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Note

Synthesis of benzylated cycloisomaltotetraose

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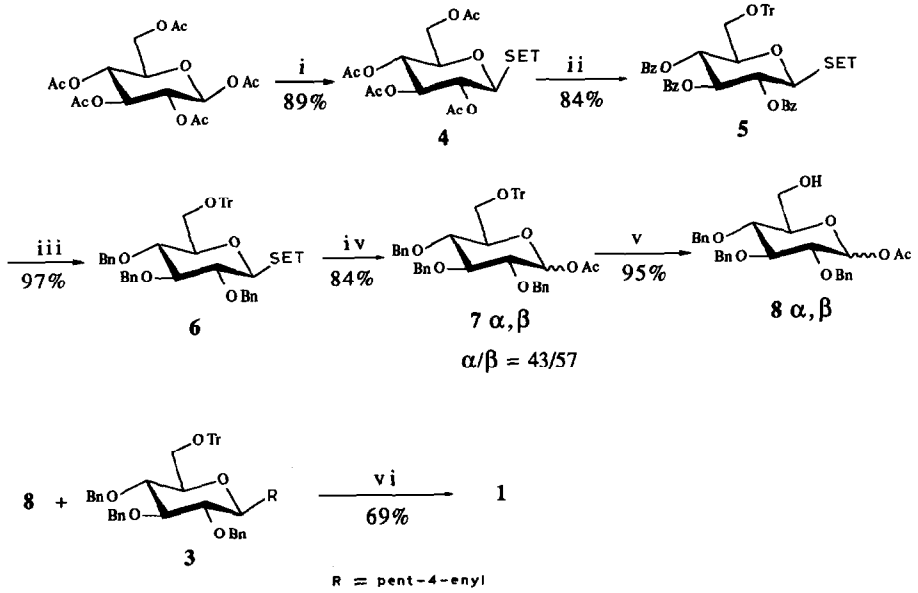
Chemical synthesis of cyclic macroethers containing glycosidic residues is an exciting but difficult challenge. Apart from the enzymic biosynthesis of cyclodextrins[1], which can provide large amounts of such natural products at a reasonable cost, there is no really efficient method available to the carbohydrate chemist because of the great number of steps necessary for such a synthesis[2–7]. The cyclization step is often, but not always[3], the main limitation for good yields. This depends on the fact that cyclization is simply an intramolecular glycosylation reaction based on more or less classical methods. Therefore, the reaction of cyclization versus lengthening of the oligosaccharide chain of the precursor is chiefly controlled by the concentration of the reaction mixture. High dilution is unfavorable to intermolecular glycosidic coupling. In this report, we describe the synthesis and characterization of the cyclic tetrasaccharide **2** having α-(1 → 6)-glycosidic linkages and D-glucopyranose residues (isomaltose series). The isomaltose derivative **1** was prepared from appropriate D-glucose derivatives, using the Fraser-Reid method for glycosylation. The glycosyl donor was pent-4-enyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-β-D-glucopyranoside[8] (**3**) and the glycosyl acceptor was 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (**8**) (Scheme 1).

The cyclo-glycosylation step was achieved by a modification of the procedure of Mukaiyama et al.[9], involving replacement of the Me_3Si ether by a trityl ether and treatment with $AgClO_4$–$SnCl_4$ (0.1 equiv) at room temperature (Scheme 2). We found that use of a trityl group instead of a trimethylsilyl group in the primary position of the acceptor was very profitable in our case[10]. The high dilution conditions of the reaction probably drastically slow down the reaction rate and this gives time for the silylated acceptor to decompose before reacting. Practically no cyclized products were isolated with Me_3Si protection while a 40% yield was obtained with the trityl group. Only the α configuration was obtained.

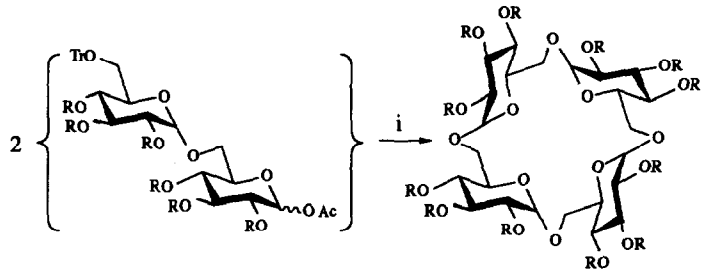
From a practical point of view, the use of trityl derivatives was also interesting because it allowed an easier identification of cyclic compounds compared to linear condensation products which give a yellow spot at the beginning of charring of the



Scheme 1. Synthesis of the linear dimer **1**. i. EtSH, $SnCl_4$, CH_2Cl_2. ii. (a) MeONa, MeOH; (b) TrCl, C_5H_5N; (c) BzCl. iii. (a) MeONa, MeOH; (b) BnBr, KOH, 18-cr-6, THF. iv. IDCP, AcOH, CH_2Cl_2. v. BF_3Et_2O, CH_2Cl_2–MeOH. vi. IDCP, $ClCH_2CH_2Cl$.

TLC plates. The reaction involves first a linear condensation of the dimer precursor, giving rise to the corresponding tritylated tetrasaccharide, followed by intramolecular cyclization. The reaction can be performed with either the α or the β anomer of **8**. No cyclic di- or hexa-saccharide has been detected.

As can be seen in the proton and carbon NMR spectra (Fig. 1) the structure of the tetrasaccharide **2** appears as completely symmetrical, giving rise only to the signals corresponding to the monomeric unit of the tribenzylated D-glucopyranose.



Scheme 2. i. $AgClO_4$–$SnCl_4$ in Et_2O, 4 days.

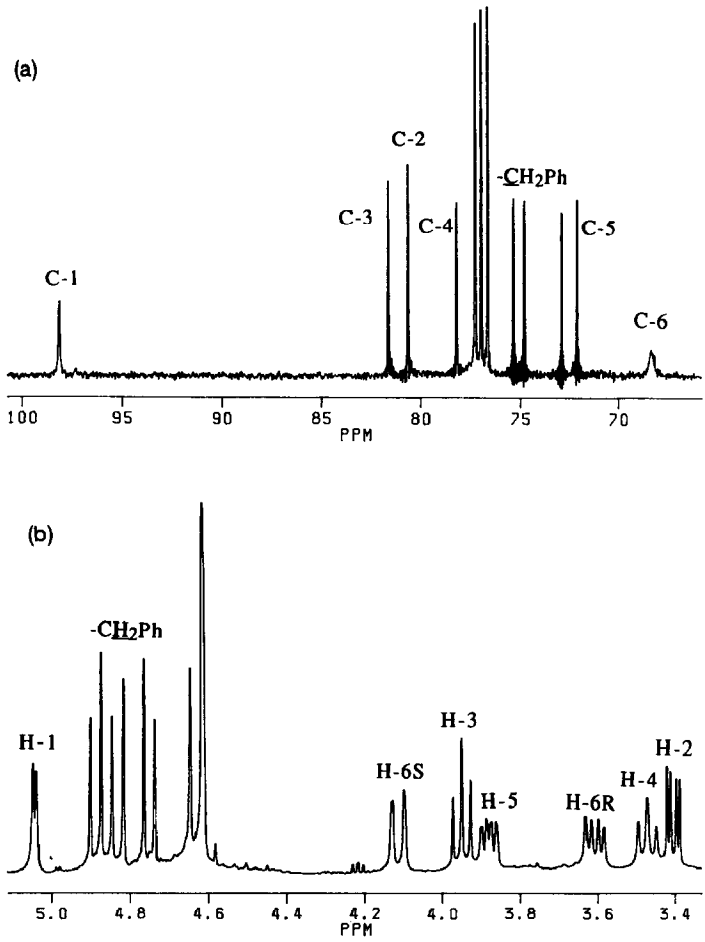


Fig. 1. ^{1}H and ^{13}C NMR spectra of **2**.

The signal assignments were obtained from 1D and 2D correlation experiments. A very good fit was observed for the chemical shifts of *O*-benzylated dextran with those for **2**[11]. Due to axial symmetry, NMR spectroscopy is unable to prove the tetrameric structure of **2**.

The FAB^{+}-mass spectrum was also disappointing in establishing the structure of **2** (Fig. 2). The peaks at *m/z* 865.2 [100%; $(M/2 + H)^{+}$] and 1862 [35%; $(M + Cs + H)^{+}$] can in fact be attributed to a cyclic dimer for the former and a tetramer associated with Cs^{+} ion for the latter. But those peaks could also be related, respectively, to a fragment ion coming from a tetramer giving no molecular ion (or a molecular ion of the cyclic dimer) and a dimeric association of cyclic dimers with Cs^{+}.

The DCI mass spectrum on the contrary showed clearly the presence of mainly one peak at *m/z* 1745 corresponding to the pseudomolecular ions $(M + NH_3)^{+}$. It is also the base peak.

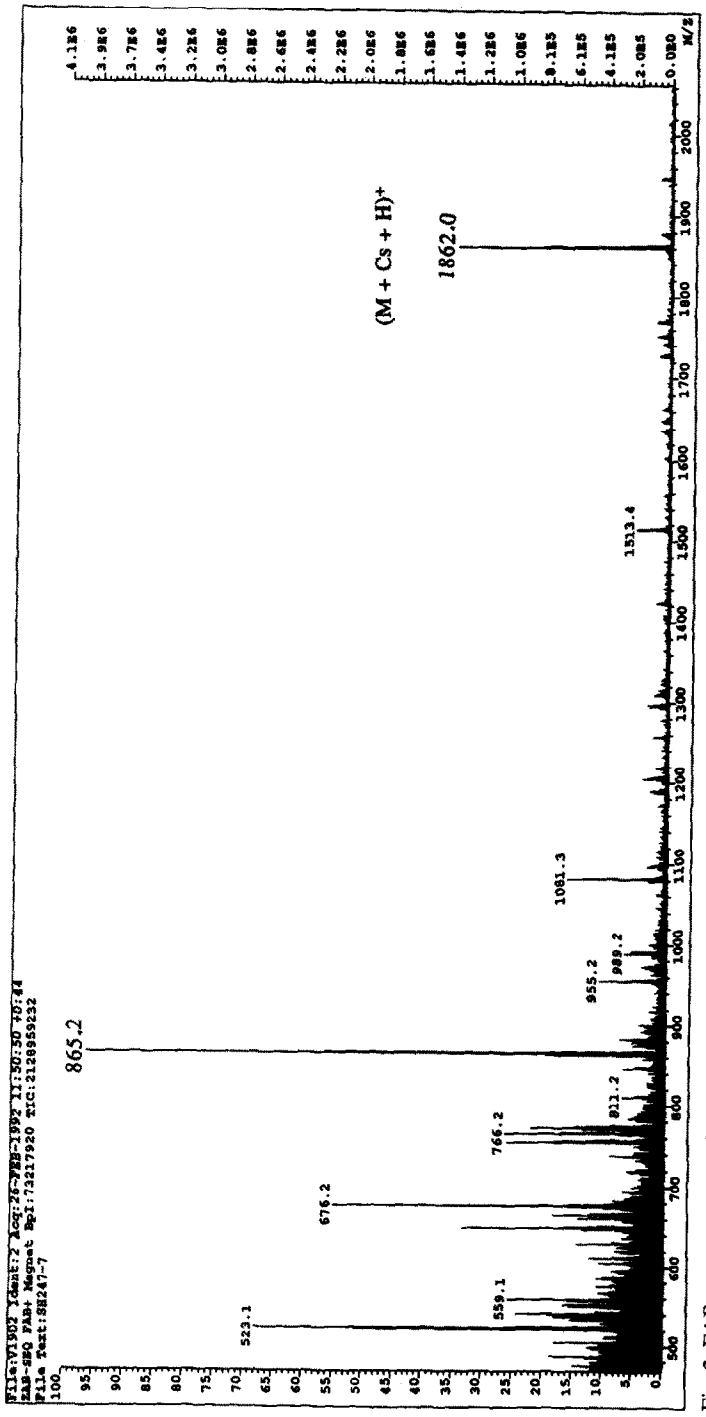


Fig. 2. FAB mass spectrum of 2. FAB: $CHCl_3$–3-$NO_2C_6H_4CH_2OH$ + CsI.

The conformational behaviour and complexation properties of **2** are under study.

EXPERIMENTAL

General methods.—All solvents were dried. The glycosylation reactions were conducted under N_2 and monitored by HPTLC (high performance TLC) on Silica Gel 60 (Merck, No. 5548), using 7:3 hexane–EtOAc and detection by charring with H_2SO_4. Flash column chromatography was performed on Silica Gel 60 (Merck, 70–230 mesh). HPLC was performed on a Merck apparatus (LC 6200) with refractive index detection, a home-packed column of SiO_2 (10 μm), and elution with 87:13 hexane–EtOAc at 2 mL/min. Merck HPLC equipment LC 6250 with an SiO_2 (7 μm) column (Hibar 250 × 25 mm) and refractometric detection was also used. The ^1H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Brüker AM400 spectrometer. Positive FAB mass spectra were recorded with a ZAB-SEQ(VG) spectrometer. DCI mass spectra were recorded with a NERMAG R10-10 spectrometer.

*Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-glucopyranoside* (**4**).—Penta-*O*-acetyl-β-D-glucopyranose (10 g, 25.6 mmol) dissolved in dry methylene chloride (50 mL) was treated with ethanethiol (2.27 mL, 30.7 mmol) and $SnCl_4$ (0.45 mL, 3.8 mmol). After 12 h, the solution was diluted with methylene chloride (100 mL), washed with satd aq $NaHCO_3$ and NaCl, dried (Na_2SO_4), and concentrated. The residue crystallized from EtOH to give **4** (8.95 g, 89%), mp 80°C. FAB$^+$-MS: *m/z* 415.1 $(M + Na)^+$, 393.1 $(M - H)^+$. NMR data ($CDCl_3$): ^1H, δ 1.27 (t, 3 H, CH_3CH_2S, J 7.43 Hz), 2.01, 2.03, 2.06, 2.08 (4 s, 12 H, OAc), 2.71 (m, 2 H, SCH_2CH_3), 3.71 (m, 1 H, $J_{4,5}$ 8.56 Hz, H-5), 4.13 (dd, 1 H, $J_{6a,6b}$ 12.24, $J_{5,6a}$ 1.64 Hz, H-6a), 4.25 (dd, 1 H, $J_{5,6b}$ 4.91 Hz, H-6b), 4.50 (d, 1 H, $J_{1,2}$ 10.04 Hz, H-1), 5.04 (t, 1 H, $J_{2,3}$ 9 Hz, H-2), 5.09 (t, 1 H, H-4), 5.23 (t, 1 H, $J_{3,4}$ 9 Hz, H-3); ^{13}C, δ 14.67 (CH_3CH_2S), 20.44, 20.58 (4 OAc), 24.02 (SCH_2CH_3), 62.00 (C-6), 68.16 (C-4), 69.66 (C-2), 73.74 (C-3), 75.71 (C-5), 83.35 (C-1), 169.25, 170.03, 170.49 (4 $COCH_3$). Anal. Calcd for $C_{16}H_{24}O_9S$: C, 48.98, H, 6.12; S, 8.16. Found: C, 48.97; H, 6.20; S, 7.89.

*Ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-trityl-1-thio-β-*D*-glucopyranoside* (**5**).—Compound **4** was deacetylated by the Zemplén method[12], tritylated, and then benzoylated[13] to give **5** (84%). FAB$^+$-MS: *m/z* 801.3 $(M + Na)^+$. NMR data ($CDCl_3$): ^1H, δ 1.38 (t, 3 H, J 7.44 Hz, CH_3CH_2S), 2.87 (m, 2 H, SCH_2CH_3), 3.27 (dd, 1 H, $J_{5,6a}$ 5.00, $J_{6a,6b}$ 10.65 Hz, H-6a), 3.36 (dd, 1 H, $J_{5,6b}$ 2.46 Hz, H-6b), 3.87 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, H-5), 4.83 (d, 1 H, $J_{1,2}$ 9.95 Hz, H-1), 5.59 (t, 1 H, $J_{2,3}$ 9–10 Hz, H-2), 5.63 (t, 1 H, $J_{3,4}$ 9–10 Hz, H-4), 5.81 (t, 1 H, H-3), 7.1–8.0 (m, 30 H, C_6H_5); ^{13}C, δ 15.14 (CH_3CH_2S), 24.00 (SCH_2CH_3), 62.54 (C-6), 69.26 (C-4), 70.71 (C-2), 74.40 (C-3), 78.02 (C-5), 83.45 (C-1), 126.7–133.1 (C_6H_5), 143.46 (CPh_3), 164.66, 165.12, 165.73 ($COCH_3$).

*Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-1-thio-β-*D*-glucopyranoside* (**6**).—Compound **5** was debenzoylated[12] and benzylated[14], and the product was purified by column

chromatography on silica gel to give **6** (97%). FAB$^+$-MS: *m/z* 243.1 $(Tr)^+$, 735.2 $(M - H)^+$, 869.1 $(M + Cs)^+$. NMR data ($CDCl_3$): ^1H, δ 1.41 (t, 3 H, CH_3CH_2S, *J*7.13 Hz), 2.88 (m, 2 H, S-CH_2CH_3), 3.22 (dd, 1 H, $J_{5,6a}$ 4.07 Hz, $J_{6a,6b}$ 10.15 Hz, H-6a), 3.43 (m, 1 H, H-5), 3.53–3.59 (m, 2 H, $J_{2,3}$ 9 Hz, H-2,6b), 3.66 (t, 1 H, $J_{3,4}$ 9 Hz, H-3), 3.81 (t, 1 H, $J_{4,5}$ 9 Hz, H-4), 4.37 (d, 1 H, CH_2Ph), 4.84 (d, 1 H, $J_{1,2}$ 9.40 Hz, H-1), 4.66–4.98 (5 d, 5 H, CH_2Ph), 6.8–7.6 (m, 30 H, C_6H_5). Anal. Calcd. for $C_{48}H_{48}O_5S$: C, 78.26; H, 6.52; S, 4.35. Found: C, 78.09; H, 6.42; S, 4.63.

1-O-Acetyl-2,3,4-tri-O-benzyl-6-O-trityl-β-D-glucopyranose (**7**).—Compound **6** (5.87 g, 7.97 mmol) was dissolved in methylene chloride (40 mL) with acetic acid (1.3 mL). The solution was stirred during 1 h in the presence of 4A molecular sieves (4 g), and iodonium dicollidine perchlorate (IDCP) was added in small portions. After 24 h, the mixture was diluted with methylene chloride (100 mL), filtered through a sintered glass funnel (No. 4), washed with aq sodium thiosulfate (10%), and co-evaporated with water and then toluene. The residual syrup was purified by chromatography on silica gel to give the anomeric mixture of **7** (4.9 g, 84%, $\alpha:\beta$ 43:57). The two anomers were separated by preparative HPLC. NMR data ($CDCl_3$): ^1H, δ (**7α**) 2.05 (s, 3 H, CH_3), 6.53 (d, 1 H, $J_{1,2}$ 3.49 Hz, H-1); (**7β**) 2.10 (s, 3 H, CH_3), 5.66 (d, 1 H, $J_{1,2}$ 7.90 Hz, H-1).

1-O-Acetyl-2,3,4-tri-O-benzyl-β-D-glucopyranose (**8β**).—Compound **7β** was detritylated[14] and the product purified by chromatography on silica gel to afford **8β** (95%). FAB$^+$-MS: *m/z* 515.3 $(M + Na)^+$. NMR data ($CDCl_3$): ^1H, δ 2.03 (s, 3 H, CH_3), 3.48 (ddd, 1 H, $J_{5,4}$ 8.09, $J_{5,6a}$ 3.93, $J_{5,6b}$ 2.36 Hz, H-5), 3.55 (t, 1 H, $J_{2,3}$ 8–9 Hz, H-2), 3.63 (t, 1 H, $J_{3,4}$ 8–9 Hz, H-4), 3.70 (dd, 1 H, $J_{6a,6b}$ 8.03 Hz, H-6a), 3.75 (t, 1 H, H-3), 3.84 (dd, 1 H, H-6b), 4.65–4.95 (6 d, 6 H, CH_2Ph), 5.63 (d, 1 H, $J_{1,2}$ 8.16 Hz, H-1), 7.2–7.4 (m, 15 H, C_6H_5).

1-O-Acetyl-2,3,4-tri-O-benzyl-6-O-(2,3,4-tri-O-benzyl-6-O-trityl-α,β-D-glucopyranosyl)-β-D-glucopyranose (**1α,β**).—Compounds **3** (683 mg, 0.90 mmol) and **8β** (464 mg, 0.94 mmol) were dissolved in dry 1,2-dichloroethane (10 mL). After addition of 4A molecular sieves, the mixture was stirred for 1.5 h under N_2. Then IDCP (824 mg, 1.8 mmol) was added in small portions during 3 h. After 24 h, the solution was diluted with methylene chloride (20 mL), washed with aq sodium thiosulfate (10%) and saturated aq NaCl, and co-evaporated with water and then toluene. The crude product was purified by flash chromatography on silica gel and the anomers were then isolated by HPLC, to give **1α** (488 mg, 46%) and **1β** (75 mg, 7%) *. FAB$^+$-MS: *m/z* 243.1 $(Tr)^+$, 1299.4 $(M + Cs)^+$. NMR data ($CDCl_3$) for **1α**: ^1H, δ 2.13 (s, 3 H, OAc), 3.14 (dd, 1 H, $J_{5',6'a}$ 4.23, $J_{6'a,6'b}$ 7.14 Hz, H-6'a), 3.45 (dd, 1 H, $J_{6'b,5'}$ 1.75 Hz, H-6'b), 3.48 (dd, 1 H, $J_{1,2}$ 3.63, $J_{2,3}$ 9.15 Hz, H-2), 3.65 (dd, 1 H, $J_{1',2'}$ 3.59, $J_{2',3'}$ 9.61 Hz, H-2'), 3.68 (dd, 1 H, $J_{3',4'}$ 8.86, $J_{4',5'}$ 10.11 Hz, H-4'), 3.80 (2 H, $J_{6a,6b}$ 12 Hz, H-5',6a), 3.85–4.00 (5 H, H-5,4,3,3',6b), 4.3–5.0

* The same results were obtained from **8α**. So, the $\alpha:\beta$ mixture of **7** need not be separated, but the resulting mixture was more complicated and the separation became more difficult.

TABLE I

NMR data [a] for **2** (δ in ppm, J in Hz)

	H-1	H-2	H-3	H-4	H-5	H-6*R*	H-6*S*
δ	5.04	3.40	3.95	3.47	3.88	3.60	4.11
J	1,2	2,3	3,4	4,5	5,6*R*	5,6*S*	6*R*,6*S*
	3.51	9.55	8.9	10.0	5.95	1.6	−12.9
	C-1	C-2	C-3	C-4	C-5	C-6	CH_2Ph
δ	98.11	80.61	81.60	78.17	72.05	68.31	75.31
							74.75
							72.84
$^1J_{CH}$	1	2	3	4	5	6	CH_2Ph
	170.9	140.8	148.1	142.2	144.3	140.0	141.0

[a] Obtained for solutions in $CDCl_3$ at 318K.

(12 d, 12 H, CH_2Ph), 5.15 (d, 1 H, H-1′), 6.31 (d, 1 H, H-1), 6.8–7.5 (m, 45 H, C_6H_5); ^{13}C, δ 21.03 (OAc), 62.30 (C-6′), 65.31 (C-6), 70.42 (C-5′), 71.99 (CH_2Ph), 74.14 (CH_2Ph), 74.76, 75.16, 75.45, 75.67 (4 CH_2Ph), 79.05 (C-2), 80.30 (C-2′), 77.78 (C-4′), 89.81 (C-1), 97.26 (C-1′), 73.06, 76.61, 81.42, 81.67 (C-3, 3′,4,5), 126.7–138.6 (C_6H_5), 143.82 (CPh_3), 169.43 ($COCH_3$). NMR data ($CDCl_3$) for **1β**: ^1H, δ 2.15 (s, 3 H, OAc), 4.38 (d, 1 H, $J_{1',2'}$ 6.99 Hz, H-1′), 6.47 (d, 1 H, $J_{1,2}$ 3.51 Hz, H-1); ^{13}C, δ 20.97 (OAc), 62.38 (C-6′), 67.73 (C-6), 89.72 (C-1), 103.56 (C-1′), 143.80 (CPh_3), 169.12 ($COCH_3$).

Cyclization[9].—Compound **1α** (R_f 0.70; 7:3 hexane–EtOAc) (42.0 mg, 36.02 μmol) was dissolved in dry ether (8 mL). A solution of $AgClO_4$–$SnCl_4$ (3.6 μmol) in dry ether (0.5 mL) was then added and the mixture was kept at room temperature for 4 days. When the reaction was complete (TLC), the mixture was concentrated and subjected to flash column chromatography (95:5 to 65:35 petroleum ether–ethyl ether). Further purification of **2** by HPLC (83:17 hexane–EtOAc at 2 mL/min; retention time, 17.1 min) gave **2** (12.0 mg, 40%), R_f 0.51 (7:3 hexane–EtOAc). NMR data are given in Table I.

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