Pergamon

Tetrahedron Letters 43 (2002) 7271–7272

TETRAHEDRON LETTERS

An efficient diastereoselective synthesis of β-1-formyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside

Frédéric Labéguère,* Jean-Pierre Lavergne and Jean Martinez

Laboratoire des Aminoacides, Peptides et Protéines, UMR-CNRS 5810-Université Montpellier II, Place E. Bataillon, 34095 Montpellier cedex 5, France

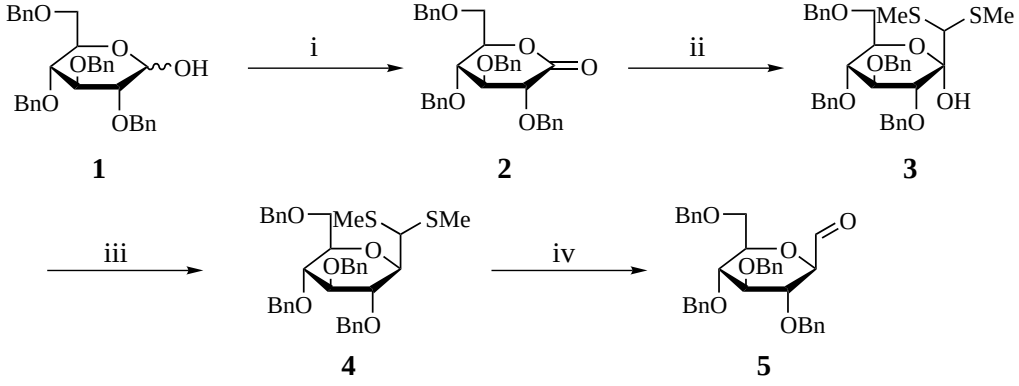
Accepted 18 July 2002

Abstract—A diastereoselective synthesis of β-1-formyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside in four steps, using an umpolung Seebach reaction is described.

In recent years, *C*-glycosides have been the subject of considerable interest in carbohydrate chemistry, as well as in organic synthesis. Several natural products contain *C*-glycosidic linkages.[1–3] Moreover, *C*-glycosides are a readily accessible source of chiral synthons possessing more carbons than *O*-glycosides.[4] Because of the stability of the carbon–carbon bond involved, they are convenient and stable analogues of hetero-glycosides for enzymatic and metabolic studies.[5,6] Thus, gaining access to various *C*-glycosides as building blocks in a diastereoselective fashion is of major interest.

Towards the goal, *C*-glycosylaldehydes constitute attractive templates since they can be substrates in various reactions like alkylation, oxidation, reduction or Wittig-type condensations. However, their synthesis is often arduous or affords α and β anomeric mixture,[7–10] which is a limitation in their utilisation.

In order to develop new diastereoselective syntheses of *C*-glycosyl-α-aminoacids, we needed formyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside as glycosylacceptor. However, the synthesis of this glycosylaldehyde, described by Dondoni et al.,[8] is not easy and results in an anomeric mixture. For this reason, we developed a highly diastereoselective synthesis of 1-formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **5** in four steps from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1** with a good overall yield. Thus, commercially available **1** was



Scheme 1. *Reagents and conditions*: (i) DMSO, Ac_2O, rt, 12 h, 99%; (ii) $(MeS)_2CH_2$ (4 equiv.), *n*-butyllithium (4 equiv.), THF, −60°C, 5 h, 74%; (iii) $BF_3{\cdot}Et_2O$ (3 equiv.), Et_3SiH (3 equiv.), CH_2Cl_2, −78°C, 5 min, then rt, 3 h; (iv) MeI (10 equiv.), $CaCO_3$ (3 equiv.), CH_3CN/H_2O (5/1), rt, 72 h.

* Corresponding author. Tel.: +33 (0) 467 143 981; fax: +33 (0) 467 144 866; e-mail: flabeguere@wanadoo.fr

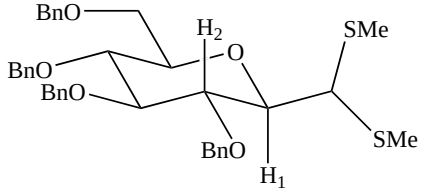
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01477-6

converted into 1-bis(methylthio)methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **3** according to the method described by Fukase et al.[11] The β pure glycosylaldehyde **5** was obtained as the only β anomer after two additional steps. The synthetic pathway is outlined in Scheme 1.

2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone **2** was obtained by oxidation of **1**.[12] After completion, addition of water and extraction with ethyl acetate was sufficient to obtain **2** in 99% yield without any further purification. The second step, described by Fukase,[11] was the umpolung Seebach reaction of **2** with bis-(methylthio)methyl carbanion. Fukase obtained 1-*C*-[bis(methylthio)methyl]-α-D-glucopyranose **3** in 80% yield by action of *n*-butyllithium on the corresponding bis(methylthio)methane using two equivalents of bis-(methylthio)methane and of *n*-butyllithium.[11] However, in our hands, these conditions afforded **3** in only 40% yield. Four equivalents of bis(methylthio)methane and *n*-butyllithium were needed to obtain **3** in 74% yield. The anomeric hydroxyl group of **3** was then stereospecifically reduced by triethylsilane[13] in the presence of boron trifluoride diethyl etherate to afford the single β anomer, β-1-bis(methylthio)methyl-tetra-*O*-benzyl-D-glucopyranoside **4**, in an excellent yield (99%). The β configuration was assigned by ^{1}H NMR spectroscopy by measuring a 8.9 Hz coupling constant between H_1 and H_2.[14] This value is representative of an axial/axial coupling, only possible with a β configuration and a chair C1 conformation (Fig. 1). Finally, dithiane alkylation and cleavage with methyl iodide and calcium carbonate[15] afforded the glycosylaldehyde **5**[16] whose data were identical to the β anomer described by Dondoni.[8]

It is noteworthy that compound **5** could be obtained in the same global yield by purifying only at the last step.

The facile synthesis of the 1-formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **5** in pure β anomeric form is an advance in *C*-glycosidic chemistry. We are now focusing on the diastereoselective synthesis of *C*-glycosyl-aminoacids using **5** as a building block.



4 $J_{1\text{-}2}$=8.9 Hz

Figure 1. β configuration and C1 conformation for **4**: the only possibility for an axial/axial coupling between H-1 and H-2.

Acknowledgements

This work was supported by the Ministère de l'Education Nationale, France.

References

1. Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett*. **1986**, *27*, 2145.
2. Okabe, T.; Nomoto, K.; Funabashi, H.; Okuda, S.; Suzuki, T.; Tanaka, N. *J. Antibiot. Ser*. **1985**, *38*, 1336.
3. Löffler, A.; Doucey, M.-A.; Jansson, A. M.; Müller, D.; de Beer, T.; Hess, D.; Meldal, M.; Richter, W.; Vliegenthart, J.; Hofsteenge, J. *Biochemistry* **1996**, *35*, 12005.
4. Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, 1983.
5. Shulman, M.; Svetlana, D.; Shiyan, S.; Khorlin, A. *Carbohydr. Res*. **1974**, *33*, 229.
6. Kate, W.; Tang, M.; Suzuki, T.; Kitajima, K.; Inoue, Y.; Inoue, S.; Fan, J.-Q.; Lee, Y. *J. Am. Chem. Soc*. **1997**, *46*, 11137.
7. Martin, O.; Khamis, F.; Rao, S. *Tetrahedron Lett*. **1989**, *30*, 6143.
8. Dondoni, A.; Schermann, M.-C. *Tetrahedron Lett*. **1993**, *34*, 7319.
9. Bertozzi, C.; Bernarski, M. *Tetrahedron Lett*. **1992**, *33*, 3019.
10. Reed, L.; Ito, Y.; Masamune, S.; Sharpless, K. *J. Am. Chem. Soc*. **1982**, *104*, 6468.
11. Fukase, H.; Horri, S. *J. Org. Chem*. **1992**, *57*, 3642.
12. Kuzuhara, H.; Fletcher, H., Jr. *J. Org. Chem*. **1967**, *32*, 2531.
13. Lewis, M.; Cha, J.; Kishi, Y. *J. Am. Chem. Soc*. **1982**, *104*, 4976.
14. Compound **4** was isolated by addition of water and extraction with ethylacetate. **4**: syrup, ^{1}H NMR (250, $CDCl_3$) δ: 2.11 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.39–3.54 (m, 2H, *H-6*, *H-6′*), 3.59–3.74 (m, 4H, *H-2*, *H-3*, *H-4*, *H-5*), 3.74 (dd, 1H, $J_{H\text{-}1,CH(SMe)(SMe)}$=1.6 Hz, $J_{H\text{-}1,H\text{-}2}$= 8.9 Hz, *H-1*), 3.92 (d, 1H, $J_{CH(SMe)(SMe),H\text{-}1}$=1.8 Hz, C$H(SMe)_2$), 4.50–4.96 (m, 8H, 4×C$H_2$Ph), 7.17–7.32 (m, 20H, 4×*Ph*).
15. Grobel, T.; Seebach, D. *Synthesis* **1977**, 357.
16. Compound **5** was isolated by silicagel column (9/1 petroleum ether/ethylacetate). Compound **5**: ^{1}H RMS: [FAB$^+$] $C_{35}H_{37}O_6$ theoretic mass: 553.2592, observed mass: 553.2590, ^{1}H NMR (250, $CDCl_3$) δ: 3.43–3.50 (m, 2H, *H-6*, *H-6′*), 3.56–3.81 (m, 4H, *H-2*, *H-3*, *H-4*, *H-5*), 4.53–4.92 (m, 9H, 4×CH_2Ph, *H-1*), 7.12–7.29 (m, 20H, 4×*Ph*), 9.61 (d, 1H, $J_{CHO,H\text{-}1}$=1.17 Hz, CHO).