An Improved Synthesis of Chacotriose

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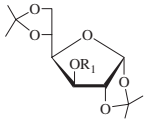
Glycosylation using the trichloroacetimidate method was investigated in order to synthetize chacotriose. In a continuation of previous studies we present here a shorter approach to the synthesis of chacotriose, α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-D-glucopyranose.

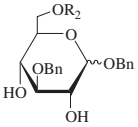
The precise molecular structure of chacotriose represents a typical structural pattern of steroidal glycoalkaloids,[1] with a β-D-glucopyranosyl group as the first sugar attached to a steroid, which in turn is glycosylated with two α-L-rhamnopyranose units substituted at the 2- and 4-positions. The many properties of the glycosteroids[2–5] 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 chacotriose[6] 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
1	H
2	Bn

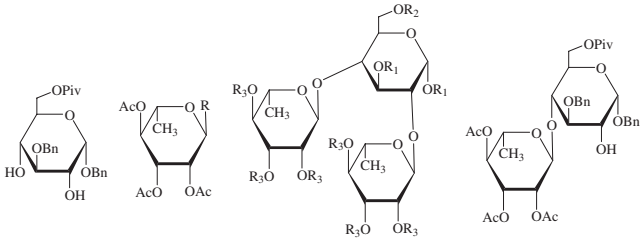


	α/*β*	R_2
3	3:1	H
4	1:0	Piv

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 bromide[8] in 83% yield. Removal of the isopropylidene groups with 3:2 AcOH–H_2O followed by selective protection of the anomeric hydroxyl with benzyl alcohol in the presence of acetyl chloride[9] afforded compound **3** (71% yield). Position 6 was then selectively protected with pivaloyl chloride[10] 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 BF_3–Et_2O as promoter[14] to give the fully protected chacotriose **7a**. The various attempts showed that the proportion of disaccharide **8** is important except when using the BF_3–Et_2O 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] BF_3 Et_2O 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 Banoub[12] 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 ^{13}C 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→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 BF_3–Et_2O (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 chacotriose[15] 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 chacotriose analogues.

References and Notes

1 H. Ripperger and K. Schreiber, The Alkaloids, Academic Press, New York (1981), Vol. 9, p 81.
2 K. W. Kuo, S. H. Hsu, Y. P. Li, W. L. Lin, L. F. Liu, L. C. Chang, C. C. Lin, C. N. Lin, and H. M. Sheu, *Biochem. Pharmacol.*, **60**, 1865 (2000).
3 J. G. Roddick, M. Weissenberg, and A. L. Leonard, *Phytochemistry*, **56**, 603 (2000).
4 B. E. Cham and B. Daunter, *Cancer Lett.*, **55**, 221 (1990).
5 T. Ikeda, H. Miyashita, T. Kajimoto, and T. Nohara, *Tetrahedron Lett.*, **42**, 2353 (2001); Y. Du, G. Gu, G. Wei, Y. Hua, and R. J. Linhardt, *Org. Lett.*, **5**, 3627 (2003).
6 M. Morillo, V. Lequart, E. Grand, G. Goethals, A. Usubillaga, P. Villa, and P. Martin, *Carbohydr. Res.*, **334**, 281 (2001).
7 I. Regnault, P. Villa, and G. Ronco, Fr. Patent 89 15985 (1989).
8 P. Y. Goueth, G. Ronco, and P. Villa, *J. Carbohydr. Chem.*, **13**, 679 (1994).
9 K. Takeo, M. Nahagen, Y. Taramoto, and Y. Nitta, *Carbohydr. Res.*, **201**, 261 (1990).
10 L. Jiang and T. K. Chan, *J. Org. Chem.*, **63**, 6035 (1998).
11 R. K. Ness, Jr., H. G. Fletcher, and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 296 (1951).
12 S. Hanessian and J. Banoub, *Adv. Chem. Ser.*, **39**, 36 (1976).
13 C. Li, B. Yu, and Y. Hui, *J. Carbohydr. Chem.*, **18**, 1107 (1999).
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→2)-[(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→4)]-3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranoside (**7a**): white solid. 74% yield. mp 91–95 °C; $[\alpha]_D^{26}$ −5.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ **glucose** 4.98 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.91, 4.32 (2d, 2H, *CH*$_2$-Ph), 4.76, 4.55 (2d, 2H, *CH*$_2$-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, *CH*$_3$), **rhamnose** 5.32 (dd, 1H, $J'_{3,4}$ = 10.0 Hz, H′-3, *Rh-(1→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→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, *CH*$_3$), 1.00 (d, 3H, H″-6), 0.92 (d, 3H, H′-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 170.3–169.0 (*C*O-), 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 (*CH*$_2$-Ph), 69.1 (C-5), 62.6 (C-6), 39.3 (*C*Me$_3$), 27.6 (C*Me*$_3$), **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 (*CH*$_3$-CO), 17.7, 17.5 (C-6). Anal. Calcd for $C_{49}H_{64}O_{21}$ (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→2)-[2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→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° (*c* 1.1, $CHCl_3$), 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 $C_{36}H_{50}O_{23}$ (850.78): C, 50.82, H, 5.92. Found: C, 50.76, H, 5.89%.

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