Stereospecific debenzylative cycloetherification of carbohydrate-derived allylic alcohols, ethers and esters to form vinyl *C*-furanosides†

Riccardo Cribiù and Ian Cumpstey*

Received (in Cambridge, UK) 22nd November 2007, Accepted 28th January 2008
First published as an Advance Article on the web 7th February 2008
DOI: 10.1039/b718060h

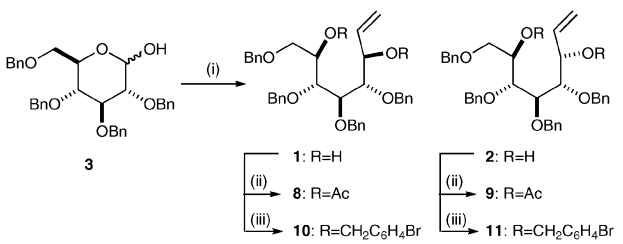
Benzyl ether protected polyhydroxylated alkene compounds containing allylic alcohol, ether or ester functionality undergo a stereospecific cyclisation reaction upon treatment with TFA–acetonitrile–toluene with inversion of configuration at the allylic position and loss of a benzyl ether to give tetrahydrofurans.

The occurrence of tetrahydrofuran (THF) motifs in a wide variety of natural products ensures a continuing interest in their synthesis.[1] Carbohydrates have been used as cheap and convenient starting materials[2] for the synthesis of highly substituted THFs, either as substructures of natural products[3] or as non-natural compounds with interesting properties.[4] *C*-furanosides, hydrolytically stable analogues of furanosides in which the exocyclic glycosidic oxygen is formally replaced by a methylene group resulting in a THF structure, are relevant in glycobiology. For example, galactofuranosides[5] or, very unusually, glucofuranosides[6] are components of bacterial polysaccharides, and structural analogues of these compounds could be used to investigate biochemical processes in bacteria, or possibly lead to new antibiotics.[7]

Our own interest in THF synthesis began with the observation that treatment of the partially protected unsaturated polyol **1** (easily obtained along with its C-1 epimer **2** by treatment of tetrabenzyl glucose **3** with vinylmagnesium bromide, Scheme 1[8]) with 90% aqueous TFA resulted in the formation of a major product, which was assigned the cyclic structure **4** (Table 1, entry 1; HMBC showed that the benzyl ether had been lost from O-4; for stereochemical assignment, see below). Similar debenzylative cyclisations have been reported before in iodoetherification reactions[9,10] or for cyclisation reactions onto good S_N2 leaving groups, *e.g.* sulfonates or epoxides.[11] Treatment of the epimer **2** under the same reaction conditions gave a major product, a different compound, that was also assigned a THF structure **5** (Table 1, entry 2). In both cases, a number of by-products were seen, but only a single stereoisomer of the respective THFs could be detected. The most significant by-products in both reactions, easily separable from the major products by column chromatography, were the THFs **6** and **7** (Fig. 1), differing in structure from the major products **4** and **5** by benzylation at O-5. This was proved by benzylation (NaH, BnBr, DMF) of THFs **4** and **5** to give compounds identical to **6** (94%) and **7** (87%), respectively. A mixture of inseparable compounds was also isolated. The NMR spectra of this mixture were inconclusive, but MS showed a peak at m/z 573, *i.e.* MNa^+ for M = 550, indicating the presence of an extra benzyl group, presumably arising from random substitution by the benzylic cation (generated on ring-closure) on the aromatic rings of the benzyl ethers. We concluded that to optimise this cyclisation reaction, we should try adding scavengers to remove this benzyl cation. However, while the addition of various scavengers did result in a decrease in the amount of benzylated by-products, it also led to excessive debenzylation (Table 1, entries 3–5). Using less acid (*e.g.* 70% TFA in water) gave less debenzylation but also a slower reaction.

After some experimentation, we discovered that treatment of **1** with 70% TFA in acetonitrile with 20 equiv. toluene gave the cyclised product **4** in good yield, with excellent purity after flash chromatography and with only traces of benzylated and debenzylated by-products seen on TLC (Table 1, entry 6). A mixture of 2- and 4-benzyltoluenes could be isolated, indicating that toluene was indeed acting as a scavenger. The epimeric diol **2** also underwent cyclisation under these conditions to give the diastereomeric THF **5** (Table 1, entry 7). The cyclisation reaction of **1** could be carried out on a 1 g scale under these conditions (Table 1, entry 8).

We then prepared the respective bis-acetate (**8** and **9**) and bis-*para*-bromobenzyl ether (**10** and **11**) derivatives of the two diols **1** and **2** (Scheme 1), and subjected these compounds to the same reaction conditions. In every case, a single cyclised product was formed, all in very good isolated yields (Table 1, entries 10–13). The stereochemical outcome of these reactions followed that of the parent diols, *i.e.* acetylation or *p*-bromobenzylation of **4** gave **12** (Ac_2O, py, 98%) or **14** ($BrCH_2C_6H_4Br$, NaH, DMF, 92%), while **5** gave **13** (Ac_2O, py, 94%) or **15** ($BrCH_2C_6H_4Br$, NaH, DMF, 88%).

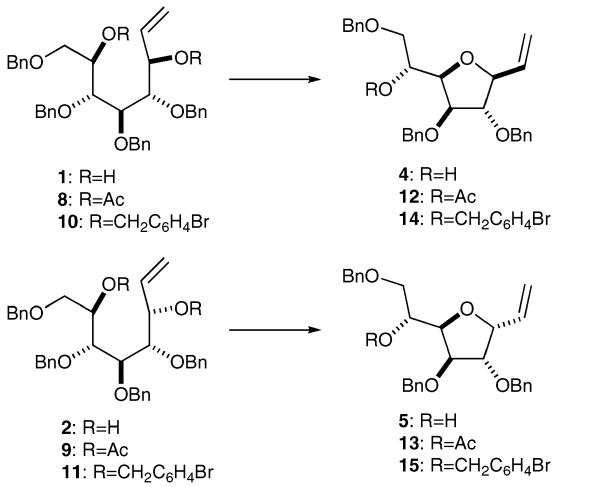


Scheme 1 *Reagents and conditions:* (i) vinylmagnesium bromide, THF, 0 °C → RT; **1**, 65%; **2**, 29%; (ii) Ac_2O, py, DMAP; **8**, 96%; **9**, 95%; (iii) $BrCH_2C_6H_4Br$, NaH, DMF; **10**, 94%; **11**, 94%.

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden. E-mail: cumpstey@organ.su.se; Fax: +46 (0)8 154908; Tel: +46 (0)8 674 7263

† Electronic supplementary information (ESI) available: Experimental details and spectra. See DOI: 10.1039/b718060h

Table 1 Cyclisation of glucose-derived compounds

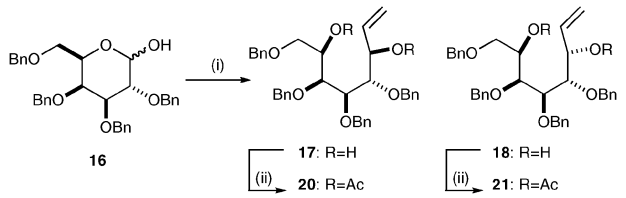


Entry	Starting material	R	Solvent[a]	Scavenger (equiv.)	t/h	Product (yield %)[b]
1	**1**	H	A	—	3	**4** (65)[c]
2	**2**	H	A	—	3	**5** (69)[c]
3	**1**	H	A	EtSH (10)	4	**4** (37)
4	**1**	H	B	PhMe (16)	3	**4** (34)
5	**1**	H	A	PhSMe (5)	0.5	—[d]
6	**1**	H	C	PhMe (20)	7.5	**4** (75)
7	**2**	H	C	PhMe (20)	8	**5** (76)
8	**1**	H	C	PhMe (20)	8	**4** (68)[e]
9	**1**	H	C	—	9	**4** (55)
10	**8**	Ac	C	PhMe (10)	5	**12** (80)
11	**9**	Ac	C	PhMe (10)	5	**13** (86)
12	**10**	PBB[f]	C	PhMe (10)	10	**14** (82)
13	**11**	PBB[f]	C	PhMe (10)	10	**15** (81)

[a] Solvent A: TFA–H_2O, 90 : 10; B: TFA–H_2O, 85 : 15; C: TFA–MeCN, 70 : 30. [b] Isolated yields. [c] Product inseparable from minor amounts of benzylated impurities. [d] No product [e] Reaction carried out using 1 g of starting material. [f] PBB = *para*-bromobenzyl.

We went on to investigate the reaction of galactose derivatives. Addition of vinylmagnesium bromide to galactose hemiacetal **16** gave the open-chain diols **17** and **18** (Scheme 2). The stereochemistry was proved by deprotection of **18** (Na in $NH_{3\,(l)}$ and THF, 71%) to give the known compound **19** (Fig. 1).[12] Treatment of diols **17** and **18** with acetic anhydride and pyridine gave the respective diacetates, **20** and **21**.

Cyclisation of the galactose diols **17** and **18** under the optimised reaction conditions gave THFs **22** and **23**, respectively, in lower yields than for glucose (Table 2, entries 1, 2). The reactions were somewhat less clean than the cyclisation reactions of the glucose derivatives **1** and **2**, and some benzylated and debenzylated products were detected on TLC. The galactose diacetates **20** and **21** underwent smooth and high yielding ring-closure to give THFs **24** and **25** (Table 2, entries 3, 4). That the stereochemical outcome of the cyclisation reaction was the same for diols and diacetates was proved by acetylation of **22** and **23** (Ac_2O, py) to obtain **24** (93%) and **25** (86%), respectively.



Scheme 2 *Reagents and conditions:* (i) vinylmagnesium bromide, THF, 0 °C → RT; **17**, 32%; **18**, 53%; (ii) Ac_2O, py, DMAP; **20**, 92%; **21**, 88%.

We assessed the stereochemistry of the *C*-glycosides by comparison with literature NMR data. Compounds **4**, **5**, **24**, **25** were converted to their respective saturated tetraacetates **26–29** by catalytic hydrogenation followed by peracetylation (Scheme 3). Each of the tetraacetates **26–29** showed good agreement in ^{13}C chemical shift data with one of a known series of α- or β- *gluco* or *galacto* configured *C*-furanoside tetraacetates for C-2–C-6.[13] Differences at C-1 would be due to the significantly different aglycon in the literature compounds. A second comparison between **4**, **5**, **22** and **23** and a series of perbenzylated vinyl *C*-xylo- or arabinofuranopentosides[14] (*i.e.* with the α- or β- *gluco* or *galacto* configurations at C-1–C-4) corroborated this assignment: a good correlation for C-1b, C-1a, C-1–C-4 was seen between each of **4**, **5**, **22** and **23** and one of the literature compounds. Chemical shifts for C-1 and C-2 were lower for α-configured compounds **5** and **23** than for the β-compounds **4** and **22**, while the shifts for C-4 were lower for *gluco* **4** and **5** than for *galacto* **21** and **22** compounds.[13,14] Finally, 2D NOESY experiments on the peracetylated compounds with well separated signals (*i.e.* **26**, **28** and **29**) gave results consistent with our assignment (see ESI†).

This means that for all the cyclisation reactions reported here, we see a stereospecific reaction with retention of configuration at C-4 and inversion of configuration at C-1. It is expected that the allylic group should be more susceptible to substitution reactions, either by an S_N1 mechanism with an intermediate stabilised allylic carbocation, or by an S_N2 mechanism where the transition state can be stabilised by the C=C π orbitals. Particularly interesting, then, is that we see *stereospecific* substitution reaction of *alcohols* with inversion of configuration under Brønsted acidic conditions. For all four cases, no other diastereomeric products can be detected. The same stereospecific reaction is seen with other leaving groups, *i.e.* acetates or *para*-bromobenzyl ethers. Brønsted and Lewis acid catalysed cyclisations of activated (*i.e.* allylic[15] or benzylic[16,17]) alcohols to give THF derivatives have been reported before, but as far as we are aware, this is the first time a cyclisation of this kind must be described as stereospecific.

The reaction products are vinyl *C*-furanosides. These are potentially useful compounds as the vinyl group may be

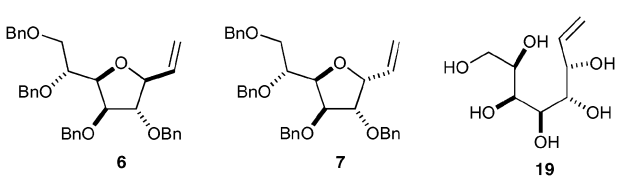
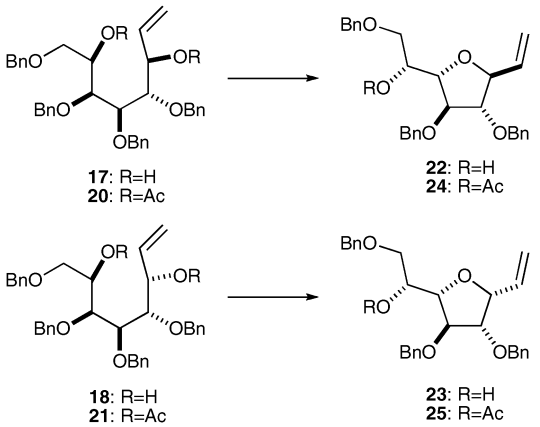


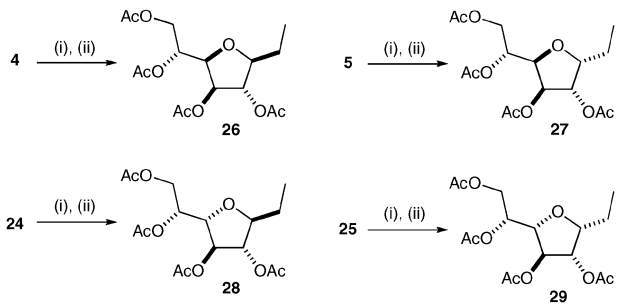
Fig. 1

Table 2 Cyclisation of galactose-derived compounds



Entry	Starting material	R	*t*/h	Product (yield %)[a]
1	**17**	H	10	**22** (51)[b]
2	**18**	H	10	**23** (60)[b]
3	**20**	Ac	5	**24** (81)[c]
4	**21**	Ac	5	**25** (84)[c]

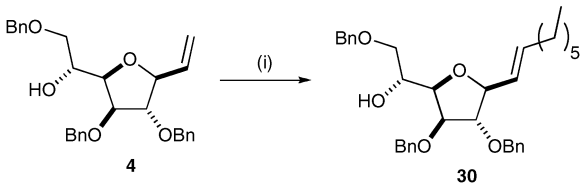
[a] Isolated yields. Reactions carried out in TFA–MeCN, 70 : 30 with [b] 20 equiv. toluene or [c] 10 equiv. toluene.



Scheme 3 *Reagents and conditions:* (i) H_2, Pd(C), EtOAc–MeOH–H_2O (2 : 4 : 1); (ii) Ac_2O, py, DMAP; **26**, 66%; **27**, 94%; **28**, 95%; **29**, 88%.

modified so that the molecules may be used as general *C*-furanoside building blocks. It has been shown that fatty chain derivatives of galactofuranose have antimycobacterial properties.[18] In order to demonstrate the potential utility of these *C*-furanosides, we carried out a cross-metathesis reaction[19] between glucose-derived THF **4** and oct-1-ene to give the long-chain *C*-glucofuranoside **30** (Scheme 4).

In conclusion, we describe a straightforward procedure whereby carbohydrate-derived allylic alcohols, ethers or acetates undergo a stereospecific debenzylative cyclisation with inversion of configuration at the allylic carbon. The reaction is carried out at room temperature without the need for anhydrous conditions or an inert atmosphere. This gives vinyl *C*-furanohexosides which may be derivatised at the aglycon C=C double bond, for example by cross-metathesis.



Scheme 4 *Reagents and conditions:* (i) oct-1-ene (6 equiv.), Grubbs' 2nd generation catalyst (0.025 equiv.), CH_2Cl_2, reflux, 8 h, 89%.

Financial support from the Swedish Research Council (Vetenskapsrådet) and the Carl Trygger Stiftelse för Vetenskaplig Forskning is gratefully acknowledged.

Notes and references

1 For recent references see: S. Hanessian and G. J. Reddy, *Synlett*, 2007, 475–479; H. Kim, C. M. Wooten, Y. Park and J. Hong, *Org. Lett.*, 2007, **9**, 3965–3968; D. C. Braddock, R. Bhuva, D. S. Millan, Y. Perez-Fuertes, C. A. Roberts, R. N. Sheppard, S. Solanski, E. S. E. Stokes and A. J. P. White, *Org. Lett.*, 2007, **9**, 445–448; T. Nakato and S. Yamauchi, *J. Nat. Prod.*, 2007, **70**, 1588–1592.

2 F. W. Lichtenthaler and S. Mondel, *Pure Appl. Chem.*, 1997, **69**, 1853–1866.

3 For recent references, see: D. K. Mohapatra, S. Mohapatra and M. K. Gurjar, *Tetrahedron Lett.*, 2006, **47**, 5943–5947; A. Cordero-Vargas, B. Quiclet-Sire and S. Z. Zard, *Org. Biomol. Chem.*, 2005, **3**, 4432–4443.

4 M. D. Smith, D. D. Long, D. G. Marquess, T. D. W. Claridge and G. W. J. Fleet, *Chem. Commun.*, 1998, 2039–2040.

5 D. C. Crick, S. Mahapatra and P. J. Brennan, *Glycobiology*, 2001, **11**, 107R–118R.

6 T. C. Ray, A. R. W. Smith, R. Wait and R. C. Hignett, *Eur. J. Biochem.*, 1987, **170**, 357–361.

7 D. J. Owen, R. J. Thomson and M. von Itzstein, *Carbohydr. Res.*, 2002, **337**, 2017–2022; J. Kovensky, A. F. Cirelli and P. Sinay, *Carbohydr. Lett.*, 1999, **3**, 271–276; J. Kovensky, M. McNeil and P. Sinay, *J. Org. Chem.*, 1999, **64**, 6202–6205; A. Caravano, D. Mengin-Lecreulx, J.-M. Brondello, S. P. Vincent and P. Sinay, *Chem.–Eur. J.*, 2003, **9**, 5888–5898.

8 I. Cumpstey, *Tetrahedron Lett.*, 2005, **46**, 6257–6259.

9 S. D. Rychnovsky and P. A. Bartlett, *J. Am. Chem. Soc.*, 1981, **103**, 3963–3964.

10 F. Nicotra, L. Panza, F. Ronchetti, G. Russo and L. Toma, *Carbohydr. Res.*, 1987, **171**, 49–57.

11 O. R. Martin, F. Yang and F. Xie, *Tetrahedron Lett.*, 1995, **36**, 47–50; B.-H. Yang, J.-Q. Jiang, K. Ma and H.-M. Wu, *Tetrahedron Lett.*, 1995, **36**, 2831–2834; H. Dehmlow, J. Mulzer, C. Seilz, A. R. Strecker and A. Kohlmann, *Tetrahedron Lett.*, 1992, **33**, 3607–3610; G. R. Gray, F. C. Hartman and R. Barker, *J. Org. Chem.*, 1964, **30**, 2020–2025; L. V. R. Reddy, A. D. Roy, R. Roy and A. K. Shaw, *Chem. Commun.*, 2006, 3444–3446.

12 A. Palmelund and R. Madsen, *J. Org. Chem.*, 2005, **70**, 8248–8251.

13 B. Wright, L. R. Hughes, S. S. Qureshi and A. H. Davidson, *Magn. Reson. Chem.*, 1988, **26**, 1062–1067.

14 R. Persky and A. Albeck, *J. Org. Chem.*, 2000, **65**, 5632–5638.

15 S. H. Kang and C. Y. Hong, *Tetrahedron Lett.*, 1987, **28**, 675–678; M. A. Tabrizi, P.G. Baraldi, M. Guarneri, S. Manfredini, G. P. Pollini and D. Simoni, *Tetrahedron Lett.*, 1991, **32**, 683–686.

16 W. Frick and R. R. Schmidt, *Liebigs Ann. Chem.*, 1989, 565–570.

17 F. F. Huerta, C. Gomez, A. Guijarro and M. Yus, *Tetrahedron*, 1995, **51**, 3375–3388; G. V. M. Sharma, K. R. Kumar, P. Sreenivas, P. R. Krishna and M. S. Chorghade, *Tetrahedron: Asymmetry*, 2002, **13**, 687–690; S. Yamauchi and Y. Kinoshita, *Biosci. Biotechnol. Biochem.*, 2001, **65**, 1559–1567.

18 C. B. Davis, R. D. Hartnell, P. D. Madge, D. J. Owen, R. J. Thomson, A. K. J. Chong, R. L. Coppel and M. von Itzstein, *Carbohydr. Res.*, 2007, **342**, 1773–1780.

19 O. Plettenburg, C. Mui, V. Bodmer-Narkevitch and C.-H. Wong, *Adv. Synth. Catal.*, 2002, **344**, 622–626.