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Symmetrical doubly connected head-to-head α-cyclodextrin dimers: a high yield synthesis of a novel type of neoglycolipid

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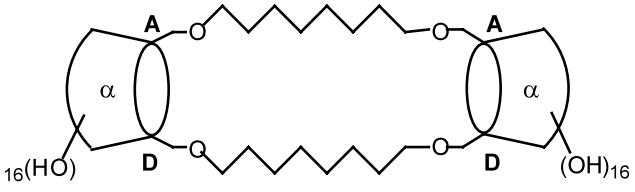
Abstract—A 'head-to-head' type α-cyclodextrin dimer, wherein the two primary rims are doubly ligated through alkyl chains, is synthesised in high yield using acyclic diene metathesis (ADM) followed by ring closing metathesis (RCM).

Cyclodextrins (CDs) are naturally occurring oligomers of α-1,4-linked D-glucose units with a unique shape like a bottomless flowerpot.[1] This chemical structure presents a hydrophobic cavity that can encapsulate various guest molecules to produce supramolecular inclusion complexes.[2,3] In order to study a potential improvement of the binding ability, a variety of singly linked CD dimers have been constructed over the years.[4] An interesting sub-class of such duplexes is made of doubly-linked CD platforms.[5] In this communication the authors report on a highly efficient synthetic path producing a new type of dimeric α-CD **1**. This new type can be described as two α-CDs which are orientated in a head-to-head (HH) fashion,† through a double polyalkyl chain ligation, as schematically depicted in Scheme 1.



1

Scheme 1. A representative example of a new type of CD-based neoglycolipid.

Our strategy was made possible through the recently discovered straightforward availability of the diol **2** (Scheme 2).

The chemical pathway converting **2** into the CD duplex **1** is disclosed in Scheme 3.[11] This sequence is characterised by the efficiency of every step (between 85 and 100%), namely the selective monoalkylation of the diol **2** (85%), the acyclic diene metathesis (95%), and the ring closing metathesis (87%). The synthesis of CD duplex **1** is thus accomplished with an overall yield of 49% from α-CD, whereas most previous preparations of doubly linked CDs were in the range 2–5%. The derivative **1** has easily been characterised as the D_2 symmetrical peracetate **9**.‡

Keywords: cyclodextrins; dimer; neoglycolipid; metathesis.

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† The nomenclature about the possible orientations between two face-to-face CD units suffers from disparity. Many authors define the secondary hydroxyl rim as the head,[6,7] whereas others prefer to identify the primary hydroxy site of the CD as the head.[8]

‡ Selected data for **9**: MS (MALDI-TOF): *m*/*z* (%): 3532.1 (100) [*M*Na+]. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 5.82 (dd, 4H, $^3J_{3,2}$ = 10.6 Hz, $^3J_{3,4}$ = 9.2 Hz, 4 H_3^C), 5.57 (dd, 4H, $^3J_{3,2}$ = 10.5 Hz, $^3J_{3,4}$ = 9.25 Hz, 4 H_3^B), 5.41 (dd, 4H, $^3J_{3,2}$ = 10 Hz, $^3J_{3,4}$ = 8.6 Hz, 4 H_3^A), 5.27 (d, 4H, $^3J_{1,2}$ = 3.75 Hz, 4 H_1^C), 5.05 (d, 4H, $^3J_{1,2}$ = 3.35 Hz, 4 H_1^B), 5.02 (d, 4H, $^3J_{1,2}$ = 3.45 Hz, 4 H_1^A), 4.86 (dd, 4H, $^3J_{2,3}$ = 10.6 Hz, $^3J_{2,1}$ = 3.35 Hz, 4 H_2^B), 4.80 (dd, 4H, $^3J_{2,3}$ = 10.6 Hz, $^3J_{2,1}$ = 3.75 Hz, 4 H_2^C), 4.76 (dd, 4H, $^3J_{2,3}$ = 10 Hz, $^3J_{2,1}$ = 3.45 Hz, 4 H_2^A), 4.62–4.55 (m, 8H, 8 H_6^C), 4.38–4.31 (m, 4H, 4 H_6^B), 4.29–4.13 (m, 12H, 8 H_5, 4 $H_6^{B'}$), 4.12–4.05 (m, 4H, 4 H_5^C), 3.98–3.82 (m, 16H, 12 H_4, 4 H_6^A), 3.80–3.75 (m, 4H, 4 $H_6^{A'}$), 3.91–3.86 (m, 8H, -CH_2-CH_2-CH_2-$\underline{CH_2}$-O), 2.34–2.02 (8s, 96H, 32 $C\underline{H_3}CO$-), 1.65 (m, 8H, -CH_2-CH_2-$\underline{CH_2}$-CH_2-O), 1.46 (m, 16H, -$\underline{CH_2}$-$\underline{CH_2}$-CH_2-CH_2-O). Data on B and C may have to be interchanged. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 171.2, 170.8, 170.4, 170.38, 170.34, 169.36, 169.33, 168.84 (32 $CH_3\underline{C}O$), 96.75, 96.45, 95.96 (12 C_1), 78.01, 77.68, 75.06, 72.63 (16 CH), 71.90 (8 C_6); 71.71, 71.41, 71.05, 70.20 (16 CH), 70.10 (8 CH), 69.91, 68.10 (8 CH), 63.23 (4 CH_2), 63.12 (4 CH_2), 29.38, 29.23, 25.77 (-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-CH_2-O).

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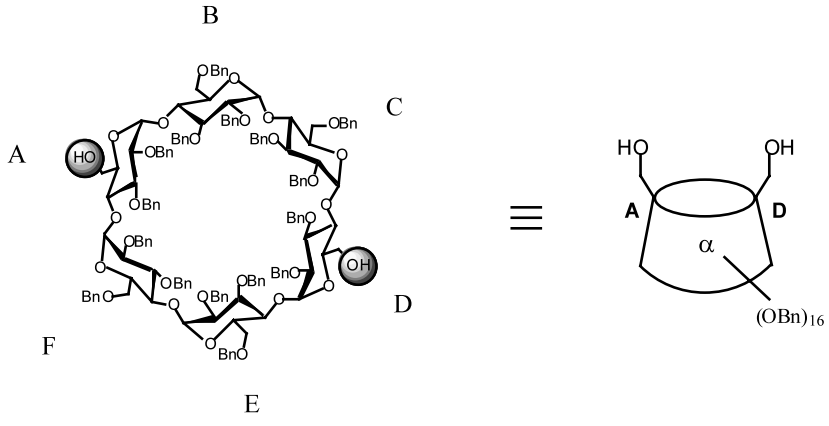
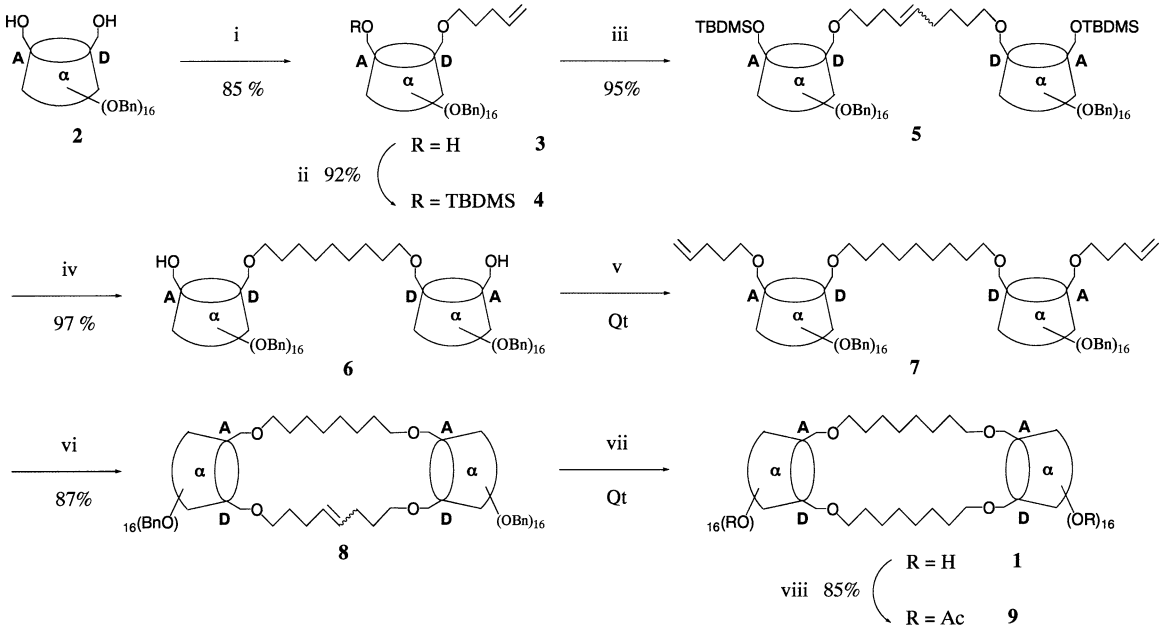
PII: S0040-4039(02)01125-5



2 (prepared in 78% yield in a two step sequence from α-CD[9,10])

Scheme 2. The key starting diol **2** used in this work.



Scheme 3. *Reagents and conditions*: (i) 5-bromo-pent-1-ene (1.8 equiv.), ^{t}BuOK (4 equiv.), ^{n}Bu$_4$NI, THF, rt, 18 h; (ii) TBDMSOTf (2 equiv.), pyridine (2 equiv.), CH_2Cl_2, rt, 2 h; (iii) $Cl_2(PCy_3)_2Ru$=CHPh (5 mol%), CH_2Cl_2 (10^{-1} M), reflux, 6 h then $Pb(OAc)_4$,[12] rt overnight; (iv) H_2, PtO_2, EtOAc, 3 h then ^{n}Bu$_4$NF (4 equiv.), THF, rt, 2 h; (v) 5-bromo-pent-1-ene (6 equiv.), NaH (6 equiv.), DMF, rt; (vi) $Cl_2(PCy_3)_2Ru$=CHPh (10 mol%), CH_2Cl_2 (10^{-3} M), reflux, 10 h then $Pb(OAc)_4$,[12] rt overnight; (vii) H_2, Pd/C 10%, Pd black, EtOAc/MeOH (1:1), rt, 2 days; (viii) Ac_2O, pyridine, DMAP, rt, 20 h.

§ Selected data for **4**: $[\alpha]_D^{23}$ +33.5 (*c* 1, $CHCl_3$). MS (FAB): *m*/*z* (%): 2619.2 (100) [*M*Na+]. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.36–7.20 (m, 80H, CH_{arom}), 5.88 (dddd, 1H, $^3J_{trans}$=16.8 Hz, $^3J_{cis}$=10.3 Hz, ^3J=^3J=6.6 Hz, CH_2=CH-CH_2-CH_2-CH_2-O), 5.37 (d, $^3J_{1,2}$=3.25 Hz, 1H, H_1), 5.32 (d, 1H, ^2J=10.7 Hz, CHPh), 5.30 (d, 1H, ^2J=10.2 Hz, CHPh), 5.30–5.17 (m, 9H, $^3J_{1,2}$=3 Hz, 4H_1, 5 CHPh), 5.18 (d, 1H, $^3J_{1,2}$=3.25 Hz, H_1), 5.1 (dd, 1H, $^3J_{trans}$=17.2 Hz, ^4J=1.5 Hz, CH_2=CH-CH_2-CH_2-CH_2-O-), 5.05 (br d, 1H, $^3J_{cis}$=10.2 Hz, CH_2=CH-CH_2-CH_2-CH_2-O), 5.0–4.92 (m, 6H, 6 CHPh), 4.66–4.49 (m, 18H, 18 CHPh), 4.44 (d, 1H, ^2J=12.1 Hz, CHPh), 4.43 (d, 1H, ^2J=12 Hz, CHPh), 4.35–3.98 (m, 22H, 6 H_3, 6 H_4, 4 H_5, 6 H_6), 3.96 (br d, 1H, $^3J_{5,4}$=9.4 Hz, H_5), 3.86 (br d, 1H, $^3J_{5,4}$=8.9 Hz, H_5), 3.75–3.52 (m, 10H, 5 H_2, 5 H_6), 3.48 (dd, 1H, $^3J_{2,1}$=3 Hz, $^3J_{2,3}$=9.1 Hz, H_2), 3.47–3.42 (m, 2H, 1 H_6, 1 CH_2=CH-CH_2-CH_2-CH_2-O), 3.32 (m, 1H, CH_2=CH-CH_2-CH_2-CH_2-O), 2.13 (m, 2H, CH_2=CH-CH_2-CH_2-CH_2-O), 1.66 (m, 2H, CH_2=CH-CH_2-CH_2-CH_2-O), 0.96 (s, 9H, SiCCH_3), 0.07, 0.06 (2s, 6H, 2 SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 139.3 (3 C_{ipso}), 139.25 (2 C_{ipso}), 139.2, 138.32 (2 C_{ipso}), 138.28 (3 C_{ipso}), 138.24, 138.23 (2 C_{ipso}), 138.1 (3 C_{ipso}), 138.05 (CH_2=CH-CH_2-CH_2-CH_2-O), 138.0 (1 C_{ipso}), 128.3–126.8 (80 CH_{arom}), 114.7 (CH_2=CH-CH_2-CH_2-CH_2-O), 98.4, 98.35, 98.3, 98.25, 98.2 (6 C_1), 81.2 (1 C_3), 81.05 (3 C_3), 81.0, 80.8 (2 C_3), 79.05 (1 CH), 79.0 (4 CH), 78.95 (2 CH), 78.9 (1 CH), 78.7, 78.5, 78.45, 78.3 (4 C_4), 75.7, 75.6, 75.5 (3 CH_2Ph), 75.4 (3 CH_2Ph), 73.4, 73.35, 73.3, 73.25, 72.85, 72.75 (6 CH_2Ph), 72.7 (3 CH_2Ph), 72.45 (1 CH_2Ph), 72.4, 71.5 (2 C_5), 71.45 (2 C_5), 71.4 (2 C_5), 71.0 (CH_2=CH-CH_2-CH_2-CH_2-O), 69.2 (1 C_6), 68.95 (4 C_6), 62.4 (1 C_6), 30.2 (CH_2=CH-CH_2-CH_2-CH_2-O), 28.8 (CH_2=CH-CH_2-CH_2-CH_2-O), 25.9 (SiCCH_3), 18.2 (SiCCH_3), −4.8, −5.2 (2 SiCH_3). Anal. calcd for $C_{159}H_{178}O_{30}Si$: C, 73.53; H, 6.91. Found: C, 73.35; H, 7.06.

Following similar lines, the diol **2** has also been easily monoallylated (90%), resulting in the synthesis of another duplex with a shorter double-ligation.[13] The α-CD has been selected in this introductory piece of work for symmetry reasons, but the extension to the β-CD is obvious and is currently underway. The easily available blocks **4**[§] and **6**[¶] are also starting molecules for the potential preparation of larger cyclic oligomers, such as CD triplex and tetraplex.

Compound **1** can be viewed as a novel type of CD based neoglycolipid,[14] presenting some similarity with the natural macrocyclic tetraethers found in the membranes of extreme thermoacidophilic Archaea, in which two polyols are linked together through two isoprenoïd chains. Indeed, the olefin metathesis approach has previously been used to synthesise either archaeal macrocyclic membrane lipids[15] or models.[16]

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¶ Selected data for **6**: $[\alpha]_D^{23}$ +33 (*c* 1, $CHCl_3$). MS (MALDI-TOF): *m*/*z* (%): 4959.3 (100) [*M*Na+]. ^1H NMR (400 MHz, $CDCl_3$, TMS): 7.31–7.17 (m, 160H, CH_{arom}), 5.49 (d, $^3J_{1,2}=3.6$ Hz, 2H, 2 H_1), 5.46 (d, $^3J_{1,2}=3.6$ Hz, 2H, 2 H_1), 5.39 (d, $^2J=10.7$ Hz, 2H, 2 CHPh), 5.34 (d, $^2J=10.7$ Hz, 2H, 2 CHPh), 5.25 (d, $^2J=10.7$ Hz, 2H, 2 CHPh), 5.18 (d, $^2J=11.0$ Hz, 2H, 2 CHPh), 5.02 (d, $^2J=11.2$ Hz, 2H, 2 CHPh), 5.02 (d, $^3J_{1,2}=3.4$ Hz, 2H, 2 H_1), 4.97–4.83 (m, 18H, 6 H_1, 12 CHPh), 4.74 (d, $^2J=12.2$ Hz, 2H, 2 CHPh), 4.69 (d, $^2J=12.2$ Hz, 2H, 2 CHPh), 4.60–4.34 (m, 38H, 38 CHPh), 4.25–4.07 (m, 20H), 4.04–3.82 (m, 26H), 3.74 (m, 4H, 4 H_6), 3.66 (m, 4H, 4 H_6), 3.58 (m, 4H, $^3J_{2,3}=9.5$ Hz, $^3J_{2,3}=9.7$ Hz, 4 H_2), 3.55–3.42 (m, 14H, 8 H_2, 4 H_6, 2 -CH_2-CH_2-CH_2-$\underline{CH_2}$-O), 3.21 (dt, $^2J=15.7$ Hz, $^3J=7.1$ Hz, 2H, -CH_2-CH_2-CH_2-$\underline{CH_2}$-O), 2.71 (br t, $^3J_{OH,6}=$ 5,4 Hz, 2H, 2*OH), 1.8–1.7 (m, 2H, 2 -$\underline{CH_2}$-CH_2-CH_2-CH_2-O), 1.55–1.45 (m, 4H, 2 -CH_2-CH_2-$\underline{CH_2}$-CH_2-O, 2 -$\underline{CH_2}$-CH_2-CH_2-CH_2-O), 1.3–1.2 (m, 4H, 2 -CH_2-CH_2-$\underline{CH_2}$-CH_2-O, 2 -CH_2-$\underline{CH_2}$-CH_2-CH_2-O), 1.1–1.0 (m, 2H, 2 -CH_2-$\underline{CH_2}$-CH_2-CH_2-O). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 139.35, 139.3 (4 C_{ipso}), 139.2 (4 C_{ipso}), 139.15, 139.1, 138.5, 138.35, 138.3, 138.2, 138.15, 138.1, 138.05, 137.95, 137.90, 137.85 (24 C_{ipso}), 128.3–126.7 (160 CH_{arom}), 98.8, 98.3, 98.1, 97.95, 97.9, 97.85 (12 C_1), 81.3, 81.2, 81.1, 80.0, 80.75, 80.7, 80.65, 80.1, 79.9, 79.8 (20 CH), 79.4, 79.2, 79.1, 78.9, 78.5, 78.0 (12 C_2), 76.1 (2 $\underline{CH_2}$Ph), 75.9 (2 CH), 75.85, 75.75 (4 $\underline{CH_2}$Ph), 74.7 (4 $\underline{CH_2}$Ph), 73.35, 73.3 (4 $\underline{CH_2}$Ph), 73.25 (4 $\underline{CH_2}$Ph), 73.1, 73.05, 72.9, 72.8 (8 $\underline{CH_2}$Ph), 72.4 (4 $\underline{CH_2}$Ph), 72.1 (2 $\underline{CH_2}$Ph), 71.75, 71.7, 71.6, 71.4, 71.25, 71.2 (12 C_5), 69.5, 69.3, 69.25, 69.2, 68.9, 69.85 (12 C_6), 61.4 (2 -CH_2-CH_2-CH_2-$\underline{CH_2}$-O), 29.9 (2 -CH_2-CH_2-$\underline{CH_2}$-CH_2-O), 29.8 (2 -CH_2-$\underline{CH_2}$-CH_2-CH_2-O), 29.6 (2 -$\underline{CH_2}$-CH_2-CH_2-CH_2-O). Anal. calcd for $C_{304}H_{326}O_{60}$: C, 73.92; H, 6.65. Found: C, 73.78; H, 6.83.

References

1. Szetjli, J. *Chem. Rev.* **1998**, *98*, 1743–1753.
2. Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803–822.
3. Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1917.
4. For examples, see: (a) Baugh, S. D. P.; Yang, Z.; Leung, D. K.; Wilson, D. M.; Breslow, R. *J. Am. Chem. Soc.* **2001**, *123*, 12488–12494; (b) van Bommel, K. J. C.; de Jong, M. R.; Metselaar, G. A.; Verboom, W.; Huskens, J.; Hulst, R.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. *Chem. Eur. J.* **2001**, *7*, 3603–3615; (c) Liu, Y.; Chen, Y.; Li, B.; Wada, T.; Inoue, Y. *Chem. Eur. J.* **2001**, *7*, 2528–2535; (d) Liu, Y.; You, C.; Li, B. *Chem Eur. J.* **2001**, *7*, 1281–1288; (e) Liu, Y.; Li, B.; You, C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2001**, *66*, 225–232; (f) Charbonnier, F.; Marsura, A.; Roussel, K.; Kovács, J.; Pintér, I. *Helv. Chim. Acta* **2001**, *84*, 535–551; (g) Edwards, W. B.; Reichert, D. E.; d'Avignon, D. A.; Welch, M. J. *Chem. Commun.* **2001**, 1312–1313; (h) De Jong, M. R.; Engbersen, J. F. J.; Huskens, J.; Reinhoudt, D. N. *Chem. Eur. J.* **2000**, *6*, 4034–4040; (i) Liu, Y.; You, C.; Wada, T.; Inoue, Y. *Tetrahedron Lett.* **2000**, *41*, 6869–6873; (j) Chiu, S.; Myles, D. C.; Garell, R. L.; Stoddart, J. F. *J. Org. Chem.* **2000**, *65*, 2792–2796; (k) Yamamura, H.; Yamada, S.; Kohno, K.; Okuda, N.; Araki, S.; Kobayashi, K.; Katakai, R.; Kano, K.; Kawai, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2943–2948; (l) Liu, Y.; You, C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 3630–3634; (m) Liu, Y.; You, C.; Chen, Y.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 7781–7787; (n) Liu, Y.; Han, B.; Sun, S.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 1487–1493; (o) French, R. R.; Wirz, J.; Woggon, W. *Helv. Chim. Acta* **1998**, *81*, 1521–1527; (p) Liu, Y.; Han, B.; Li, B.; Zhang, Y.; Zhao, P.; Chen, Y.; Wada, T.; Inoue, Y. *J. Org. Chem.*, **1998**, *63*. 1444–1454; (q) Breslow, R.; Yang, Z.; Ching, R.; Trojandt, G.; Odobel, F. *J. Am. Chem. Soc.* **1998**, *120*, 3536–3537; (r) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1997**, *119*, 1676–1681; (s) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1996**, *118*, 8495–8496; (t) Descheneaux, R.; Greppi, A.; Ruch, T.; Kriemler, H.; Raschdorf, F.; Ziessel, R. *Tetrahedron Lett.* **1994**, *35*, 2165–2168; (u) Jiang, T.; Lawrence, D. S. *J. Am. Chem. Soc.* **1995**, *117*, 1857–1858; (v) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353–9354; (w) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1992**, *114*, 5882–5883; (x) Breslow, R.; Greenspoon, N.; Guo, T.; Zarzycki, R. *J. Am. Chem. Soc.* **1989**, *111*, 8296–8297; (y) Fujita, K.; Ejima, S.; Imoto, T. *Chem. Lett.* **1985**, 11–12; (z) Fujita, K.; Ejima, S.; Imoto, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1277–1278.
5. (a) Sasaki, K.; Nagasaka, M.; Kuroda, Y. *Chem. Commun.* **2001**, 2630–2631; (b) Breslow, R.; Halfon, S.; Zhang, B. *Tetrahedron* **1995**, *51*, 377–388; (c) Brelow, R.; Chung, S. *J. Am. Chem. Soc.* **1990**, *112*, 9659–9660; (d) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614–1615.
6. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325–1357.
7. Bonnet, P.; Jaime, C.; Morin-Allory, L. *J. Org. Chem.* **2001**, *66*, 689–692.
8. Okabe, Y.; Yamamura, H.; Obe, K.; Ohta, K.; Kawai, M.; Fujita, K. *J. Chem. Soc., Chem. Commun.* **1995**, 581–582.

9. Pearce, A. J.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3610–3612.
10. Sato, T.; Nakamura, H.; Ohno, Y. *Carbohydr. Res.* **1990**, *199*, 31–35.
11. Each intermediate **3**–**8** has been isolated in pure form and presents data (^{1}H NMR, mass spectrum, and elemental analysis) in agreement with the structure.
12. Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259–1261.
13. This work has been presented as a poster: Lecourt, T.; Mallet, J.-M.; Sinaÿ, P. Synthesis of a duplex α-CD using olefin metathesis, XIth European Carbohydrate Symposium, Lisboa (Portugal), September 2–7 2001, p. 251.
14. Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F. *J. Am. Chem. Soc.* **1990**, *112*, 3860–3868.
15. Arakawa, K.; Eguchi, T.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 4741–4745.
16. Espinola, C. G.; Pérez, R.; Martin, J. D. *Org. Lett.* **2000**, *2*, 3161–3164.