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Convergent, Stereoselective Synthesis of the Caloporoside Disaccharide

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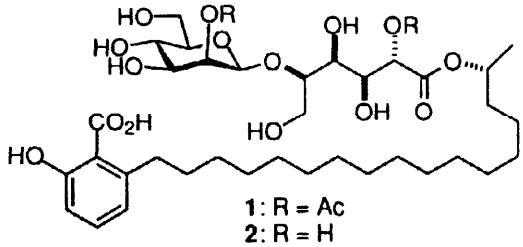
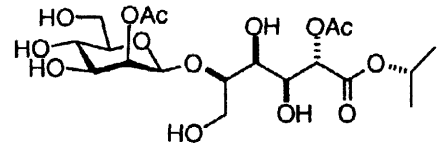
Abstract. A concise, convergent synthesis of the caloporoside disaccharide is described in which the key step involves direct, stereoselective formation of the β–mannosidic linkage by the sulfoxide method.

Keywords: carbohydrates; glycosidation; sulfoxides

Caloporoside (**1**) is a novel inhibitor of phospholipase C, that was isolated several years ago from *Caloporous dichrous* by Steglich and co-workers.[1] Desacetyl caloporoside (**2**), a further fungal metabolite, is reported to inhibit, *in vitro*, the binding of ^{35}S-labelled *t*-butylbicyclophosphorothionate to the $GABA_A$/benzodiazepine chloride channel receptor complex.[2] Both substances are characterized by the highly unusual β-(1→5)-linkage of a D-mannopyranoside unit to a D-mannonate ester. The stereoselective chemical synthesis of the β-mannopyranosidic linkage is a well-known problem in carbohydrate chemistry[3-5] and this, together with the interesting biological activity, has drawn our attention to these molecules, in particular to caloporoside with its additional requirement for regioselective esterification. A recent synthesis of **1**, by Fürstner,[6] which employs an indirect route to the β-mannoside unit prompts us to disclose here our synthesis of the caloporoside disaccharide **3**. The simpler desacetyl caloporoside (**2**) has been prepared by Tatsuda using a related, convergent route, but with a coupling selectivity of only 2:1 in favor of the β-anomer in the mannosylation step.[7]



1: R = Ac
2: R = H



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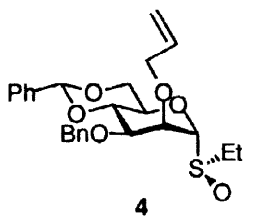
We have recently reported on a new direct method for the highly stereoselective synthesis of β–mannospyranosides.[3,8,9] The method, which is an evolution of Kahne's sulfoxide glycosidation protocol,[10,11] involves the *in situ* conversion of a mannosyl sulfoxide to an α-mannosyl triflate[12,13] which subsequently takes part in an S_N2-like reaction on exposure to a glycosyl acceptor. Our intended application of this strategy to the formation of the key β-mannopyranoside linkage permits **3** to be dissected into two subunits **4** and **5**, with **5** itself being readily derived from **4** by a simple three step protocol. The mannosyl sulfoxide **4**, which had previously served us well in our synthesis of the trisaccharide component of the *Hyriopsis schlegelii* Glycosphingolipid: β-D-Xyl-(1→2)-β-D-Man-(1→4)-α-D-Glc-OMe,[14,15] is therefore the precursor to both sections of the target making this a very convergent route.



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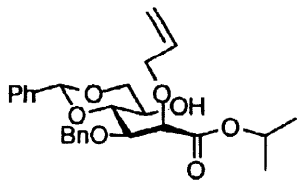

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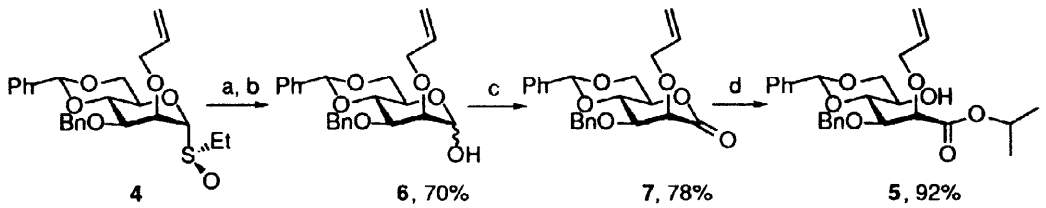
Thus, sulfoxide **4** was prepared as previously described[14,15] and exposed to triflic anhydride (Tf_2O) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at –78 °C in CH_2Cl_2 followed by quenching with wet Et_2O to give the pyranose **6** in 70% yield. Oxidation of **6** with tetrapropylammonium perruthenate (TPAP)[16] provided a 78% yield of the mannonolactone **7**, which on treatment with *iso*-propanol afforded the glycosyl acceptor **5** in 92% yield (Scheme 1).

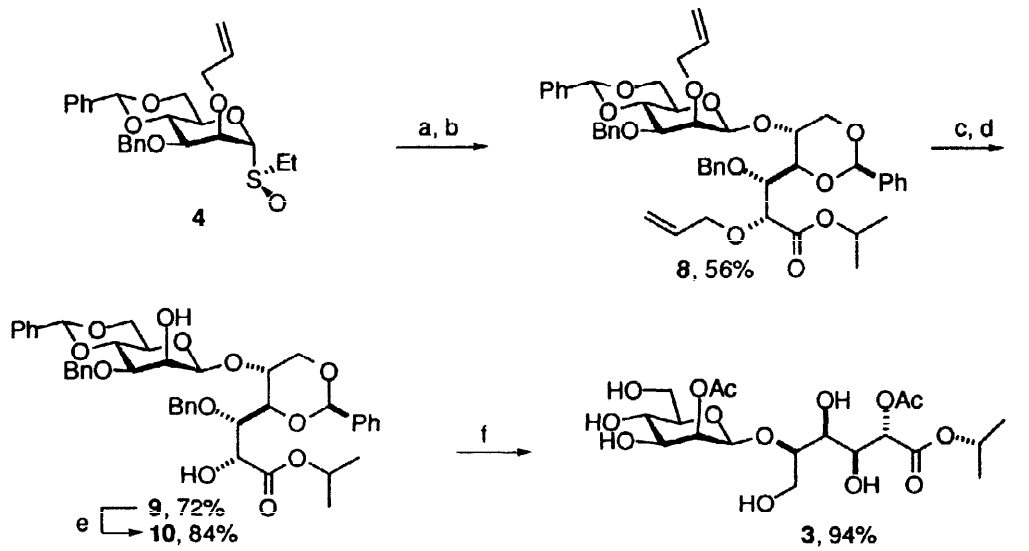


4 **6**, 70% **7**, 78% **5**, 92%

Scheme 1 (a) Tf_2O, DTBMP, CH_2Cl_2, -78 °C; (b) Et_2O/H_2O, -78 °C - 0 °C; (c) TPAP, CH_2Cl_2, rt; (d) *i*-PrOH, DMAP, rt, 48 h.

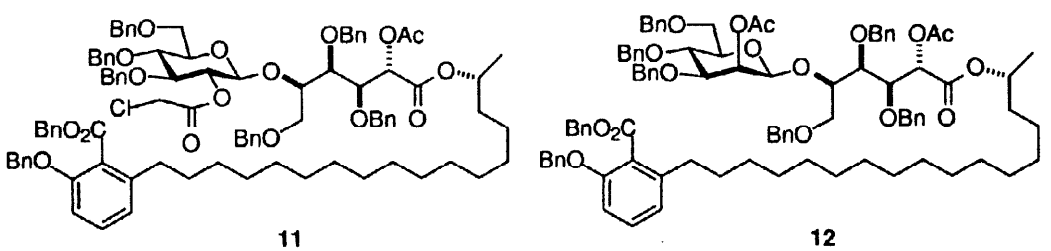
Coupling of **5** and **4** was achieved by activation of **4** at –78 °C in CH_2Cl_2 with Tf_2O and DTBMP, followed by addition of **5**. The disaccharide **8** was isolated in 56% yield in the form of a pure β-mannoside, whose stereochemistry was indicated by the typical upfield chemical shift (δ 3.24) of the *H*-5 resonance in the pyranoside ring[3] and subsequently confirmed by the $^1J_{CH}$ coupling[17] of 154.6 Hz between *C*-1 and *H*-1 in the same ring. The two allyl protecting groups were next removed by isomerization with $(MePh_2P)_2(COD)Ir^IPF_6$[18] and subsequent hydrolysis of the enol ethers with $HgCl_2/HgO$ in aqueous acetone giving the diol **9** in 72% yield. Acetylation then provided the diacetate **10**. Finally, hydrogenolytic removal

of the benzyl and benzylidene groups over Pearlman's catalyst in methanol led to the isolation of the target disaccharide **3** in excellent yield (Scheme 2).



Scheme 2 (a) Tf_2O, DTBMP, CH_2Cl_2, -78 °C; (b) **5**, -78 °C; (c) Ir(I) cat; (d) $HgO/HgCl_2$, acetone/water; (e) Ac_2O, DMAP, pyridine; (f) H_2, $Pd(OH)_2$, EtOH

This concise, direct synthesis of **3** is to be contrasted with the recent synthesis of Fürstner[6] in which the corresponding glucose based disaccharide **11** was prepared and then converted to **12** in a three step deprotection/activation/inversion sequence. Self-evidently, a highly stereoselective glycosylation reaction coupling two mannose units derived from a common precursor will always be more efficient than a protocol that couples glucose to mannose followed by a three step inversion protocol. Further progress toward the synthesis of **1**, by the direct β-mannosylation method, will be reported in due course.



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References

1. Weber, W.; Schu, P.; Anke, T.; Velten, R.; Steglich, W. *J. Antibiot.* **1994,** *47,* 1188-1194.
2. Shan, R.; Anke, H.; Nielsen, M.; Sterner, O.; Witt, M. R. *Nat. Prod. Lett.* **1994,** *4,* 171-178.
3. Crich, D.; Sun, S. *Tetrahedron* **1998,** *54,* 8321-8348.
4. Barresi, F.; Hindsgaul, O. Synthesis of β-D-Mannose Containing Oligosaccharides. In *Modern Methods in Carbohydrate Synthesis;* Khan, S. H.; O'Neill, R. A. Eds.; Harwood Academic Publishers: Amsterdam, 1996; pp. 251-276.
5. Kaji, E.; Lichtenthaler, F., W. *Trends in Glycosi. Glycotechnology* **1993,** *5,* 121-142.
6. Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998,** *63,* 3072-3080.
7. Tatsuta, K.; Yasuda, S. *Tetrahedron Lett.* **1996,** *37,* 2453-2456.
8. Crich, D.; Sun, S. *J. Org. Chem.* **1997,** *62,* 1198-1199.
9. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998,** *120,* 435-436.
10. Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989,** *111,* 6881-6882.
11. Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996,** *118,* 9239-9248.
12. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997,** *119,* 11217-11223.
13. Other mechanisms have also been demonstrated: Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998,** *120,* 5961-5969.
14. Crich, D.; Dai, Z. *Tetrahedron Lett.* **1998,** *53,* 1681-1684.
15. For the configuration at sulfur in these α-mannosyl sulfoxides see: Crich, D.; Mataka, J.; Sun, S.; Wink, D. J. *J. Chem. Soc., Chem. Commun.* **1998,** 0000-0000.
16. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994,** 639-666.
17. Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974,** 293-297.
18. Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc., Chem. Commun.* **1978,** 694-695.