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Synthesis of α-*C*-glycosides via tandem Tebbe methylenation and Claisen rearrangement

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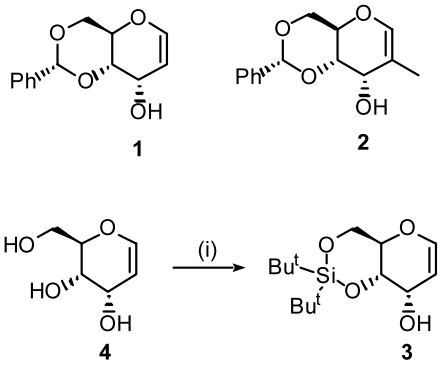
Abstract—A variety of α-*C*-glycosides may be accessed in an entirely stereoselective fashion from 3-OH glycal esters, by way of the tandem reaction sequence of Tebbe methylenation and Claisen rearrangement. In contrast with previous studies in the corresponding β-series, careful control of conditions for Claisen rearrangement is required in order to avoid loss of integrity of anomeric stereochemistry; thermal rearrangements are best carried out in xylene in a sealed tube.

The synthesis of *C*-glycosides[1] remains a significant occupation of the synthetic community.[2] This may be as part of natural product total synthesis, or in order to furnish glycomimetics as tools for glycobiology or as potential therapeutic agents. In particular, stereocontrolled access to a wide variety of *C*-glycosides would provide materials for biological screening programs, which may shed further light on the proposed ability of *C*-glycosides to act as non-hydrolysable mimics of their natural *O*-linked counterparts.[3]

As part of our ongoing studies into the development of an approach designed at allowing access to a wide variety of *C*-glycosides in a parallel synthetic manner, we recently reported[4] the use of glucal derived carbohydrate esters to allow access to a variety of β-*C*-glycosides in high yield and with complete control of anomeric stereochemistry. Herein we report studies allowing synthetic access to the corresponding α-*C*-glycosides, again by use of a tandem reaction sequence involving Tebbe methylenation[5] of glycal esters followed by Claisen rearrangement.[6]

The synthesis of the corresponding α-*C*-glycosides necessarily entails the use of glycal esters derived from allose, which is epimeric at the 3-position to glucose. To this end we undertook the synthesis of the known 4,6-*O*-benzylidene protected allal **1** and the corresponding C-2 methyl substituted derivative **2**, following literature procedures.[7] In addition the corresponding 4,6-*O*-silyl protected compound **3** was itself accessed from allal **4**[8] by regioselective silylation by treatment with di-*tert*-butylsilyl ditriflate in DMF at low temperature (77% yield, Scheme 1).

Treatment of glycal **1** with benzoyl chloride and catalytic DMAP in pyridine furnished the benzoate ester **5a**, acetylation with acetic anhydride in pyridine yielded the acetate **5b**, whilst treatment with either palmitic acid or Boc protected 4-amino butyric acid, together with DCC and catalytic DMAP, correspondingly gave the palmitic **5c** and amino butyric esters **5d**, respectively. Similarly glycal **2** was converted into its benzoate **6** by treatment with benzoyl chloride, whilst silyl protected glycal **3** was converted into palmitic ester **7**. Methylenation of all esters proceeded smoothly by treatment with an excess



Scheme 1. *Reagents and conditions*: (i) ^{t}Bu$_2$Si(OTf)$_2$, DMF, −40°C to rt, 77%.

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

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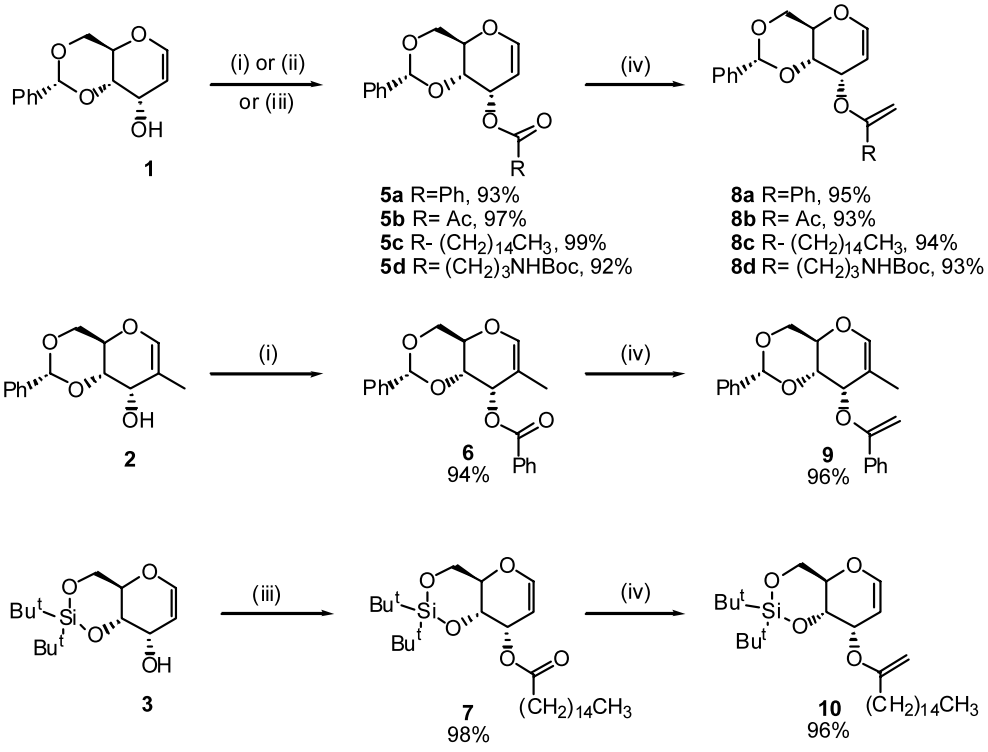


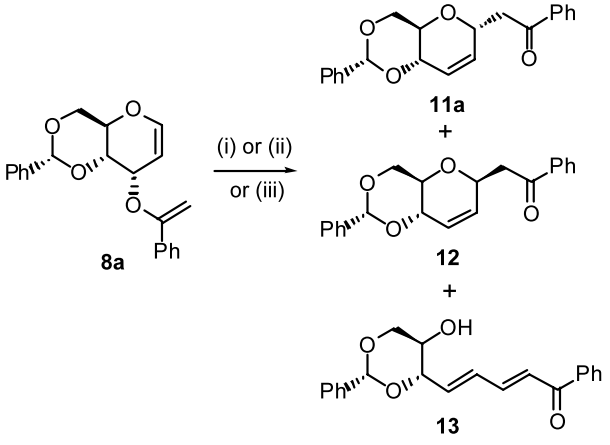
Scheme 2. *Reagents and conditions*: (i) PhCOCl, DMAP, pyridine, 0°C; (ii) Ac_2O, pyridine, rt; (iii) RCO_2H, DCC, DMAP, CH_2Cl_2, rt; (iv) Tebbe, THF:pyridine, 4:1, –40°C.

of Tebbe reagent (~2 equivalents) at –40°C in a mixture of THF and pyridine (ratio ~4:1), to yield the corresponding enol ethers **8**–**10** (Scheme 2).

With a selection of vinyl ethers in hand attention turned to the subsequent Claisen rearrangement. Thermal rearrangement of enol ether **8a**, was attempted following conditions that had successfully yielded the corresponding β-*C*-glycosides.[4] However it was found that heating **8a** to 180°C in benzonitrile as solvent produced a mixture of both α- and β-*C*-glycoside products **11a** and **12**, albeit in a favourable ratio of α:β 5:1 (Scheme 3). In addition small amounts of the open chain diene **13**[9] were also observed, indicating the probable mechanism by which the α- and β-*C*-glycosides interconverted.[10] Although in the previously studied β-series the minor amounts of epimerisation that had occasionally been observed during thermal rearrangement could be suppressed by changing the solvent to tri-*n*-butylamine, in the α-series this proved not to be the case and once again mixtures of anomers were formed.

Although these observations were in contrast to literature accounts of a similar Claisen rearrangement which had not reported competitive formation of the β-anomer,[6e] related work had indeed indicated the ease by which the α-*C*-glycosides products may be epimerised to their thermodynamically more favoured β-counterparts.[11] It was therefore clear that if this competitive anomerisation process were to be suppressed then careful choice and control of reaction conditions would be required. However since the potential advantage of the tandem Tebbe/Claisen approach to *C*-glycoside synthesis over alternative intermolecular approaches resided solely in the ability to furnish totally anomerically pure products, the search for reaction conditions that could yield pure α-*C*-glycosides became somewhat of a prerogative.

Lewis acid catalysed reactions were investigated as an alternative to thermal rearrangement. A selection of Lewis acids, including $NaBF_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, $Yb(OTf)_3$, and $TiCl_4$ was screened under a variety of reaction conditions, but unfortunately in all cases mixtures of epimeric products were formed, together with variable amounts of open chain diene **13**. Although in



Scheme 3. *Reagents and conditions*: (i) Bu_3N, 180°C; (ii) PhCN, 180°C; (iii) various Lewis acids at low temperature.

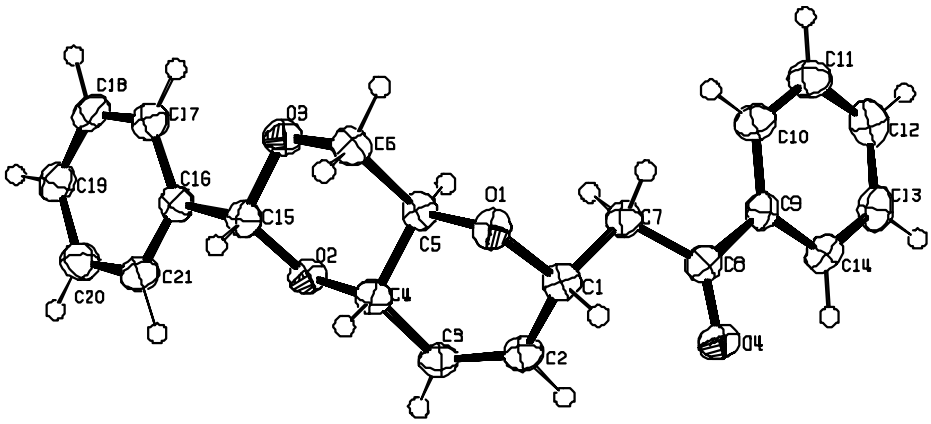
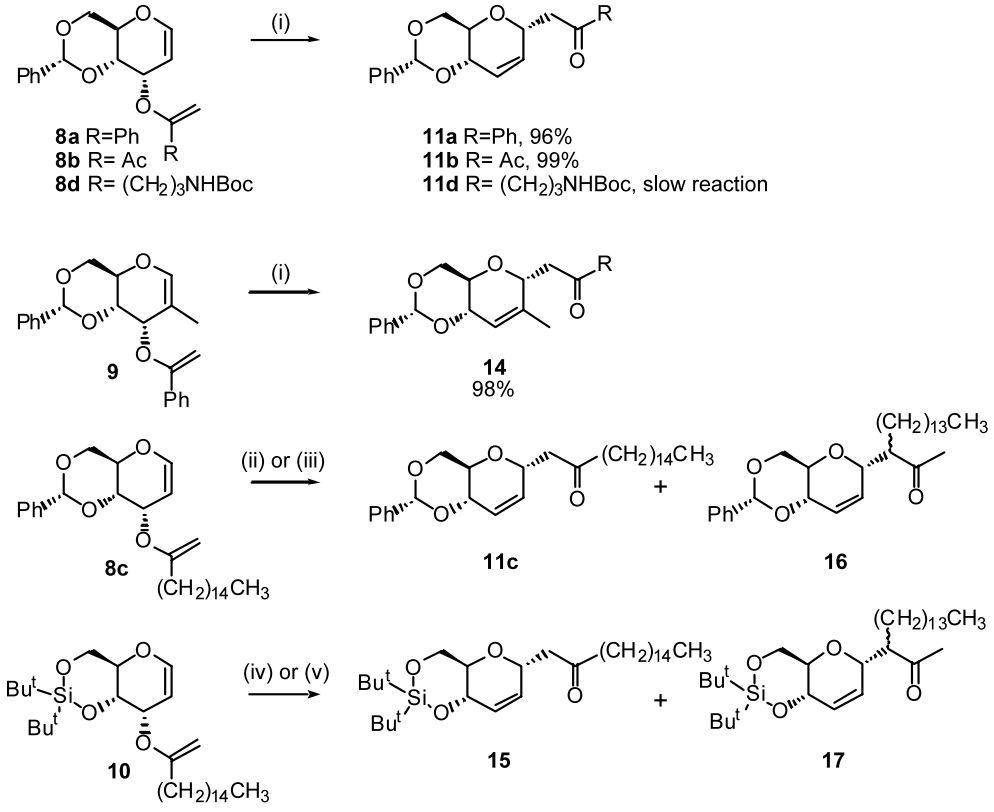


Figure 1. Crystal structure of *C*-glycoside **11a** showing crystallographic numbering scheme [thermal ellipsoid plot (ORTEP-34) at 40% probability].

some cases the ratio of products was favourable towards the desired α-anomer (e.g. α:β ratio of 16:1, for $BF_3{\cdot}OEt_2$), the yields for these reactions were at best modest (~60%) and since the goal was complete control of anomeric stereochemistry alternative reaction conditions were continually pursued.

In the face of the persistent anomerisation problem it was thought prudent to monitor the rate of formation of the undesired β-anomer relative to the Claisen rearrangement. To this end a series of NMR reactions were performed in deuterated benzene as the solvent in a sealed tube. Rather surprisingly when the thermal rearrangement of **11a** was performed in d_6-benzene in a sealed tube the reaction proceeded smoothly and *no formation of the undesired β-anomer was observed*. This initially pointed the way to the use of benzene as the solvent for the rearrangement reaction. Indeed a series of thermal rearrangements in benzene did produce pure α-*C*-glycosides. However mindful of the undesirable properties of benzene, a selection of alternative solvents were screened at a variety of temperatures. Thermal rearrangement in xylene at 195°C proved to be optimum, and gratifyingly enol ethers **8a**, **8b** and **9** all



Scheme 4. *Reagents and conditions*: (i) xylene, sealed tube, 195°C; (ii) xylene, sealed tube, 195°C, ratio **11c**:**16**, 1.3:1, yield 85%; (iii) d_6 benzene, 195°C, sealed tube, ratio **11c**:**16**, 1:1, yield 84%; (iv) xylene, sealed tube, 195°C, **15** only, yield 85%; (v) d_6 benzene, 195°C, sealed tube, ratio **15**:**17**, 1.4:1, yield 94%.

rearranged smoothly in excellent yield and most importantly, entirely stereoselectively, to yield only the α-*C*-glycoside products **11a**, **11b**, and **14** respectively (Scheme 4). The anomeric stereochemistry of *C*-glycoside **11a** was confirmed by X-ray crystallography (Fig. 1),[12] whilst the anomeric configuration of the other α-*C*-glycosides was confirmed by NOE difference experiments.[13]

However Boc protected amine **8d** reacted only very slowly under these conditions, and no appreciable amount of product was observed-the starting material being recovered in this case. Moreover during rearrangement of the two palmitic esters **8c** and **10** to produce the desired α-*C*-glycosides **11c** and **15** the formation of two side products was occasionally observed. These side products were identified as the α-*C*-glycosides **16** and **17**,[14] and are presumably formed via partial isomerisation of the glycal enol ethers **8c** and **10** to the thermodynamically preferred more substituted tautomers before rearrangement. Frustratingly the relative amounts of these products formed appeared to be quite variable. For example in one instance the use of xylene as solvent for rearrangement of **10** completely suppressed the formation of **17**, whilst during a similar NMR experiment with d_6 benzene as solvent resulted in the formation of **17** in an almost equal amount to that of the desired product **15**. However the formation of **16** from **8c** was observed even in xylene as solvent. Complete suppression of the formation of these products in this case has not yet proved possible,[15] although further investigations are ongoing.

In summary, the tandem Tebbe methylenation and thermal Claisen rearrangement has been extended to allow the synthesis of a variety of α-*C*-glycosides.[16] In particular to obtain pure α-products careful control of reaction conditions is required in order to avoid competing formation of the thermodynamically more stable β-*C*-glycoside products. This is currently best achieved by performing the thermal reactions in either xylene or benzene as solvent in a sealed tube, though in the case of palmitic enol ethers isomerisation prior to rearrangement is found to be a competing process. Further investigations into the use of the tandem Tebbe/Claisen approach for the synthesis of a wide variety of *C*-glycosides, *C*-glycosyl amino acids and *C*-oligosaccharides as potential glycomimetics are currently in progress and results will be reported in due course.

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8. Allal (see Ref. 7c) was itself synthesised from diacetone glucose, by a sequence of oxidation and stereoselective reduction. Full details will be published separately.
9. The *EE* configuration of diene **13** is suggested by the coupling constants between H-2 and H-3, and H-4 and H-5 which were both ~15 Hz (ketone numbered as C-1).
10. Epimerisation probably occurs through a retro-Michael reaction of the desired α-*C*-glycoside to produce the open chain diene, which is then followed by re-closure of the 5-hydroxyl group onto the alternative face of the alkene.
11. Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522–528.
12. Crystal data for **11a**: $C_{21}H_{20}O_4$; M = 336.39; monoclinic; space group $P2_1$; $a = 4.7401(4)$, $b = 10.8660(7)$, $c = 16.1935(14)$ Å; $\alpha = 90.00$, $\beta = 92.686$, $\gamma = 90.00°$; cell volume = 833.1 Å^3, $Z = 2$; calculated density = 1.341 Mg/m^3; $R = 0.0335$; $wR = 0.0366$. Diffraction data were measured at 150 K using an Enraf–Nonius Kappa CCD diffractometer (graphite-monochromated MoKα radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package. Crystallographic data (excluding structure factors) has been deposited with the Cambridge

Crystallographic Data Centre as supplementary publication number CCDC 203253. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

13. In all cases NOE difference experiments revealed no enhancements between H-1 and H-5 (original carbohydrate numbering), whilst enhancements were observed between H-5 and the two protons of the anomeric methylene carbon.
14. Both are formed as single diastereomers but it has not yet been possible to unequivocally assign their stereochemistry.
15. Indeed it has subsequently been discovered that sealed tube rearrangement of palmitic esters in the β-series (detailed in Ref. 4) in xylene at 195°C also leads to the formation of these isomeric products, whereas none were previously observed during thermal rearrangement at 180°C in either benzonitrile or tributylamine.
16. All new compounds possess spectroscopic data consistent with their structures, together with satisfactory microanalytical and/or high-resolution mass spectral data.