Toward the Supramolecular Cyclodextrin Dimers Using Nucleobase Pairs

Vanessa Legros,[a] Florian Hamon,[a] Bruno Violeau,[a] Frédéric Turpin,[b] Florence Djedaini-Pilard,[c] Jérôme Désiré,[a] Christophe Len*[d]

[a] Université de Poitiers, UMR 6514 CNRS, Synthèse et Réactivité des Substances Naturelles, 40 avenue du Recteur Pineau, 86022 Poitiers cedex, France

[b] Biocydex, 40 avenue du Recteur Pineau, 86022 Poitiers cedex, France

[c] Université de Picardie Jules Verne, UMR 6219 CNRS, Laboratoire des Glucides, 33 rue Saint Leu, 80039 Amiens, France

[d] Université de Technologie de Compiègne, Ecole Supérieure de Chimie Organique et Minérale, EA 4297 UTC/ESCOM, 1 allée du Réseau Jean-Marie Buckmaster, 60200 Compiègne, France
Fax +33(3)44971591; E-mail: christophe.len@utc.fr

Received 1 September 2010; revised 20 October 2010

Abstract: The synthesis of eleven new cyclodextrin derivatives having nucleobase moiety – thymin-1-yl, adenin-9-yl, and guanin-9-yl – is described. These two moieties are linked by different spacers, such as aminoethyl and 1,2,3-triazolyl group. Direct nucleophilic substitution and 1,3-dipolar cycloaddition were performed in good yields (13–73%) for some of the synthesized compounds.

Key words: click chemistry, nucleobase, cyclodextrin

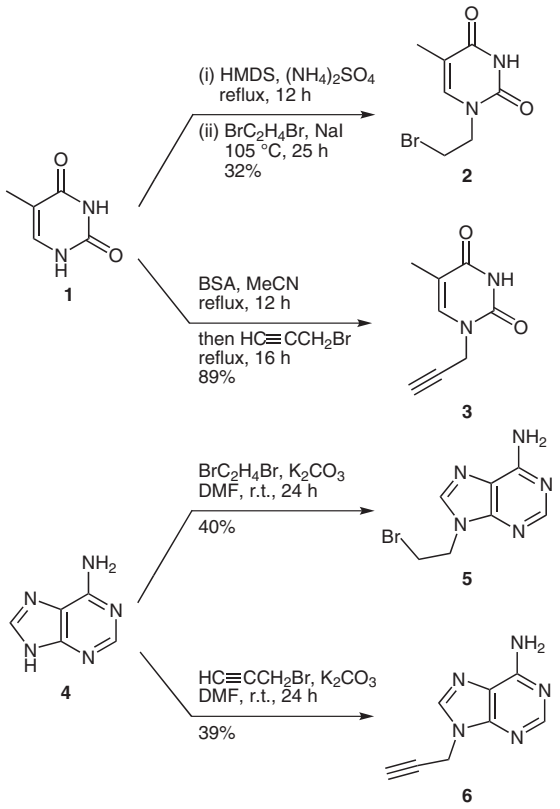
Cyclodextrins (CDs) are versatile macrocyclic maltooligosaccharides composed of α-(1→4)-linked D-glucopyranose units in $^4C_1$ chair conformation and are produced from starch by enzymatic conversion in nature. The most common CDs have six, seven, and eight D-glucopyranose units and are referred to as α-, β-, and γ-CD, respectively. In the case of β-CD, the polyhydroxylated compound has got a primary face of 7 hydroxy groups and a secondary face of 14 hydroxy groups. As a consequence of the structure, the molecule is hydrophilic and features a conical cavity that is essentially hydrophobic in nature. It is well known that CDs can form inclusion complexes with a variety of guest molecules due to its unique hydrophobic cup-like structure. Among these properties, the ability to form drug carrier,[1–3] separation reagents,[4–6] enzyme mimics,[7,8] photochemical sensors,[9,10] catalysis,[11,12] host–guest interactions,[13] and molecular recognition[14] are probably the most commercially valuable. Compared to CD monomers, the bridged bis(β-CD) derivatives with functional linkers have two hydrophobic cavities in a close proximity constituting an improved development.[15] This property may afford distinctly different association abilities and molecular selectivities.[16] Various structural architectures of covalent CD dimers could be prepared, but one challenge will be to obtain supramolecular CD dimers with noncovalent interactions such as H bonding, staking, electrostatic, and charge-transfer interactions. The equilibrium between the noncovalent dimers and the corresponding monomers could permit modulation of association. To the best of our knowledge, these molecular organization behaviors have not been extensively investigated.[17] The supramolecular assembly could be obtained by association of nucleobases such as adenine and thymine or guanine and cytosine. Few examples of CD derivatives having nucleobase were described in the literature, but only the study of CD monomers were reported.[18–23] As previously reported by Len's group,[18] the apparent association constant between two nucleobases appended permethylated cyclodextrin derivatives was determined by NMR in $CDCl_3$. The self-assembly property of CD derivatives **13b** and **14b** was $K_{TT} = 22\ M^{-1}$ and $K_{AA} = 16\ M^{-1}$ respectively. The association constant for heterodimerization of **13b** and **14b** in a 1:1 stoichiometry was $K_{AT} = 385\ M^{-1}$ supporting the formation of supramolecular heterodimer of modified cyclodextrins. The presence of bulky CDs did not perturb the interactions between nucleobases. In this paper, we report our contribution regarding the synthesis of different CD monomers having a nucleobase such as adenine, thymine, and guanine. Such compounds are obtained by nucleophilic substitution and by click chemistry coupling. In order to access dimers having different physical properties, three major structural variations have been studied: (i) glycone moiety such as monoamino-β-CD, monoazido-β-CD, monoamino permethylated or monoazido permethylated β-CD derivatives; (ii) nature of the linker such as aminoethyl group or 1,2,3-triazol-4-yl methyl group; and (iii) modulation of the nucleobase such as adenine, thymine, or guanine.

Synthesis of 2-Bromoethyl and Alkynyl Precursors for β-CD

Alkylation of pyrimidine bases gave predominantly N1-monosubstituted, N1,N3-bis-substituted and O4-monosubstituted derivatives. Regioselective N1-alkylation using silylation of the nucleobase strategy was developed to furnish the bromoethyl and propargyl derivatives. Coupling of dibromoethane with silylated thymine in the presence of NaI at 105 °C without solvent furnished the bromide **2**[24–27] in 32% yield. Coupling of propargyl bromide with silylated thymine at 80 °C in acetonitrile gave the alkyne **3**[28,29] in 89% yield. Alkylation of purine furnished often a ratio of N7/N9 isomers. The N9-alkylated adenine derivatives **5**[27] and **6**[28,29] were obtained from unprotected adenine (**4**). Starting from **4**, selective alkylation

SYNTHESIS 2011, No. 2, pp 0235–0242
Advanced online publication: 10.12.2010
DOI: 10.1055/s-0030-1258354; Art ID: P13610SS

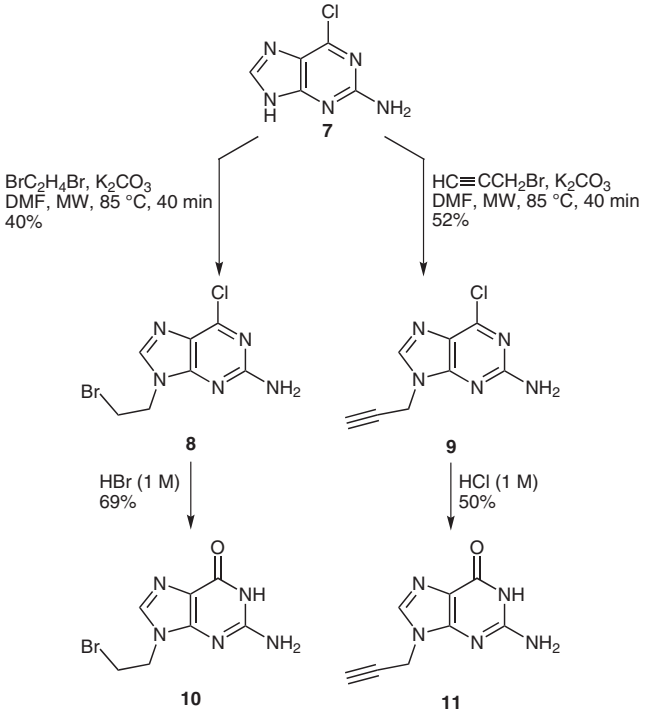
with dibromoethane and propargyl bromide using K_2CO_3 in DMF gave the derivatives **5** and **6** in 40 and 39% yield, respectively (Scheme 1). The regioselectivity of N9 (versus N7) alkylation of guanine derivative was improved through the use of 2-amino-6-chloropurine (**7**) as initial substrate. Taddei et al. reported a simple regioselective preparation of 9-(2-bromoethyl)purine derivative **8** (56% yield) starting from 6-chloro derivative **7** and dibromoethane using K_2CO_3 in DMF at room temperature for 48 hours[27] (Scheme 2).



Scheme 1 Synthesis of alkylated nucleobases **2**, **3**, **5**, and **6**

Lindsell et al. described the synthesis of (prop-2-ynyl)purine derivative **9** (69%) as a regioisomeric mixture of N9 and N7 (ratio 82:18) starting from compound **7** and propargyl bromide using Na_2CO_3 in DMF at room temperature for 44 hours.[29] The methodology developed to obtain adenine derivatives **5** and **6** was applied under microwave (MW) irradiation at 85 °C for 40 minutes. In our hands, starting from 6-chloropurine derivative **7**, regioselective alkylation furnished the N9 isomers **8** and **9** in 40% and 52% yield, respectively. The 2-bromoethyl derivative **8** was dissolved in aqueous HBr (1 N) and heated at reflux for six hours to furnish the guanine derivative **10** in 69% yield. The propargyl derivative **9** in aqueous HCl (1 N) gave the guanine analogue **11** in 50% yield (Scheme 2).

The monoamino-β-CD, monoazido-β-CD, monoamino permethylated, or monoazido permethylated β-CD derivatives were prepared as described in the literature. The hydroxylated mono-6-azido β-CD was prepared by using a two-step approach with tosylation of the native β-CD fol-



Scheme 2 Synthesis of alkylated guanine derivatives **10** and **11**

lowed by sodium azide substitution, as described previously. Total azidolysis using Staudinger conditions afforded the hydroxylated mono-6-amino β-CD. The permethylated monoazido β-CD was synthesized by the reaction of the hydroxylated mono-6-azido β-CD with methyl iodide in basic conditions. The permethylated monoamino β-CD was obtained using a similar method as described above.[30]

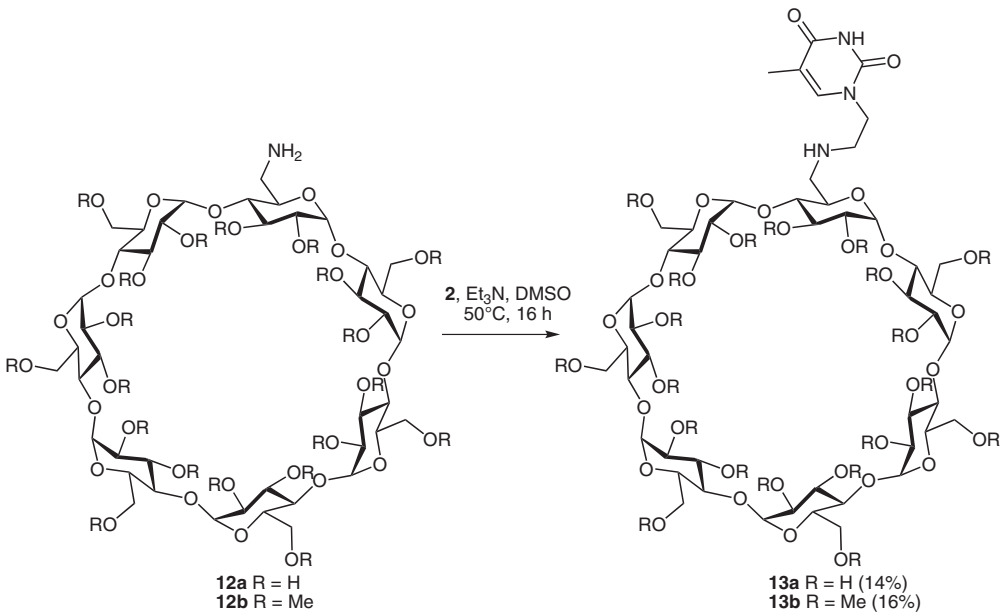
Synthesis of Aminoethyl-β-CD Derivatives Having 1-Pyrimidine and 9-Purine Moiety

Reaction of β-CD derivative **12a** with an excess of bromide **2** in anhydrous DMSO at 50 °C for 16 hours furnished the desired CD derivative **13a** in 14% yield (Scheme 3).

Starting from β-CD derivative **12a** and permethylated analogue **12b**, application of this procedure afforded the cyclodextrin derivatives **13b**, **14a**,**b**, and **15** in 16, 38, 44, and 20% yield, respectively (Scheme 3 and Figure 1). Using the same protocol, reaction of hydroxylated 6-amino β-CD **12a** and 9-(2-bromoethyl)guanine **10** did not generate the hydroxylated guanine analogue.

Synthesis of 1,2,3-Triazol-β-CD Derivatives Having 1-Pyrimidine and 9-Purine Moiety

The Huisgen 1,3-dipolar cycloaddition reaction of organic azides and alkynes[31] is an extremely useful method in organic chemistry due to the development of Cu(I) catalysis in 2001,[32] which offers a major improvement in both rate and regioselectivity of the reaction. Few examples of Huisgen 1,3-dipolar cycloaddition were described in the area of CD chemistry using 6-azido β-CD[18,33] or analogues.[34] To the best of our knowledge, only one paper re-



Scheme 3 Synthesis of CD derivatives **13** having thymine nucleobase

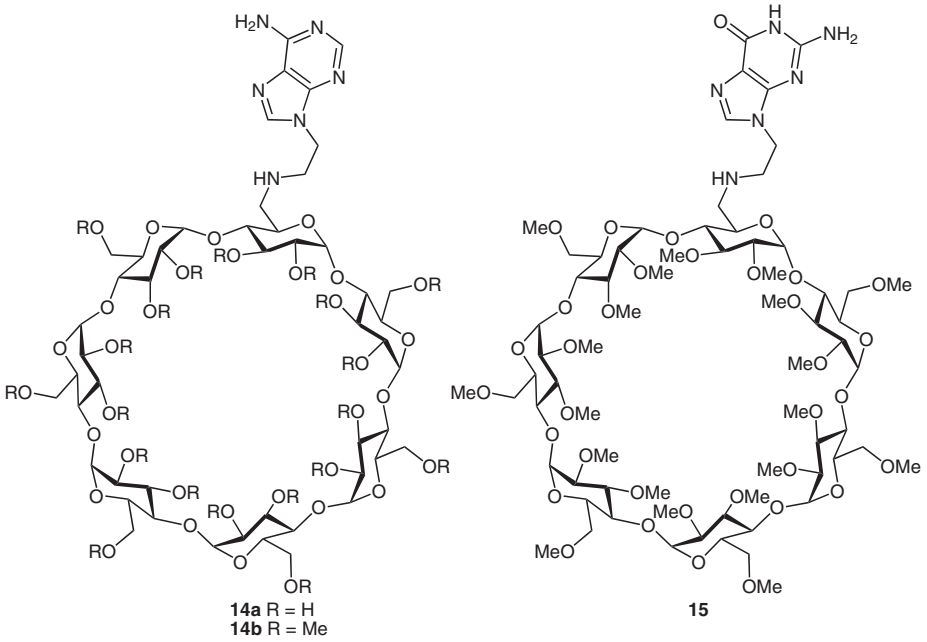


Figure 1 CD derivatives **14a**,**b** and **15** having adenine and guanine nucleobases

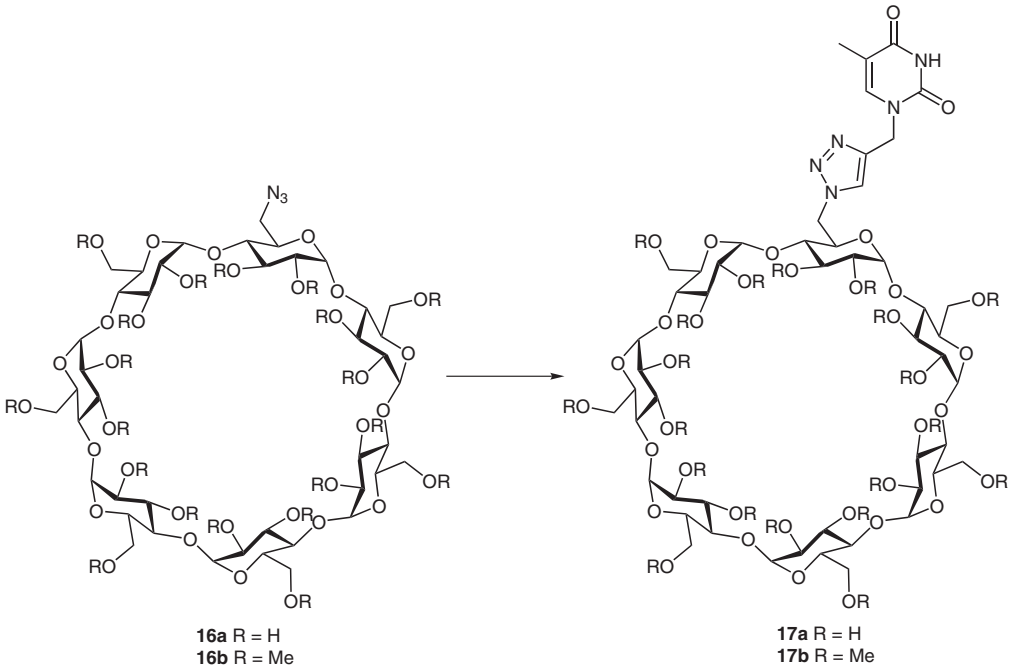
ported the synthesis of nucleobase and CD having a 1,2,3-triazole-4-methyl group.[18] Starting from the mono-6-azido β-CD **16a** and the permethylated analogue **16b**, the Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) was investigated for the transformation of the propargylated nucleobases **3**, **6**, and **11** under various conditions (Scheme 4 and Table 1). Two sources of Cu(I) – CuI and $(EtO)_3PCuI$ – were tested using the methodology described in the literature (Table 1, entries 1–12). First, treatment of azido derivative **16a** with alkyne **3** in the presence of CuI in a large excess in aqueous *t*-BuOH solution under microwave irradiation furnished the 1,2,3-triazo-4-yl compound **17a** in 32% yield (Scheme 4 and Table 1, entry 1).

Starting from mono-6-azido β-CD **16a**, the use of alkynes **6** and **11** gave the cycloadducts **18a** and **19a** in 57% and 60% yield, respectively (Table 1, entries 2 and 3). In our hands, similar methodology with conventional heating gave after 24 hours the target compound **17a** in 12% yield. The CuAAC reaction using $(EtO)_3PCuI$ as a source of Cu(I) benefits from increased solubility in organic solvents such as DMF. The azido derivative **16a** with alkyne **3** in the presence of $(EtO)_3PCuI$ as catalyst in DMF at 90 °C for two days afforded the 1,2,3-triazol-4-yl compound **17a** in 31% yield (Table 1, entry 7). From mono-6-

Table 1 CuAAC Reactions Starting from 6-Azido CDs **16a** and **16b** and Propargylated Nucleobase Derivatives

Entry	6-Azido CD	Alkyne	1,2,3-Triazole CD	Cu source	Reducing agent	Irradiation	Solvent	Temp (°C)	Time (h)	Yield (%)
1	**16a**	**3**	**17a**	CuI	–	MW	*t*-BuOH–H_2O	85	0.6	32
2	**16a**	**6**	**18a**	CuI	–	MW	*t*-BuOH–H_2O	85	0.6	57
3	**16a**	**11**	**19a**	CuI	–	MW	*t*-BuOH–H_2O	85	0.6	60
4	**16b**	**3**	**17b**	CuI	–	MW	*t*-BuOH–H_2O	85	0.6	61
5	**16b**	**6**	**18b**	CuI	–	MW	*t*-BuOH–H_2O	85	0.6	73
6	**16b**	**11**	**19b**	CuI	–	MW	*t*-BuOH–H_2O	85	0.6	34
7	**16a**	**3**	**17a**	$(EtO)_3PCuI$	–	no	DMF	90	48	31
8	**16a**	**6**	**18a**	$(EtO)_3PCuI$	–	no	DMF	90	48	33
9	**16a**	**11**	**19a**	$(EtO)_3PCuI$	–	no	DMF	90	48	13
10	**16b**	**3**	**17b**	$(EtO)_3PCuI$	–	no	DMF	90	48	64
11	**16b**	**6**	**18b**	$(EtO)_3PCuI$	–	no	DMF	90	48	51
12	**16b**	**11**	**19b**	$(EtO)_3PCuI$	–	no	DMF	90	48	30
13	**16a**	**3**	**17a**	$CuSO_4$	NaAsc	no	DMSO	85	12	50
14	**16a**	**6**	**18a**	$CuSO_4$	NaAsc	no	DMSO	85	12	26
15	**16a**	**11**	**19a**	$CuSO_4$	NaAsc	no	DMSO	85	12	15
16	**16b**	**3**	**17b**	$CuSO_4$	NaAsc	no	DMSO	85	12	24
17	**16b**	**6**	**18b**	$CuSO_4$	NaAsc	no	DMSO	85	12	14
18	**16b**	**11**	**19b**	$CuSO_4$	NaAsc	no	DMSO	85	12	17

azido β-CD **16a**, application of this method using the alkynes **6** and **11** led to the 1,2,3-triazole derivatives **18a** and **19a** (Figure 2) in 33% and 13% yield, respectively (Table 1, entries 8 and 9). An important factor seems to be the maintenance of the Cu(I) at a high level at all time during the reaction. The possibility to use Cu(II) source with



Scheme 4 Synthesis of CD derivatives **17a**,**b** having thymine nucleobase

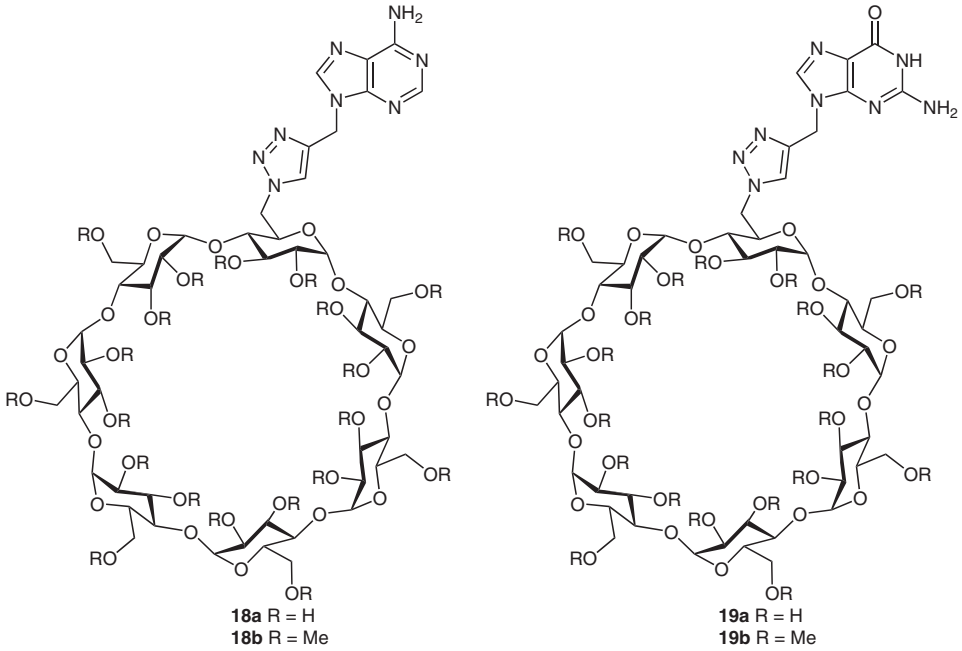


Figure 2 CD derivatives **18a**,**b** and **19a**,**b** having adenine and guanine nucleobases

addition of a reducing agent in excess has been one of the preferred methods. In general the presence of reducing agents renders the reaction much less susceptible to oxygen enabling the reaction to be run under open-air conditions. Treatment of azido derivative **16a** with alkyne **3** in the presence of a $CuSO_4 \cdot 5\ H_2O$/sodium ascorbate (NaAsc) mixture in DMSO at 85 °C for 24 hours gave the cycloadduct **17a** in 50% yield (Table 1, entry 13). Starting from mono-6-azido β-CD **16a**, treatment with the alkynes **6** and **11** led to the triazole moiety **18a** and **19a** in 26% and 15% yield, respectively (Table 1, entries 14 and 15). Using the three methods described above, the use of the permethylated mono-6-azido β-CD **16b** afforded the cycloadducts **17b–19b** in 14–73% yields, respectively (Table 1, entries 4–6, 10–12, 16–18). In accordance with the literature, the MW-assisted protocol (Table 1, entries 1–6) offered good yields (32–73%) and shortened the reaction time (0.6 h versus 12–48 h).

In conclusion, nucleobases such as thymine, adenine, and guanine and cyclodextrin moieties were linked by aminoethyl and 1,2,3-triazole groups to provide eleven novel potential supramolecular elements. Extension of this work concerning the G-quartet formation with the guanine analogues **15**, **19a**,**b** will be reported in due course.

All reagents were used as purchased from commercial suppliers without further purification. Solvents (DMF, THF) were distilled under anhyd conditions. Petroleum ether (PE) refers to the fraction boiling in the range 45–65 °C. TLC plates (Macherey-Nagel, ALUGRAM® SIL G/UV_{254}, 0.2 mm silica gel 60 Å) were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of phosphomolibdic acid (3 g) in EtOH (100 mL) followed by heating with a heat gun. Flash column chromatography was performed using Macherey-Nagel silica gel 60 (15–40 μm). Semi-preparative HPLC purifications were performed using a C18 reversed phase column and a H_2O–MeCN system (98.2 to 70:30 for 20 min) as eluent. NMR experiments were recorded with a Bruker Avance 400 spectrometer at 400 MHz for ^1H and at 100 MHz for ^{13}C, or with a Bruker Avance 500 spectrometer at 500 MHz for ^1H nuclei and at 125 MHz for ^{13}C at 23 °C (r.t.). The chemical shifts are expressed in part per million (ppm) relative to TMS (δ = 0 ppm) and the coupling constant *J* in hertz (Hz). For NMR assignments of cyclodextrin-nucleobase conjugates, numbers 1–6′ are referred to CD while alphabets a–i are referred to modified nucleobases. Microwave irradiations were performed with a CEM Discover apparatus. High-resolution electrospray mass spectra (ESI-HRMS) in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole time-of-flight instrument (Waters-Micromass), equipped with a pneumatically assisted electrospray (Z-spray) ionization source and an additional sprayer (Lock Spray) for the reference compound. The purified compounds were dissolved in methanol (0.01 mg/mL) and the solutions were directly introduced (5 μL/min) through an integrated syringe pump into the electrospray source. The source and desolvation temperatures were 80 and 150 °C, respectively. N_2 was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. Typically, the capillary voltage was 3.5 kV and the cone voltage 110 V. Lock mass correction, using appropriate cluster ions of an orthophosphoric acid solution (0.1% in H_2O–MeCN, 50:50, v/v), was applied for accurate mass measurements. The mass range was 50–2000 Da and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10,000 (FWMH). Data acquisition and processing were performed with MassLynx 4.0 software.

9-(2-Bromoethyl)-6-chloro-9*H*-purin-2-amine (8)

2-Amino-6-chloropurine (0.25 g, 1.47 mmol) and K_2CO_3 (0.81 g, 5.87 mmol, 4 equiv) were dissolved in anhyd DMF (5 mL). Propargyl bromide (0.30 mL, 3.68 mmol, 2.5 equiv.) was added and the resulting solution was irradiated with MW (200 W) at 85 °C for 40 min. Then Et_2O (15 mL) was added and the precipitate was collected by filtration to give **8** as a yellow solid (0.163 g, 40%). Physical data were in accordance with the literature;[27] R_f = 0.70 (7% MeOH–CH_2Cl_2).

^1H NMR (400 MHz, DMSO-d_6): δ = 3.90 (t, *J* = 6.0 Hz, 2 H, CH_2Br), 4.46 (t, *J* = 6.0 Hz, 2 H, NCH_2), 6.97 (s, 2 H, NH_2), 8.16 (s, 1 H, 8-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.5 (CH_2Br), 45.2 (NCH_2), 123.8 (C-5), 143.7 (C-8), 150.1 (C-4), 154.7 (C-6), 160.4 (C-2).

6-Chloro-9-(prop-2-ynyl)-9*H*-purin-2-amine (9)

To a solution of 2-amino-6-chloropurine (0.25 g, 1.47 mmol, 1.04 equiv) in anhyd DMF (5 mL) were added successively K_2CO_3 (0.20 g, 1.44 mmol, 1.02 equiv) and propargyl bromide (0.12 mL, 1.41 mmol). The resulting solution was irradiated with MW (200 W) at 85 °C for 40 min, then CH_2Cl_2 (15 mL) was added, and the precipitate formed was collected by filtration. The desired product **9** was obtained as a yellow solid (0.152 g, 52%), which was directly used without further purification. Physical data were in accordance with the literature;[29] R_f = 0.60 (7% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.50 (s, 1 H, C≡CH), 4.93 (s, 2 H, CH_2), 7.05 (s, 2 H, NH_2), 8.18 (s, 1 H, 8-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.4 (CH_2), 76.1 (C≡*C*H), 77.8 (*C*≡CH), 123.0 (C_5), 142.3 (C-8), 149.5 (C-4), 153.5 (C-6), 159.9 (C-2).

2-Amino-9-(2-bromoethyl)-1*H*-purin-6(9H)-one (10)

The bromoethyl derivative **8** (0.17 g, 0.62 mmol) was dissolved in aq 1 M HBr (5 mL). The solution was heated at reflux for 7 h. After cooling, the solution was neutralized with 10% aq NaOH. The precipitate was collected and washed with H_2O (20 mL) to give the desired product (0.11 g, 69%); R_f = 0.30 (10% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.84 (t, *J* = 6.3 Hz, 2 H, CH_2Br), 4.34 (t, *J* = 6.3 Hz, 2 H, NCH_2), 6.48 (s, 2 H, NH_2), 7.72 (s, 1 H, 8-H), 10.57 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.5 (CH_2Br), 45.2 (NCH_2), 123.8 (C-5), 143.7 (C-8), 150.1 (C-4), 154.7 (C-6), 160.4 (C-2).

HRMS (ESI): *m*/*z* calcd for $C_7H_8BrN_5O$ + Na [M + Na]$^+$: 279.9810; found: 279.9816.

2-Amino-9-(prop-2-ynyl)-1*H*-purin-6(9*H*)-one (11)

Compound **9** (0.13 g, 0.63 mmol) was dissolved in aq 1 M HCl (5 mL). The solution was heated at reflux for 6 h. After cooling, the solution was neutralized with 10% aq NaOH. The precipitate formed was collected and washed with H_2O (20 mL) to give the desired product (0.066 g, 50%) as a white solid. Physical data were in accordance with the literature;[35] R_f = 0.30 (10% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.40 (s, 1 H, C≡CH), 4.80 (s, 2 H, CH_2), 6.56 (s, 2 H, NH_2), 7.77 (s, 1 H, 8-H), 10.69 (s, 1 H, 1-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.0 (CH_2), 75.7(C≡*C*H), 78.5 (*C*≡CH), 116.3 (C-5), 136.7 (C-8), 150.8 (C-4), 153.8 (C-2), 156.7 (C-6).

Nucleophilic Substitution Reactions between Mono-6-amino-β-CD 12a,b and Nucleobases 2, 5, and 10; General Procedure

Mono-6-amino-β-CD (0.14 mmol) and the respective nucleobase derivative (0.15 mmol, 1.1 equiv) were dissolved in anhyd DMSO (5 mL). Et_3N (0.05 mL) was added and the mixture was stirred at 50 °C for 16 h. The crude was then purified, either by column chromatography on silica gel with PE–CH_2Cl_2 then CH_2Cl_2–MeOH as eluents for the permethylated CD derivatives, or by semi-preparative HPLC for the hydroxy-CD derivatives.

***N*-[6^A-Deoxy-β-cyclodextrin]-*N*1-aminoethylthymine (13a)**

Yield: 14%; mp 200 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 7.48 (s, 1 H), 5.14–5.08 (m, 7 H), 4.30–4.10 (m, 3 H), 4.03–3.81 (m, 25 H), 3.72–3.50 (m, 15 H), 3.47 (m, 2 H), 3.39 (m, 1 H), 1.91 (s, 3 H).

^{13}C NMR (125 MHz, D_2O): δ = 166.8, 153.0, 142.2, 111.5, 102.0–101.0, 83.3–80.8, 71.5–70.5, 67.5, 60.5–59.5, 48.8, 47.6, 45.0, 11.3.

HRMS (ESI): *m*/*z* calcd for $C_{49}H_{79}N_3O_{36}$ [M + H]$^+$: 1286.4522; found: 1286.4581.

***N*-[6^A-Deoxy-2^A, 3^A-di-*O*-methylhexakis(2$^{B–G}$, 3$^{B–G}$, 6$^{B–G}$-tri-*O*-methyl)-β-cyclodextrin]-*N*1-aminoethylthymine (13b)**

Yield: 16%; mp 200 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 7.56 (s, 1 H), 5.36–5.24 (m, 5 H), 4.00 (s, 2 H), 3.89–3.54 (m, 33 H), 3.64–3.62 (m, 21 H), 3.55–3.52 (m, 21 H), 3.43–3.37 (m, 7 H), 3.41–3.40 (m, 21 H), 3.23 (br s, 2 H), 3.18 (br s, 2 H), 1.94 (s, 3 H).

^{13}C NMR (125 MHz, D_2O): δ = 166.8, 152.4, 143.1, 110.6, 97.6–96.6, 81.4–75.9, 71.2–69.6, 59.9–58.1, 48.5, 47.4, 47.0, 11.4.

HRMS (ESI): *m*/*z* calcd for $C_{69}H_{119}N_3O_{36}$ [M + H]$^+$: 1566.7532; found: 1565.7573.

***N*-[6^A-Deoxy-β-cyclodextrin]-*N*9-aminoethyladenine (14a)**

Yield: 38%; mp 200 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 8.52 (s, 1 H), 8.40 (s, 1 H), 5.17–5.10 (m, 7 H), 4.38 (s, 2 H), 4.00–3.50 (m, 39 H), 3.31 (t, *J* = 9.0 Hz, 1 H), 3.11 (m, 2 H), 2.95 (d, *J* = 13.0 Hz, 1 H), 2.77 (m, 1 H).

^{13}C NMR (125 MHz, D_2O): δ = 155.4, 152.2, 149.5, 142.5, 118.5, 102.0–101.7, 101.0, 83.5, 81.2–80.1, 73.1–70.2, 60.3–59.9, 48.2, 47.0, 43.2.

HRMS (ESI): *m*/*z* calcd for $C_{49}H_{78}N_6O_{34}$ [M + H]$^+$: 1295.4637; found: 1295.4574.

***N*-[6^A-Deoxy-2^A, 3^A-di-*O*-methylhexakis(2$^{B–G}$, 3$^{B–G}$, 6$^{B–G}$-tri-*O*-methyl)-β-cyclodextrin]-*N*9-aminoethyladenine (14b)**

Yield: 44%; mp 200 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 8.31 (s, 1 H), 8.23 (s, 1 H), 5.29–5.24 (m, 5 H), 5.17 (s, 1 H), 4.98 (s, 1 H), 4.44 (br s, 2 H), 3.88–3.51 (m, 26 H), 3.64–3.62 (m, 21 H), 3.55–3.52 (m, 21 H), 3.41–3.32 (m, 14 H) 3.41–3.40 (m, 21 H), 3.24 (br s, 2 H), 3.05 (br s, 2 H).

^{13}C NMR (125 MHz, D_2O): δ = 155.5, 152.4, 149.3, 142.6, 118.5, 97.7–96.5, 80.9–76.5, 71.1–70.7, 60.0–58.0, 48.1, 47.5, 43.2.

HRMS (ESI): *m*/*z* calcd for $C_{69}H_{118}N_6O_{34}$ [M + H]$^+$: 1575.7673; found: 1575.7654.

***N*-[6^A-Deoxy-2^A, 3^A-di-*O*-methylhexakis(2$^{B–G}$, 3$^{B–G}$, 6$^{B–G}$-tri-*O*-methyl)-β-cyclodextrin]-*N*9-aminoethylguanine (15)**

Yield: 20%; R_f = 0.50 (10% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.51 (s, 1 H, NH), 7.57 (s, 1 H, He), 6.53 (s, 2 H, NH_2), 5.01(m, 6 H, 1-H_{CD}), 4.73 (m, 1 H, 1-$H_{CD}{}^A$), 3.95 (m, 2 H, Hg), 3.71–3.57 (m, 14 H, H_{CD}), 3.46–3.16 (m, 79 H, H_{CD}, OCH_3), 3.05–2.87 (m, 11 H, 2-H_{CD}, Hh, 6-$H_{CD}{}^A$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.8 (Cc), 153.4 (Ca), 151.2 (Cf), 137.9 (Ce), 116.6 (Cd), 97.7 (1-C_{CD}, 7 C), 81.7–79.1 (2-C_{CD}, C_{CD}), 71.4–70.9 (6-$C_{CD}{}^{B–G}$, C_{CD}), 70.4–60.6 (C_{CD}, OCH_3), 58.2–57.5 (C_{CD}, OCH_3), 48.7–48.4 (6-$C_{CD}{}^A$, Ch), 43.1 (Cg).

HRMS (ESI): *m*/*z* calcd for $C_{69}H_{118}N_6O_{35}$ [M + H]$^+$: 1591.7716; found: 1591.7714.

CuAAC Reactions between Mono-6-azido-β-CDs 16a,b and Nucleobases 3, 6, and 11; General Procedures

General Procedure A: Mono-6-azido-β-CD (1.10 mmol, 1 equiv), the alkyne derivative (1.1 equiv), and CuI (9 equiv) were suspended in a mixture of *t*-BuOH–H_2O (1:1, 10 mL). The mixture was irradiated with MW (200 W) at 85 °C for 40 min. Acetone (15 mL) was then added and the precipitate was collected by filtration. The crude was then purified by semi-preparative HPLC for the hydroxy cyclodextrins or by silica gel column chromatography for the permethylated cyclodextrins (CH_2Cl_2–MeOH, 100:0 to 30:70).

General Procedure B: Mono-6-azido-β-CD (1.55 mmol, 1 equiv), the alkyne derivative (1 equiv), and $CuSO_4 \cdot 5H_2O$ (0.5 equiv) were dissolved in DMSO (3 mL). To the solution was added sodium ascorbate (1 equiv), then the mixture was stirred at r.t. overnight. Acetone (10 mL) was added and the precipitate was collected by filtration. The crude was then purified by semi-preparative HPLC for the hydroxy cyclodextrins or by silica gel column chromatography for the permethylated cyclodextrins (PE–CH_2Cl_2, 50:50, then CH_2Cl_2–MeOH, 30:70).

General Procedure C: Mono-6-azido-β-CD (4.30 mmol, 1 equiv), the alkyne derivative (1.5 equiv), and $(EtO)_3PCuI$ (0.5 equiv) were dissolved in DMF (3 mL). The mixture was stirred at 90 °C for 48 h. Acetone (15 mL) was then added and the precipitate was collected by filtration. The crude was then purified by semi-preparative HPLC for the hydroxy cyclodextrins or by silica gel column chromatography for the permethylated cyclodextrins (CH_2Cl_2–MeOH, 100:0 to 30:70).

***N*1-[1-(6^A-Deoxy-β-cyclodextrin)-1,2,3-triazol-4-ylmethyl]thymine (17a)**

Mp 200 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 8.10 (s, 1 H), 7.66 (s, 1 H), 5.20 (s, 1 H), 5.10–5.03 (m, 9 H), 4.63 (s, 1 H), 4.30 (s, 1 H), 4.08–3.50 (m, 37 H), 3.01 (s, 1 H), 2.70 (s, 1 H), 1.92 (s, 3 H).

^{13}C NMR (125 MHz, D_2O): δ = 167.1, 152.2, 142.4, 126.5, 111.2, 101.9–101.4, 83.2–80.5, 73.0–70.4, 60.3, 59.1, 51.4, 42.9, 11.3.

HRMS (ESI): *m*/*z* calcd for $C_{50}H_{77}N_5O_{36}$ + Na [M + Na]$^+$: 1346.4246; found: 1346.4211.

***N*1-{[6^A-Deoxy-2^A, 3^A-di-*O*-methylhexakis(2$^{B–G}$, 3$^{B–G}$, 6$^{B–G}$-tri-*O*-methyl)-β-cyclodextrin]-1,2,3-triazol-4-ylmethyl}thymine (17b)**

R_f = 0.40 (7% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, D_2O): δ = 8.08 (s, 1 H, Hi), 7.61 (s, 1 H, Hf), 5.31–4.94 (m, 10 H, 1-H_{CD}, Hg, 6-H_{CD}^A), 4.55 (m, 1 H, 6′-H_{CD}^A), 4.17 (m, 1 H, 5-H_{CD}^A), 4.00 (m, 1 H, H_{CD}), 3.87–3.55 (m, 53 H, 3-H_{CD}, 4-H_{CD}, 5-H_{CD}, 6-$H_{CD}^{C–G}$, OCH_3), 3.49–3.46 (m, 22 H, OCH_3), 3.35–3.32 (m, 21 H, OCH_3), 3.06 (s, 3 H, H_{CD}), 2.86–2.74 (m, 2 H, 6-H_{CD}^B, 6′-H_{CD}^B), 1.85 (s, 3 H, He).

^{13}C NMR (100 MHz, D_2O): δ = 166.5 (Cc), 151.7 (Ca), 142.1–142.3 (Ch, Cf, 2 C), 126.6 (Ci), 111.1 (Cd), 97.5–96.9 (1-C_{CD}, 7 C), 81.1–76.4 (C_{CD}), 70.8–70.2 (C_{CD}, 5-C_{CD}^A, 6-C_{CD}^B), 59.9–57.8 (OCH_3, C_{CD}), 58.4–57.8 (OCH_3, C_{CD}), 51.5 (6-C_{CD}^A), 42.9 (Cg), 11.5 (Ce).

HRMS (ESI): *m*/*z* calcd for $C_{70}H_{117}N_5O_{36}$ + Na [M + Na]$^+$: 1626.7376; found 1626.7381.

***N*9-[1-(6^A-Deoxy-β-cyclodextrin)-1,2,3-triazol-4-ylmethyl]adenine (18a)**

Mp 200 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 8.29 (s, 1 H), 8.26 (s, 1 H), 7.99 (s, 1 H), 5.60 (s, 2 H), 5.15–5.00 (m, 7 H), 4.97 (d, *J* = 5.0 Hz, 1 H), 4.59 (dd, *J* = 5.0, 10.0 Hz, 1 H), 4.11 (t, *J* = 5.0 Hz, 1 H), 4.00–3.40 (m, 37 H), 2.78 (d, *J* = 10.0 Hz, 1 H), 2.60 (d, *J* = 9.5 Hz, 1 H).

^{13}C NMR (125 MHz, D_2O): δ = 155.6, 152.7, 148.9, 142.6, 142.1, 125.9, 118.6, 101.9, 81.3–80.4, 73.1–70.6, 60.0–58.8, 51.2, 38.4.

HRMS (ESI): *m*/*z* calcd for $C_{50}H_{76}N_8O_{34}$ + Na [M + Na]$^+$: 1355.4362; found: 1355.4363.

***N*9-{[6^A-Deoxy-2^A, 3^A-di-*O*-methylhexakis(2$^{B–G}$, 3$^{B–G}$, 6$^{B–G}$-tri-*O*-methyl)-β-cyclodextrin]-1,2,3-triazol-4-ylmethyl}adenine (18b)**

R_f = 0.30 (6% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, D_2O): δ = 8.20 (s, 1 H, He), 8.10 (s, 2 H, Ha, Hi), 5.45 (s, 2 H, Hg), 5.21–4.97 (m, 7 H, 1-H_{CD}, 6-H_{CD}^A), 4.46 (m, 1 H, 6′-H_{CD}^A), 4.03 (t, *J* = 9.0 Hz, 1 H, 5-H_{CD}^A), 3.90 (m, 1 H, H_{CD}), 3.72–3.38 (m, 75 H, H_{CD}, OCH_3), 3.26–3.16 (m, 21 H, H_{CD}, OCH_3), 2.55–2.53 (d, *J* = 10.3 Hz, 1 H, 6′-H_{CD}^B), 2.23 (m, 1 H, 6-H_{CD}^B).

^{13}C NMR (100 MHz, D_2O): δ = 155.4 (Cb), 152.5 (Ca), 148.4 (Cf), 141.8 (Ce, Ch), 126.4 (Ci), 118.2 (Cd), 97.5–97.0 (1-C_{CD}, 7 C), 81.1–76.5 (C_{CD}), 70.7–70.1 (5-C_{CD}^A, 6-$C_{CD}^{B–G}$, C_{CD}), 59.9–57.8 (OCH_3, C_{CD}), 51.5 (6-C_{CD}^A), 38.2 (Cg).

HRMS (ESI): *m*/*z* calcd for $C_{70}H_{116}N_8O_{34}$ + Na [M + Na]$^+$: 1635.7492; found: 1635.7488.

***N*9-[1-(6^A-Deoxy-β-cyclodextrin)-1,2,3-triazol-4-ylmethyl]guanine (19a)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.58 (s, 1 H, NH), 7.94 (s, 1 H, He), 7.64 (s, 1 H, Hi), 6.42 (s, 2 H, NH_2), 5.84–5.61 (m, 14 H), 5.15 (s, 2 H, Hg), 4.97 (s, 1 H, 1-H_{CD}^A), 4.82–4.72 (m, 7 H, 1-$H_{CD}^{B–G}$, 6-H_{CD}^A), 4.53–4.46 (m, 6 H), 4.31 (t, *J* = 5.7 Hz, 1 H, 6-OH_{CD}^B), 3.91 (m, 1 H, 5-H_{CD}^A), 3.59–3.26 (m, 37 H, 2-H_{CD}, 3-H_{CD}, 4-H_{CD}, 5-$H_{CD}^{B–G}$, 6-$H_{CD}^{C–G}$), 3.04 (d, *J* = 6.8 Hz, 1 H, 6-H_{CD}^B), 2.83 (m, 1 H, 6′-H_{CD}^B).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.9 (Cb), 153.6 (Ca), 151.1 (Cf), 142.4 (Ch), 137.3 (Ci), 124.5 (Ce), 116.3 (Cd), 102.2–101.4 (1-C_{CD}, 7 C), 83.4–81.2 (4-C_{CD}, 7 C), 73.2–71.8 (2-C_{CD}, 3-C_{CD}, 5-$C_{CD}^{B–G}$, 20 C), 70.0 (5-C_{CD}^A), 60.1–59.9 (6-$C_{CD}^{C–G}$), 59.1 (6-C_{CD}^B), 50.4 (6-C_{CD}^A), 37.8 (Cg).

HRMS (ESI): *m*/*z* calcd for $C_{50}H_{76}N_8O_{35}$ + Na [M + Na]$^+$: 1371.4311; found: 1371.4312.

***N*9-{[6^A-Deoxy-2^A, 3^A-di-*O*-methylhexakis(2$^{B–G}$, 3$^{B–G}$, 6$^{B–G}$-tri-*O*-methyl)-β-cyclodextrin]-1,2,3-triazol-4-ylmethyl}guanine (19b)**

R_f = 0.40 (7% MeOH–CH_2Cl_2).

^{1}H NMR (400 MHz, D_2O): δ = 8.08 (s, 1 H, He), 7.82 (s, 1 H, Hi), 5.41–4.99 (m, 10 H, Hg, 1-H_{CD}, 6-H_{CD}^A), 4.43 (m, 1 H, 6′-H_{CD}^A), 4.03 (m, 1 H, 5-H_{CD}^A), 3.87 (m, 1 H, H_{CD}), 3.71–3.40 (m, 72 H, H_{CD}, OCH_3), 3.26–2.90 (m, 24 H, H_{CD}, OCH_3), 2.60 (m, 2 H, 6′-H_{CD}^B, 6-H_{CD}^B).

^{13}C NMR (100 MHz, D_2O): δ = 158.0 (Cb), 153.1 (Ca), 141.7 (Ch, Ci), 126.0 (Ce), 106.2 (Cd), 97.3–96.9 (1-C_{CD}, 7 C), 80.7–76.8 (C_{CD}), 70.3–69.7 (5-C_{CD}^A, 6-C_{CD}^B, C_{CD}), 59.7–57.3 (C_{CD}, OCH_3), 51.0 (6-C_{CD}^A), 37.6 (Cg).

HRMS (ESI): *m*/*z* calcd for $C_{70}H_{116}N_8O_{35}$ + Na [M + Na]$^+$: 1651.7441; found: 1651.7448.

Acknowledgment

The authors are deeply indebted to the 'Ministère de l'Enseignement Supérieur et de la Recherche', the 'Centre National de la Recherche Scientifique' (CNRS), the 'Université de Poitiers' and « Biocydex » for their constant support. The authors gratefully acknowledge Dr. Serge Pilard of Université de Picardie Jules Verne (UPJV) for the mass spectrometry measurements.

References

(1) Klein, S.; Zoeller, T. *Pharm. Unserer Zeit* **2008**, *153*, 24.
(2) Perly, B.; Moutard, S.; Djedaini-Pilard, F. *Pharm. Chem.* **2005**, *4*, 4.
(3) Li, J.; Xiao, H.; Li, J.; Zhong, Y. P. *Int. J. Pharm.* **2004**, *278*, 329.
(4) Bhushan, R.; Kumar, R. *J. Chromatogr., A* **2009**, *1216*, 3413.

(5) Mauri-Aucejo, A.; Llobat-Estelles, M.; Escarti-Carrasco, M.; Marin-Saez, R. *Anal. Lett.* **2006**, *39*, 183.
(6) Takahisa, E.; Engel, K. H. *J. Chromatogr., A* **2005**, *1076*, 148.
(7) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997.
(8) Kataky, R.; Morgan, E. *Biosens. Bioelectron.* **2003**, *18*, 1407.
(9) Surpateanu, G. G.; Becuwe, M.; Lungu, N. C.; Dron, P. I.; Fourmentin, S.; Landy, D.; Surpateanu, G. *J. Photochem. Photobiol., A.* **2007**, *185*, 312.
(10) Ueno, A.; Ikeda, H. *Mol. Supramol. Photochem.* **2001**, *8*, 461.
(11) Bjerre, J.; Fenger, T. H.; Marinescu, L. G.; Bols, M. *Eur. J. Org. Chem.* **2007**, 704.
(12) Blach, P.; Landy, D.; Fourmentin, S.; Surpateanu, G.; Bricout, H.; Ponchel, A.; Hapiot, F.; Monflier, E. *Adv. Synth. Catal.* **2005**, *347*, 1301.
(13) Huskens, J.; Deij, M. A.; Reinhould, D. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 4467.
(14) Hamada, F.; Kondo, Y.; Ishikawa, K.; Itto, H.; Suzuki, I.; Osa, T.; Ueno, A. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 267.
(15) (a) Aime, S.; Gianolio, E.; Arena, F.; Barge, A.; Martina, K.; Heropoulos, G.; Cravotto, G. *Org. Biomol. Chem.* **2009**, *7*, 370. (b) Sliwa, W.; Girek, T.; Koziol, J. J. *Curr. Org. Chem.* **2004**, *8*, 1445. (c) Liu, Y.; Chen, Y. *Acc. Chem. Res.* **2006**, *39*, 681.
(16) (a) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1997**, *119*, 1676. (b) Yan, J.; Breslow, R. *Tetrahedron Lett.* **2000**, *41*, 2059. (c) Nelissen, H. F. M.; Schut, A. F. J.; Venema, F.; Feiters, M. C.; Nolte, R. J. M. *Chem. Commun.* **2000**, 577. (d) Liu, Y.; You, C. C.; Wada, T.; Inoue, Y. *Tetrahedron Lett.* **2000**, *41*, 6869. (e) Baugh, S. D. P.; Yang, Z.; Leung, D. K.; Wilson, D. M.; Breslow, R. *J. Am. Chem. Soc.* **2001**, *123*, 12488. (f) van Bommel, K. J. C.; de Jong, M. R.; Metselaar, G. A.; Verboom, W.; Huskens, J.; Hulst, R.; Kooijman, H.; Spek, A. L.; Reinhould, D. N. *Chem. Eur. J.* **2001**, *7*, 3603. (g) Liu, Y.; Li, L.; Zhang, H. Y.; Song, Y. *J. Org. Chem.* **2003**, *68*, 527.
(17) Casas-Solvas, J. M.; Ortiz-Salmeron, E.; Fernandez, I.; Garcia-Fuentes, L.; Santoyo-Gonzales, F.; Vargas-Berengel, A. *Chem. Eur. J.* **2009**, *15*, 8146.
(18) Hamon, F.; Violeau, B.; Turpin, F.; Bellot, M.; Bouteiller, L.; Djedaini-Pilard, F.; Len, C. *Synlett* **2009**, 2875.
(19) Liu, Y.; Zhang, Q.; Chen, Y. *J. Phys. Chem., B* **2007**, *111*, 12211.
(20) Nagai, K.; Kondo, H.; Tsuruzoe, N.; Hayakawa, K.; Kanematsu, K. *Heterocycles* **1982**, *19*, 53.
(21) Nagai, K.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1984**, *49*, 1022.
(22) Nagai, K.; Hayakawa, K.; Ukai, S.; Kanematsu, K. *J. Org. Chem.* **1986**, *51*, 3931.
(23) Djedaini-Pilard, F.; Perly, B.; Dupas, S.; Miocque, M.; Galons, H. *Tetrahedron Lett.* **1993**, *34*, 1145.
(24) Kato, Y.; Nishizawa, S.; Teramae, N. *Org. Lett.* **2002**, *4*, 4407.
(25) Murray, P. E.; McNally, V. A.; Lockyer, S. D.; Williams, K. J.; Stratford, I. J.; Jaffar, M.; Freeman, S. *Bioorg. Med. Chem.* **2002**, *10*, 525.
(26) Nawrot, B.; Michalak, O.; Olejniczak, S.; Wieczorek, M. W.; Lis, T.; Stec, W. J. *Tetrahedron* **2001**, *57*, 3979.
(27) Ciapetti, P.; Taddei, M. *Tetrahedron* **1998**, *54*, 11305.
(28) Lock, L.; Pohlsgaard, J.; Jepsen, A. S.; Hansen, L. H.; Nielsen, H.; Steffansen, S. I.; Sparving, L.; Nielsen, A. B.; Vester, B.; Nielsen, P. *J. Med. Chem.* **2008**, *51*, 4957.
(29) Lindsell, W. E.; Murray, C.; Preston, P. N.; Woodman, T. A. J. *Tetrahedron* **2000**, *56*, 1233.
(30) 6-Azido-β-CD, 6-amino-β-CD, 6-azido permethylated and 6-amino permethylated β-CD derivatives were furnished by Biocydex.
(31) (a) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (b) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613.
(32) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, B. K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
(33) Recent examples: (a) We, J.; He, H.; Gao, C. *Macromolecules* **2010**, *43*, 2252. (b) Zhang, Y. M.; Chen, Y.; Li, Z. Q.; Li, N.; Liu, Y. *Bioorg. Med. Chem.* **2010**, *18*, 1415. (c) Kim, H. Y.; Sohn, J.; Wijewickrama, G. T.; Edirisinghe, P.; Gherezghiher, T.; Hemachandra, M.; Lu, P. Y.; Chandrasena, R. E.; Molloy, M. E.; Tonetti, D. A. *Bioorg. Med. Chem.* **2010**, *18*, 809. (d) Cravotto, G.; Fokin, V. V.; Garella, D.; Binello, A.; Boffa, L.; Barge, A. *J. Comb. Chem.* **2010**, *12*, 13. (e) Mallard-Favier, I.; Blach, P.; Cazier, F.; Delattre, F. *Carbohydr. Res.* **2009**, *344*, 161. (f) Liu, H.; Zhang, Y.; Hu, J.; Li, C.; Liu, S. *Macromol. Chem. Phys.* **2009**, *210*, 2125. (g) Munteanu, M.; Choi, S. W.; Ritter, H. *Macromolecules* **2008**, *41*, 9619. (h) Mourer, M.; Hapiot, F.; Tilloy, S.; Monflier, E.; Menuel, S. *Eur. J. Org. Chem.* **2008**, 5723. (i) Mourer, M.; Hapiot, F.; Monflier, E.; Menuel, S. *Tetrahedron* **2008**, *64*, 7159. (j) Amajjahe, S.; Choi, S.; Munteanu, M.; Ritter, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3435. (k) Liu, Y.; Ke, C. F.; Zhang, H. Y.; Cui, J.; Ding, F. *J. Am. Chem. Soc.* **2008**, *130*, 600. (l) Liu, Y.; Yang, Z. X.; Chen, Y. *J. Org. Chem.* **2008**, *73*, 5298. (m) Cravotto, G.; Mendicuti, F.; Martina, K.; Tagliapietra, S.; Robaldo, B.; Barge, A. *Synlett* **2008**, 2642.
(34) Recent examples: (a) Gu, Z. Y.; Guo, D. S.; Sun, M.; Liu, Y. *J. Org. Chem.* **2010**, *75*, 3600. (b) Casas-Solvas, J. M.; Ortiz-Salmeron, E.; Fernandez, I.; Garcia-Fuentes, L.; Santoyo-Gonzalez, F.; Vargas-Berenguel, A. *Chem. Eur. J.* **2009**, *15*, 8146. (c) Felici, M.; Contreras-Carballada, P.; Vida, Y.; Smits, J. M. M.; Nolte, R. J. M.; De Cola, L.; Williams, R. M.; Feiters, M. C. *Chem. Eur. J.* **2009**, *15*, 13124. (d) Felici, M.; Marza-Perez, M.; Hatzakis, N. S.; Nolte, R. J. M.; Feiters, M. C. *Chem. Eur. J.* **2008**, *14*, 9914.
(35) Lu, W.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Org. Chem.* **2007**, *72*, 5012.