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Stereoselective synthesis of *C*-glycosides via Tebbe methylenation and Claisen rearrangement

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Abstract

A variety of β-*C*-glycosides may be readily accessed in a stereoselective fashion from 3-OH glycal esters, via the use of Tebbe methylenation and subsequent thermal Claisen rearrangement. The use of carbohydrate ester substrates allows the formation of β(1→6) linked *C*-disaccharides.

Keywords: *C*-glycosides; carbohydrates; glycals; Tebbe reagent; Claisen rearrangement.

The combination of the natural occurrence of *C*-glycosides,[1] be it either discretely or as fragments of larger biologically active natural products, together with the idea that such materials may possess potential therapeutic benefits by acting as carbohydrate mimetics,[2] has provoked a large amount of interest from the synthetic community.[3]

The development of high throughput screening processes has provided much of the impetus for the development of combinatorial and parallel synthetic techniques in the pharmaceutical industry. Due to the well-established importance of carbohydrates in a plethora of biological processes[4] it would therefore seem a logical progression to develop parallel synthetic routes to glycomimetics, and in particular *C*-glycosides, for biological screening purposes.

When considering the development of a new parallel synthetic approach to *C*-glycosides, two important factors should be considered. The first of these is the stereochemical outcome of the *C*-glycosylation reaction, which must be at least highly stereoselective, if not stereospecific, and the second is the potential generality of the overall reaction sequence. In order to address the former consideration it seemed that one can profitably use a thermal sigmatropic rearrangement for the construction of the new carbon–carbon bond at the anomeric centre with complete control of stereochemistry. In addition, rather than choosing to adopt the classic Claisen–Ireland approach,[5] it was envisaged that a tandem process involving Tebbe methylenation[6] of a

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glycal ester could be followed by thermal sigmatropic rearrangement, and thereby allow stereoselective access to *C*-glycosides (Fig. 1).[7]

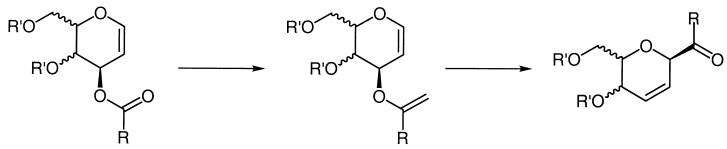
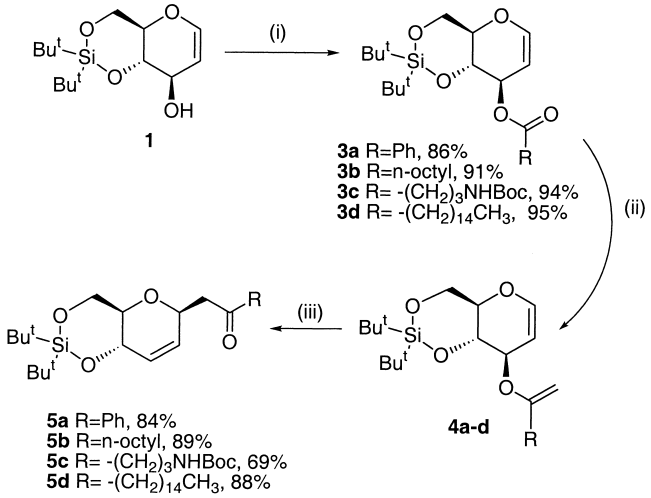


Fig. 1.

Since any carboxylic acid could in theory be used for the esterification step, then this sequence would provide a straightforward parallel synthetic route to a wide range of *C*-glycosides.

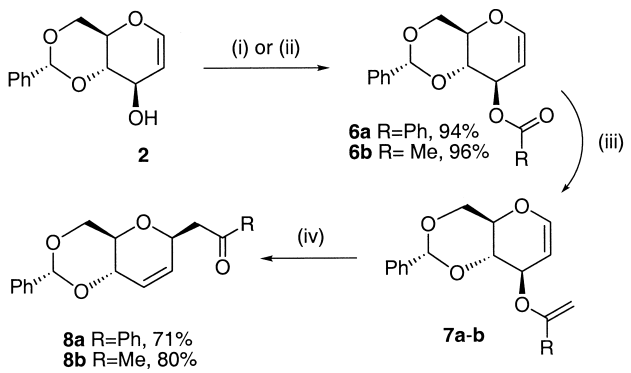
Such a strategy initially requires access to selectively protected glycals in which the 3-hydroxyl group is free for esterification. To this end the known silyl protected glucose-derived glycal **1**[8] was synthesised from glucose β-pentaacetate in four steps following literature procedures (72% overall yield). The corresponding 4,6-benzylidene protected glycal **2** was also synthesised as a starting material, this time by a more protracted literature procedure.[9]

Esterification of **1** with either benzoic, octanoic, Boc-protected 4-amino butyric, or palmitic acids was achieved by treatment of the glycal with the corresponding carboxylic acid and DCC, with catalytic DMAP, yielding esters **3a**–**d** in excellent yields. The two step sequence of Tebbe methylenation and Claisen rearrangement was then undertaken. Tebbe reaction proceeded smoothly to yield the corresponding enol ethers **4a**–**d**. Thermal rearrangement of enol ethers **4a**–**d**, which occurred upon heating to 180°C in either benzonitrile or tributylamine,[10] then produced the corresponding β-*C*-glycosides **5a**–**d**[11] in good to excellent yield (Scheme 1, reaction yields quoted over two steps of methylenation and rearrangement). The success of the Tebbe methylenation and subsequent rearrangement of the Boc-protected amino ester **4c** is notable, since this indicates that Boc-protected amino acids may be suitable substrates for this reaction sequence, thereby allowing access to *C*-glycosyl amino acids, which have recently become the objects of synthetic interest.[12]



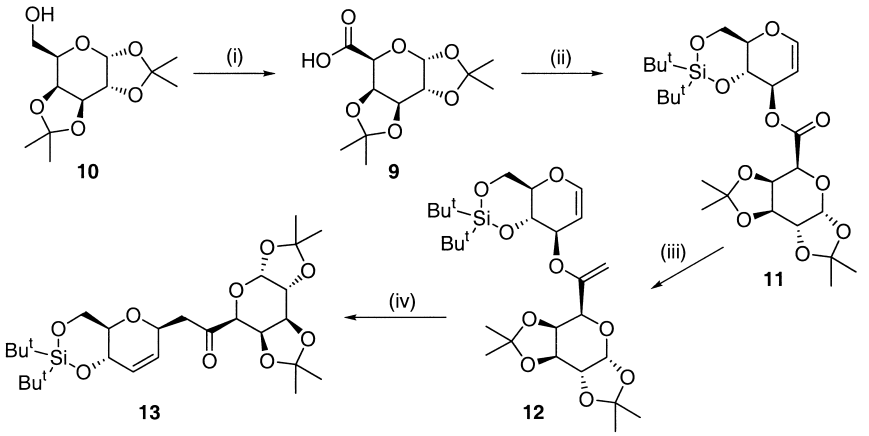
Scheme 1. (i) RCO_2H, DCC, DMAP, CH_2Cl_2, rt; (ii) Tebbe, THF, pyridine, –40°C; (iii) 180°C, PhCN or Bu_3N

A similar sequence of reactions was undertaken for the benzylidene protected glycal **2**. In this case the benzoate **6a** and acetate **6b** were accessed by the use of benzoyl chloride and acetic anhydride, respectively (94 and 96% yields). Tebbe methylenation again yielded the intermediate enol ethers **7a** and **7b**. Thermal rearrangement proceeded rapidly upon heating to 180°C in tributylamine to yield the β-*C*-glycosides **9a** and **9b** (71 and 80% yields over two steps, Scheme 2).



Scheme 2. (i) BzCl, DMAP, pyridine, 0°C; (ii) Ac_2O, pyridine, rt; (iii) Tebbe, THF, pyridine, –40°C; (iv) 180°C, Bu_3N

An appealing feature of this *C*-glycosylation strategy is, as previously mentioned, the potential range of carboxylic acids which may be used for the esterification reaction. In order to exemplify the flexibility of this approach the synthesis of a β-*C*-disaccharide was undertaken. Thus, the known galacturonic acid **9**,[13] which was obtained in high yield by ruthenium-mediated[14] oxidation of diacetone galactose **10**, was coupled with glycal **1** to yield the ester **11**. Tebbe methylenation of **11** was found to be much more sluggish than the previous examples, but by the use of an extended reaction time (24 h) a satisfactory yield of the desired enol ether **12** was obtained (72% yield based on recovered starting material; it should be noted that the reaction could not be driven to completion). Claisen rearrangement of enol ether **12** occurred rapidly at 180°C, in this instance to yield the desired β-*C*-disaccharide **13**[15] in a satisfactory 56% yield (Scheme 3).



Scheme 3. (i) $RuCl_3$, $NaIO_4$, $CHCl_3$, MeCN, H_2O, 82%; (ii) **1**, DCC, DMAP, CH_2Cl_2, 91%; (iii) Tebbe, THF, pyridine, –40°C to rt, 72%; (iv) 180°C, PhCN, 56%

In summary it is clear that the combined use of Tebbe methylenation and thermal Claisen rearrangement provides a powerful and potentially general route to stereodefined *C*-glycosides. By the use of uronic acids as coupling partners such methodology may be applied to the synthesis of 1→6 linked *C*-disaccharides. The use of suitably protected amino acids will also allow access to *C*-glycosyl amino acids, which are the required building blocks for the synthesis of *C*-glycopeptides. It should be noted that the use of the corresponding allose-derived glycals will allow access to the corresponding α-*C*-glycosides and that in addition simple iteration of the process using uronic acid substrates will allow access to 1→6 linked *C*-oligosaccharides. Further investigations in this area are currently in progress and will be reported in due course.

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References

1. See: Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Tetrahedron Organic Chemistry Series, Pergamon: Oxford, 1995; Vol. 13, pp. 7–10.
2. For a recent review see: Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324.
3. For a recent review see: Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.
4. Varki, A. *Glycobiology* **1993**, *3*, 97–130. Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720.
5. Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205–3207. Ireland, R. E.; Anderson, R. C.; Badoub, R.; Fitzsimmons, B. J.; McGarvey, G.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988–2006. Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518–522. Curran, D. P.; Suh, Y. G. *Carbohydr. Res.* **1987**, *111*, 161–191.
6. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.
7. For a recent example of the use of Claisen–Ireland rearrangement for the synthesis of *C*-glycosides see: Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677–5680.
8. Hoberg, J. O. *Carbohydr. Res.* **1997**, *300*, 365–367.
9. Pedretti, V.; Mallet, J.-M.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *244*, 247–257.
10. In certain cases some epimerisation at the anomeric centre was observed during the thermal rearrangement step, leading to the formation of α-*C*-glycosides as minor products. Presumably this occurs via a retro Michael reaction, which is possibly Lewis acid catalysed, followed by re-closure of the 5-hydroxyl group onto the alternative face of the alkene (for base catalysed examples see Ohrui, H.; Jones, G. H.; Moffat, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602–4613). When observed this undesirable side reaction could be completely avoided by switching to tributylamine as the solvent employed for the Claisen rearrangement step (note that heating α-*C*-glycosides to 180°C in tributylamine did not lead to any epimerisation).
11. The stereochemistry of the newly formed anomeric linkage was demonstrated by NOE difference experiments, which in all cases revealed enhancements between H-1 and H-5 (original carbohydrate numbering).
12. See for example: Colombo, L.; Casiraghi, G.; Pittalis, A.; Rassu, G. *J. Org. Chem.* **1991**, *56*, 3897–3900. Westermann, B.; Walter, A.; Diedrichs, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 3384–3386. Campbell, A. D.; Paterson, D. E.; Taylor, R. J. K.; Raynham, A. M. *Chem. Commun.* **1999**, 1599–1600. Nishikawa, T.; Ishikawa, M.; Isobe, M. *Synlett* **1999**, 123–125.

13. Torii, S.; Inokuchi, T.; Sugiura, T. *J. Org. Chem.* **1986**, *51*, 155–161. Sell, H. M.; Link, K. P. *J. Am. Chem. Soc.* **1938**, *60*, 1813–1814.
14. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
15. All new compounds possess spectroscopic data consistent with their structures, together with satisfactory microanalytical and/or high-resolution mass spectral data.