

An Improved Synthesis of Chacotriose

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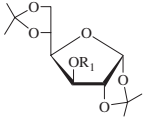
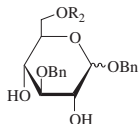
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Glycosylation using the trichloroacetimidate method was investigated in order to synthesize chacotriose. In a continuation of previous studies we present here a shorter approach to the synthesis of chacotriose, α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)]-D-glucopyranose.

The precise molecular structure of chacotriose represents a typical structural pattern of steroidal glycoalkaloids,¹ with a β -D-glucopyranosyl group as the first sugar attached to a steroid, which in turn is glycosylated with two α -L-rhamnopyranose units substituted at the 2- and 4-positions. The many properties of the glycosteroids²⁻⁵ and the difficulty of obtaining them in great quantity drew our attention. In a previous publication,⁶ we described the preparation of the peracetylated chacotriose, while herein we report an improved approach to the synthesis of this type of trisaccharide.

The previous synthesis of peracetylated chacotriose⁶ consisted of 13 steps starting from 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose.⁷ We initially undertook to reduce this number, particularly in the preparation of glycosyl acceptor. The strategy adopted was to partially protect the glucose unit leaving only the 2- and 4-hydroxy groups available for the glycosylation reaction with the two L-rhamnopyranose units.

Table 1. Preparation of glycosyl acceptor

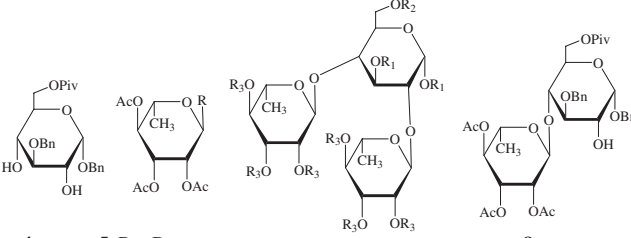
			
	R ₁		R ₂
1	H	3	3:1
2	Bn	4	1:0

Compound **4** was prepared in 3 steps (Table 1) starting from 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose **1**.⁷ Compound **2** was prepared by condensing **1** with benzyl bromide⁸ in 83% yield. Removal of the isopropylidene groups with 3:2 AcOH–H₂O followed by selective protection of the anomeric hydroxyl with benzyl alcohol in the presence of acetyl chloride⁹ afforded compound **3** (71% yield). Position 6 was then selectively protected with pivaloyl chloride¹⁰ in pyridine to give the benzyl 3-*O*-benzyl-6-*O*-pivaloyl- α -D-glucopyranoside **4** in 82% yield.

The 2- and 4-hydroxy groups of glucose acceptor **4** were glycosylated (Table 2) following two methods: either with 2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl bromide (**5**)¹¹ by using AgOTf as promoter,¹² or with the 2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl trichloroacetimidate (**6**)¹³ by using BF₃–Et₂O as promoter¹⁴ to give the fully protected chacotriose **7a**. The vari-

ous attempts showed that the proportion of disaccharide **8** is important except when using the BF₃–Et₂O at a temperature of –60 °C (Entry 4).

Table 2. Regiospecific glycosylation of compound **4**

				
4	5 : R = Br 6 : R = OC(NH)CCl ₃	7a : R ₁ = Bn, R ₂ = Piv, R ₃ = Ac 7b : R ₁ = H, R ₂ = Piv, R ₃ = Ac 7c : R ₁ = R ₂ = R ₃ = Ac	8	
Run	Donnor	Temp/°C	Yield 7a /%	7a-8
1	5 ^a	20	45	63–37
2	6 ^b	–20	29	37–63
3	6 ^b	–40	53	72–28
4	6 ^b	–60	74	100–0

^a AgOTf was used. ^b BF₃ Et₂O was used.

Glycosylation of glucose derivative **4** with 2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl bromide (**5**)¹¹ in the presence of AgOTf by the method of Hanessian and Banoub¹² mainly provided the desired di-*O*-glycosylated product **7a** (45% yield). However the disaccharide 4-*O*-glycosylated product **8** was also obtained in 27% yield while no 2-*O*-glycosylated product was isolated. The ¹³C NMR spectrum of **8** showed two anomeric carbons at δ 100.2 and 97.1 ppm and a HMBC experiment indicated a correlation between C-1 of the rhamnose unit and H-4 of the glucose unit indicating (1 $\rightarrow$ 4) glycosylation in **8**.

To increase the yield, we have used another glycosylation method described by Schmidt.¹⁴ Glycosylation of diol **4** with 2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl trichloroacetimidate (**6**)¹³ under the promotion of BF₃–Et₂O (Table 2, Runs 2–4) provided a mixture of tri and disaccharide (**7a** and **8**, respectively). As the temperature was decreased, the yield of the 4-*O*-glycosylated product diminished until, at –60 °C, we did not observe the disaccharide and we obtained the desired protected chacotriose¹⁵ in 74% yield.

Protected trisaccharide **7a** was treated with hydrogen in the presence of Pd/C (10%) to give **7b** and then with NaOH to remove the benzyl and acetyl groups and subsequently acetylated to give the desired peracetylated chacotriose **7c**.¹⁶

In conclusion, we have devised an improved method for the synthesis of chacotriose starting from the 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose with a total yield of 17%. In order to

establish structure-activity relations, our objective is now to synthesize some chactriose analogues.

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- 14 R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem.*, **50**, 21 (1994).
- 15 Benzyl-2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-[2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)]-3-*O*-benzyl-6-*O*-pivaloyl- α -D-glucopyranoside (**7a**): white solid. 74% yield. mp 91–95 °C; $[\alpha]_D^{26} -5.7^\circ$ (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ **glucose** 4.98 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1), 4.91, 4.32 (2d, 2H, CH₂-Ph), 4.76, 4.55 (2d, 2H, CH₂-Ph), 4.45 (dd, 1H, $J_{5,6a} = 2.2$ Hz, $J_{6a,6b} = 12.4$ Hz, H-6a), 4.22 (dd, 1H, $J_{5,6b} = 3.3$ Hz, H-6b), 4.01 (t, 1H, $J_{3,4} = 9.3$ Hz, H-3), 3.90 (m, 1H, H-5), 3.78 (t, 1H, $J_{4,5} = 9.1$ Hz, H-4), 3.71 (dd, 1H, $J_{2,3} = 9.6$ Hz, H-2), 2.21–2.03 (3s, 9H, CH₃), **rhamnose** 5.32 (dd, 1H, $J'_{3,4} = 10.0$ Hz, H'-3, *Rh*-(1 $\rightarrow$ 2)), 5.23 (m, 2H, $J'_{2,3} = 3.5$ Hz, $J''_{3,4} = 9.2$ Hz, H'-2, H''-3), 5.16 (d, 1H, $J''_{2,3} = 3.4$ Hz, H''-2, *Rh*-(1 $\rightarrow$ 4)), 5.03 (t, 1H, $J'_{4,5} = 9.9$ Hz, H'-4), 5.00 (t, 1H, $J''_{4,5} = 9.7$ Hz, H''-4), 4.96 (m, 2H, H'-1, H''-1), 4.06 (m, $J'_{5,6} = 6.1$ Hz, H'-5), 3.70 (m, 1H, $J''_{5,6} = 6.4$ Hz, H''-5), 1.32–1.21 (6s, 18H, CH₃), 1.00 (d, 3H, H''-6), 0.92 (d, 3H, H'-6); ¹³C NMR (75 MHz, CDCl₃): δ **glucose** 170.3–169.0 (CO-), 139.2–127.6 (Ph), 100.3 (C-1), 81.1 (C-3), 79.6 (C-2), 76.1 (C-4), 76.0 et 69.8 (CH₂-Ph), 69.1 (C-5), 62.6 (C-6), 39.3 (CMe₃), 27.6 (CMe₃), **rhamnose** 97.2, 97.1 (C-1'), 71.1 (2 C-4), 70.2, 70.0, 69.9, 69.3 (C-2, C-3), 67.7, 67.3 (C-5), 22.0, 21.9 (CH₃-CO), 17.7, 17.5 (C-6). Anal. Calcd for C₄₉H₆₄O₂₁ (989.54): C, 59.51, H, 6.52. Found: C, 59.47, H, 6.50.
- 16 2,3,4-Tri-*O*-acetyl- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-[2,3,4-tri-*O*-acetyl- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)]-1,3,6-tri-*O*-acetyl-D-glucopyranose (**7c**): white solid. 79% yield (α/β 2:1); mp 95–98 °C; $[\alpha]_D^{25} +1.5^\circ$ (c 1.1, CHCl₃), ESI-Q-TOF-MS and ESI-Q-TOF-MS-MS: $[M+Na]^+$ m/z 874, $[M + Na - AcOH]^+$ m/z 814, $[M + Na - 2AcOH]^+$ m/z 754, $[M + Na - 2AcOH - C_{12}H_{16}O_7]^+$ m/z 482, $[M + Na - AcOH - C_{12}H_{16}O_7]^+$ m/z 542. Anal. Calcd for C₃₆H₅₀O₂₃ (850.78): C, 50.82, H, 5.92. Found: C, 50.76, H, 5.89%.