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Convergent, Stereoselective Synthesis of the Caloporoside Disaccharide

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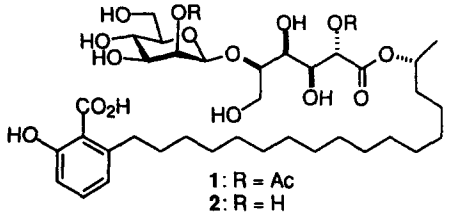
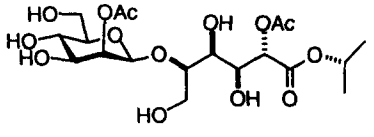
Abstract. A concise, convergent synthesis of the caloporoside disaccharide is described in which the key step involves direct, stereoselective formation of the β–mannosidic linkage by the sulfoxide method.

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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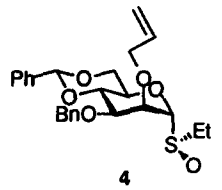
We have recently reported on a new direct method for the highly stereoselective synthesis of β-mannospyranosides.[3,8,9] The method, which is an evolution of Kahne's sulfoxide glycosidation protocol,[10,11] involves the *in situ* conversion of a mannosyl sulfoxide to an α-mannosyl triflate[12,13] which 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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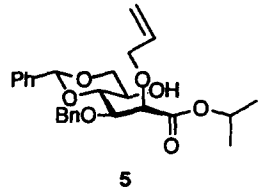

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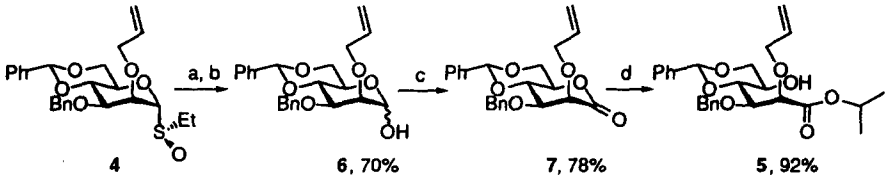
Thus, sulfoxide **4** was prepared as previously described[14,15] and exposed to triflic anhydride (Tf_2O) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at –78 °C in CH_2Cl_2 followed by quenching with wet Et_2O to give the pyranose **6** in 70% yield. Oxidation of **6** with tetrapropylammonium perruthenate (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).

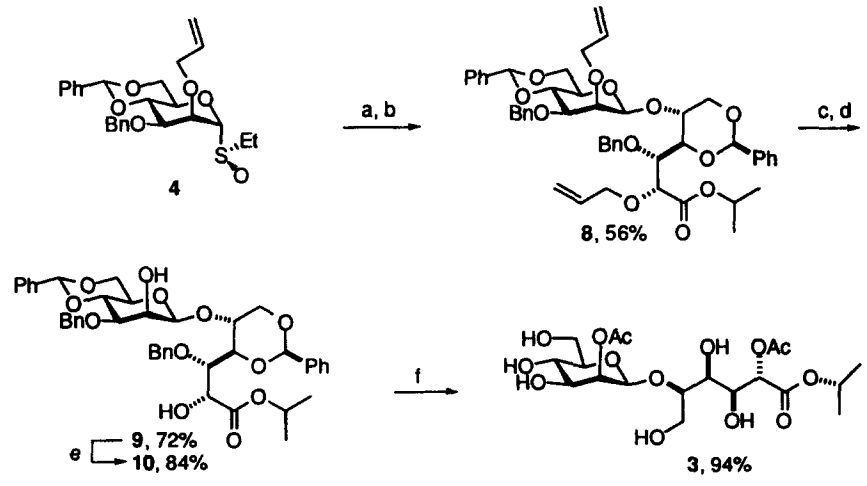


4 **6**, 70% **7**, 78% **5**, 92%

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.

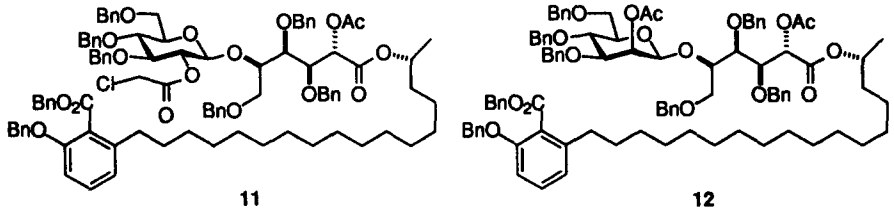
Coupling of **5** and **4** was achieved by activation of **4** at –78 °C in CH_2Cl_2 with Tf_2O and DTBMP, followed by addition of **5**. The disaccharide **8** was isolated in 56% yield in the form of a pure β-mannoside, whose stereochemistry was indicated by the typical upfield chemical shift (δ 3.24) 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.



11 **12**

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