.1; ^{1}H

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NMR δ 9.29 [s, 1H, isoxazole C(5)−H], 8.41 (m, 1H, NH), 7.70 (m, 2H, PhH), 7.46 (m, 3H, PhH), 5.85−5.69 (m, 14H), 4.89−4.80 (m, 7H), 4.56−4.44 (m, 6H), 3.81−3.29 (m, 42H); ^{13}C NMR δ 160.9 (isoxazole C-5), 160.7 and 159.8 (quaternary), 130.0, 128.6 and 128.5 (methine, Ph), 127.8 (quaternary, Ph), 115.7 (isoxazole C-4), 102.4−101.8 (CD C-1), 83.8 and 81.8−81.3 (CD C-4), 73.0−72.0 and 69.8 (CD C-2, C-3, and C-5) 60.1−59.7 (CD C-6); ESI-MS *m*/*z* 1327 (M + Na^+). Anal. Calcd for $C_{52}H_{76}N_2O_{36}\cdot 3H_2O$: C, 45.95; H, 6.08; N, 2.06. Found: C, 46.19; H, 5.85; N, 2.12.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-5-(aminocarbonyl)-3-(4-*tert*-butylphenyl)isoxazole (13a).** The title compound was prepared as a 1.5:1 mixture with the regioisomer **12a**, in 86% yield, as described above from reaction of the CD **6** with the nitrile oxide **11a** in DMF. It was isolated by recrystallization and had the following: HPLC t_R = 1.1; ^{1}H NMR δ 8.76 (m, 1H, NH), 7.82 (d, 2H, *J* = 8.5 Hz, PhH), 7.58 [s, 1H, isoxazole C(4)−H], 7.54 (d, 2H, *J* = 8.5 Hz, PhH), 5.88−5.70 (m, 14H), 4.95−4.77 (m, 7H), 4.53−4.35 (m, 6H), 3.84−3.26 (m, 42H), 1.31 (s, 9H, *t*-Bu); ^{13}C NMR δ 164.0, 162.2, 155.9 and 153.3 (quaternary), 126.5 and 126.0 (methine, Ph), 125.1 (quaternary, Ph), 104.4 (isoxazole C-4), 102.4−101.6 (CD C-1), 84.3 and 81.5−81.3 (CD C-4), 73.1−72.0 and 69.7 (CD C-2, C-3, and C-5), 60.0−59.3 (CD C-6), 34.7 (quaternary, *t*-Bu), 31.1 (methyl, *t*-Bu); ESI-MS (50 eV) *m*/*z* 1383 (M + Na^+). Anal. Calcd for $C_{56}H_{84}N_2O_{36}\cdot 9H_2O$: C, 44.15; H, 6.74; N, 1.83. Found: C, 44.00; H, 6.63; N, 1.59.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-5-(aminocarbonyl)-3-(4-biphenyl)isoxazole (13b).** The title compound was prepared as a 5:1 mixture with the regioisomer **12b**, in 93% yield, as described above from reaction of the CD **6** with the nitrile oxide **11b** in DMF. It was isolated by recrystallization and had the following: HPLC t_R = 1.3; ^{1}H NMR δ 8.81 (br s, 1H, NH), 8.00 (d, *J* = 4.2 Hz, 2H, PhH), 7.85 (d, *J* = 7.5 Hz, 2H, PhH), 7.75 (d, *J* = 7.5 Hz, 2H, PhH), 7.66 [s, 1H, isoxazole C(4)−H], 7.50 (m, 2H, PhH), 7.41 (m, 1H, PhH), 5.86−5.64 (m, 14H), 4.96−4.77 (m, 7H), 4.54−4.36 (m, 6H), 3.90−3.28 (m, 42H); ^{13}C NMR δ 164.2, 162.1, 155.7, 142.1 and 139.2 (quaternary), 129.1, 127.5, 127.4 and 126.8 (methine, Ph), 128.1 (quaternary, Ph), 104.4 (isoxazole C-4), 102.4−101.4 (CD C-1), 84.3 and 81.7−81.1 (CD C-4), 73.3−71.9 and 69.5 (CD C-2, C-3, and C-5), 60.1−59.7 (CD C-6); ESI-MS (50 eV) *m*/*z* 1403 (M + Na^+). Anal. Calcd for $C_{58}H_{80}N_2O_{36}\cdot 3H_2O$: C, 48.54; H, 6.04; N, 1.95. Found: C, 48.60; H, 5.82; N, 2.03.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-5-(aminocarbonyl)-3-phenylisoxazole (13c).** The title compound was prepared as a 10:1 mixture with the regioisomer **12c**, in 87% yield, as described above from reaction of the CD **6** with the nitrile oxide **11c** in DMF. It was isolated by recrystallization and had the following: HPLC t_R = 3.1; ^{1}H NMR δ 8.78 (m, 1H, NH), 7.91 (m, 2H, PhH), 7.61 [s, 1H, isoxazole C(4)−H], 7.53 (m, 3H, PhH), 5.87−5.67 (m, 14H), 4.95−4.77 (m, 7H), 4.53−4.35 (m, 6H), 3.90−3.19 (m, 42H); ^{13}C NMR δ 164.3, 162.5 and 155.9 (quaternary), 130.8, 129.5 and 126.9 (methine, Ph), 128.0 (quaternary, Ph), 104.5 (isoxazole C-4), 102.4−101.5 (CD C-1), 84.3 and 81.7−81.2 (CD C-4), 73.3−72.0 and 69.6 (CD C-2, C-3, and C-5), 60.1−59.4 (CD C-6); ESI-MS *m*/*z* 1328 (M + Na^+). Anal. Calcd for $C_{52}H_{76}N_2O_{36}\cdot 6H_2O$: C, 44.19; H, 6.28; N, 1.98. Found: C, 44.09; H, 6.05; N, 1.91.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-4-(aminocarbonyl)-3-(4-*tert*-butylphenyl)-4,5-dihydroisoxazole (14a).** The title compound was prepared as a 2.3:1 mixture with the regioisomer **15a**, in 100% yield, as described above from reaction of the CD **8a** with the nitrile oxide **11a** in aqueous solution. It was isolated by HPLC (acetonitrile/water, 10% v/v) and had the following: HPLC t_R = 1.6; ^{1}H NMR δ 7.96 (br s, 1H, NH), 7.46 (d, 2H, *J* = 8.0 Hz, PhH), 7.37 (d, 2H, *J* = 8.0 Hz, PhH), 5.86−5.63 (m, 14H), 4.84−4.75 (m, 7H), 4.66 [m, 1H, isoxazole C(5)−H], 4.60 [m, 1H, isoxazole C(5)−H′], 4.53−4.47 (m, 2H), 4.43−4.35 (m, 5H), 3.72−3.20 (m, 42H), 1.29 (s, 9H, *t*-Bu); ^{13}C NMR δ 169.1, 155.6 and 152.6 (quaternary), 126.6 and 125.2 (methine, Ph), 125.7 (quaternary, Ph), 102.2−101.6 (CD C-1), 83.4 and 81.6 (CD C-4), 73.1−71.8 and 70.3 (CD C-2, C-3, and C-5), 60.4 (isoxazole C-5), 59.9−59.5 (CD C-6), 54.8 (isoxazole C-4), 34.6 (quaternary, *t*-Bu), 31.2 (methyl, *t*-Bu); ESI-MS *m*/*z* 1385 (M + Na^+). Anal. Calcd for $C_{56}H_{86}N_2O_{36}\cdot 7H_2O$: C, 45.16; H, 6.77; N, 1.88. Found: C, 45.38; H, 6.68; N, 1.49.

***trans*-*N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-4-(aminocarbonyl)-3-(4-*tert*-butylphenyl)-4,5-dihydroisoxazole-5-carboxylic acid (14c).** The title compound was prepared as a 3:1 mixture with the regioisomer **15c**, in 100% yield, as described above from reaction of the CD **8b** with the nitrile oxide **11a** in aqueous solution. It was isolated by HPLC (acetonitrile/water, 10% v/v) and had the following: HPLC t_R = 1.0; ^{1}H NMR δ 8.27 (br s, 1H, NH), 7.47 (d, 2H, *J* = 8.0 Hz, PhH), 7.37 (d, 2H, *J* = 8.0 Hz, PhH), 5.88−5.64 (m, 15H), 4.92−4.53 (m, 15H), 3.69−3.12 (m, 42 H) 1.27 (s, 9H, *t*-Bu); ^{13}C NMR δ 170.9 and 168.2 (C═O), 155.1 and 153.1 (quaternary), 126.8 and 125.4 (methine, Ph), 125.1 (quaternary, Ph), 102.5−101.6 (CD C-1), 83.1 and 81.8−81.3 (CD C-4), 82.7 (isoxazole C-5), 73.3−71.9 and 70.2 (CD C-2, C-3, and C-5), 60.4−59.7 (CD C-6), 58.3 (isoxazole C-4), 34.7 (quaternary, *t*-Bu), 31.2 (methyl, *t*-Bu); ESI-MS (90 eV) *m*/*z* 1406 (M^+). Anal. Calcd for $C_{57}H_{86}N_2O_{38}\cdot 8H_2O$: C, 44.13; H, 6.63; N, 1.81. Found: C, 44.14; H, 6.77; N, 1.75.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-5-(aminocarbonyl)-3-(4-*tert*-butylphenyl)-4,5-dihydroisoxazole (15a).** The title compound was prepared as a 4:1 mixture with the regioisomer **14a**, in 87% yield, as described above from reaction of the CD **8a** with the nitrile oxide **11a** in DMF. It was isolated by recrystallization and had the following: HPLC t_R = 1.3; ^{1}H NMR δ 7.93 (m, 1H, NH), 7.61 (d, 2H, *J* = 8.5 Hz, PhH), 7.47 (d, 2H, *J* = 8.5 Hz, PhH), 5.84−5.68 (m, 14H), 5.09 [m, 1H, isoxazole C(5)−H], 4.89−4.81 (m, 7H), 4.74−4.34 (m, 6H), 3.86−3.14 (m, 44 H) 1.29 (s, 9H, *t*-Bu); ^{13}C NMR δ 169.7, 156.4 and 153.2 (quaternary), 126.7 and 125.7 (methine, Ph), 125.9 (quaternary, Ph), 102.3−101.8 (CD C-1), 83.8 and 81.6−81.4 (CD C-4), 78.9 (isoxazole C-5), 73.0−72.0 and 69.8 (CD C-2, C-3, and C-5), 59.8−60.3 (CD C-6), 34.7 (quaternary, *t*-Bu), 31.0 (methyl *t*-Bu); ESI-MS *m*/*z* 1385 (M + Na^+). Anal. Calcd for $C_{56}H_{86}N_2O_{36}\cdot 7H_2O$: C, 45.16; H, 6.77; N, 1.88. Found: C, 44.93; H, 6.47; N, 1.68.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-5-(aminocarbonyl)-3-phenyl-4,5-dihydroisoxazole (15b).** Reaction of the CD **8a** with the nitrile oxide **11c** in either aqueous solution or DMF, as described above, gave the title compound **15b** as the only detectable cycloadduct. It was isolated by recrystallization and had the following: ^{1}H NMR δ 7.95 (m, 1H, NH), 7.68 (m, 2H, PhH), 7.44 (m, 3H, PhH), 5.84−5.67 (m, 14H), 5.10 [m, 1H, isoxazole C(5)−H], 4.89−4.80 (m, 7H), 4.52−4.36 (m, 6H), 3.82−3.10 (m, 44 H); ^{13}C NMR δ 169.6 and 156.6 (quaternary), 130.4, 128.9 and 126.8 (methine, Ph), 128.7 (quaternary, Ph), 102.3−101.7 (CD C-1), 83.9 and 81.6−81.4 (CD C-4), 79.0 (isoxazole C-5), 73.0−72.0 and 69.7 (CD C-2, C-3, and C-5), 60.2−59.6 (CD C-6); ESI-MS *m*/*z* 1306 (M^+). Anal. Calcd for $C_{52}H_{78}N_2O_{36}\cdot 7H_2O$: C, 43.57; H, 6.47; N, 1.95. Found: C, 43.84; H, 6.55; N, 2.02.

***N*-(6^A-Deoxy-*β*-cyclodextrin-6^A-yl)-5-(aminocarbonyl)-3-(4-*tert*-butylphenyl)-4-(ethoxycarbonyl)-4,5-dihydroisoxazole (15c).** The title compound was prepared as a 15:1 mixture with the regioisomer **14c**, in 64% yield, as described above from reaction of the CD **8b** with the nitrile oxide **11a** in DMF. It was isolated by HPLC (acetonitrile/water, 10% v/v) and had the following: HPLC t_R = 5.7; ^{1}H NMR δ 8.25 (br s, 1H, NH), 7.49 (d, 2H, *J* = 8.5 Hz, PhH), 7.40 (d, 2H, *J* = 8.5 Hz, PhH), 5.92−5.64 (m, 14H), 5.14 [d, 1H, *J* = 6.5 Hz, isoxazole C(5)−H], 4.92−4.77 (m, 8H), 4.55−4.48 (m, 3H), 4.41−4.36 (m, 3H), 4.19 (m, 2H, OCH_2CH$_3$), 3.70−3.12 (m, 42 H) 1.29 (s, 9H, *t*-Bu), 1.25 (t, 3H, *J* = 7.5 Hz, OCH$_2$CH_3); ^{13}C NMR δ 169.2 and 168.0 (C═O), 155.1 and 153.4 (quaternary), 126.8 and 125.6 (methine, Ph), 124.8 (quaternary, Ph), 102.4−101.7 (CD C-1), 82.9 and 81.4−81.2 (CD C-4), 82.1 (isoxazole C-5), 73.0−71.9 and 69.8 (CD C-2, C-3, and C-5), 61.7 (OCH_2-CH$_3$), 60.4−59.7 (CD C-6), 58.2 (isoxazole C-4), 34.7 (quaternary, *t*-Bu), 31.1 (methyl, *t*-Bu), 14.1 (OCH$_2$$CH_3$); ESI-MS *m*/*z* 1435 ($M^+$). Anal. Calcd for $C_{59}H_{90}N_2O_{38}\cdot 6H_2O$: C, 45.91; H, 6.66; N, 1.82. Found: C, 45.81; H, 6.28; N, 2.11.

3-(4-*tert*-Butylphenyl)-5-(methoxycarbonyl)isoxazole (17). To a stirred solution of methyl propynoate (**16**) (25 mg,

0.30 mmol) in water (2.5 cm^3) was added 4-*tert*-butylbenzonitrile oxide (**11a**) (69.2 mg, 0.33 mmol) and NEt_3 (45.6 μL, 0.33 mmol). The mixture was allowed to stir at ambient temperature for 15 h, after which water (5 cm^3) was added. The resultant solution was extracted with CH_2Cl_2 (2 × 10 cm^3), and the organic extracts were concentrated in vacuo. Flash chromatography of the residue (ethyl acetate/petroleum ether, 3:7) yielded the title compound **17** (R_f = 0.93) as a colorless solid (69 mg, 90%). The analogous reaction in DMF afforded the title compound **17** in 94% yield: mp = 64−65 °C; ^{1}H NMR δ 7.89 [s, 1H, isoxazole C(4)−H], 7.88 (d, 2H, J = 8.0 Hz, PhH), 7.53 (d, 2H, J = 8.0 Hz, PhH), 3.92 (s, 3H, OCH_3), 1.29 (s, 9H, *t*-Bu); ^{13}C NMR δ 162.9, 160.3, 157.0 and 153.8 (quaternary), 126.8 and 126.2 (methine, Ph), 124.9 (quaternary, Ph), 108.2 (isoxazole C-4), 53.1 (OCH_3), 34.8 (quaternary, *t*-Bu), 31.1 (methyl, *t*-Bu); ESI-MS *m*/*z* 260 ($M + H^+$). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.38; H, 6.65; N, 5.06.

5-(Aminocarbonyl)-3-(4-*tert*-butylphenyl)-4,5-dihydroisoxazole (19). To a stirred solution of propenamide (**18**) (10 mg, 0.14 mmol) in water (1.0 cm^3) were added 4-*tert*-butylbenzonitrile oxide (**11a**) (32.8 mg, 0.15 mmol) and NEt_3 (21.6 μL, 0.15 mmol). The mixture was allowed to stir at ambient temperature for 15 h, after which water (5 cm^3) was added. The resultant solution was extracted with CH_2Cl_2 (2 × 10 cm^3), and the organic extracts were concentrated in vacuo. Flash chromatography of the residue (ethyl acetate/petroleum ether, 1:1) yielded the title compound **19** (R_f = 0.21) as a colorless solid (6 mg, 17%). The analogous reaction in DMF afforded the title compound **19** in 93% yield: mp = 200−201 °C; ^{1}H NMR δ 7.62 and 7.42 (2s, 2H, NH_2), 7.60 (d, 2H, J = 8.5 Hz, PhH), 7.45 (d, 2H, J = 8.5 Hz, PhH), 5.02 [dd, 1H, J = 7.0 and 12.0 Hz, isoxazole C(5)−H], 3.63 [dd, 1H, J = 17.0 and 7.0 Hz, isoxazole C(4)−H], 3.51 [dd, 1H, J = 17.0 and 12.0 Hz, isoxazole C(4)−H′], 1.26 (s, 9H, *t*-Bu); ^{13}C NMR δ 172.3 (C═O), 156.2 and 153.2 (quaternary), 126.7 and 125.7 (methine, Ph), 126.0 (quaternary, Ph), 78.8 (isoxazole C-5), 38.6 (isoxazole C-4), 34.7 (quaternary, *t*-Bu), 31.0 (methyl, *t*-Bu); ESI-MS (40 eV) *m*/*z* 246 ($M + H^+$). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.08; H, 7.35; N, 11.16.

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