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Template-directed Intramolecular *C*-Glycosidation. Stereoselective Synthesis of Monocyclic *C*-Glycosides

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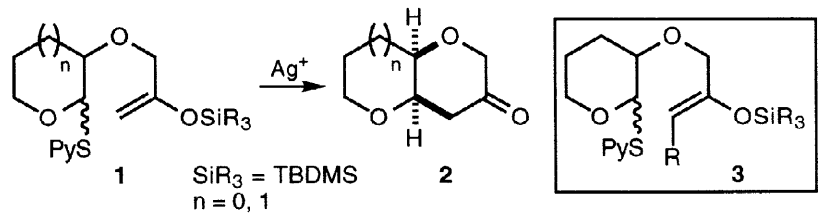
Abstract: *S*-Glycosides possessing silyl enol ether groups tethered via an ether linkage undergo highly selective cation-mediated cyclisation reactions to give *C*-glycosidic ketotetrahydropyran-containing bicyclo[4.4.0] systems. These may be converted into a variety of monocyclic *C*-glycosides and their derivatives using oxidative and reductive tether-cleaving reactions.

C-Glycosides are ubiquitous structural fragments in natural products, and many strategies have been developed for their assembly.[1] The key C–C bond-forming reactions in these transformations have involved reactive intermediates having cationic, radical or anionic character at the anomeric centre, and many of these processes are highly stereoselective. We have been looking at template-directed intramolecular *C*-glycosidation, in which a group appended to the sugar template serves to deliver nucleophilic carbon functionality to the electrophilic site formed by ionisation in situ at the anomeric position.[2] Our first report in this area[3] described reactions with silver triflate of *S*-glycosidic silyl enol ethers **1**, which gave bicyclic *C*-glycosides **2** as single, cis-fused diastereomers for both the 5- and the 6-membered templates. We now describe the extension of this methodology to more highly substituted substrates **3**, and show that cyclisation of such precursors delivers the target bicycles with high stereoselectivity. We report also the elaboration of these materials to give the *mono*cyclic products of overall in*ter*molecular reaction.



1 SiR_3 = TBDMS, n = 0, 1 **2** **3**

As with our previous work, the synthesis of **3** began from the diol **4**, made by oxidation of 3,4-dihydro-2*H*-pyran with *m*-CPBA.[4] In order to shorten the sequence for the synthesis of cyclisation substrates, we were keen to attach the latently nucleophilic side-chains directly to templates already containing the anomeric leaving group. To this end, treatment of **4** with PySSPy–*n*-Bu_3P[5] gave selectively the hydroxylated *S*-glycoside **5**. The tosylates **6** required for allylation of **5** were prepared by sequential carbocupration of propargyl alcohol[6] followed by tosylation under standard conditions. We were mindful of the possibility of loss of the thiopyridyl leaving group during introduction of the side-chain, and consequently devised two allylation procedures to obviate this anticipated problem. Method A involved the use of phase-transfer conditions, whilst in Method B *pre-mixed* DMF solutions of **5** and **6** were added to dry sodium hydride, thereby minimising the time available

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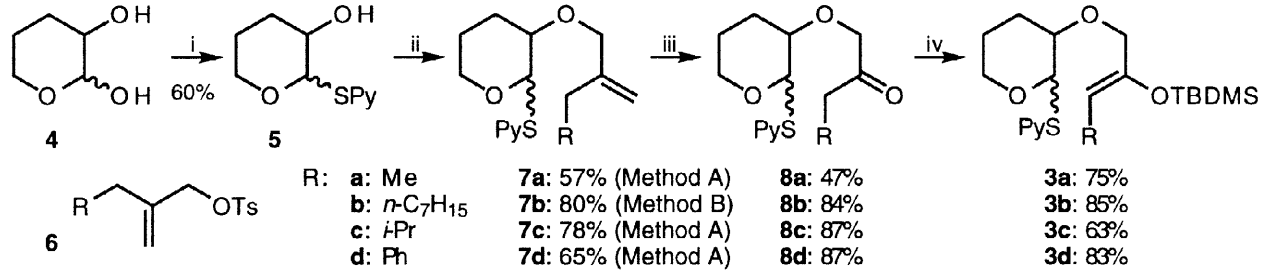
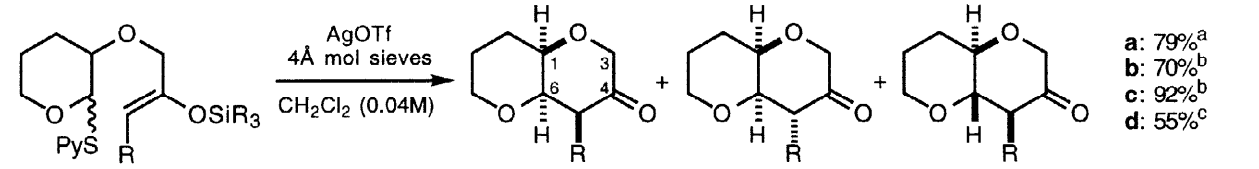
for unimolecular decomposition of the conjugate base of **5**.[7] The product olefins **7**[8] were subjected to ozonolysis to give ketones **8** and then enol etherification, giving **3** as single geometric isomers[9] with almost complete regioselectivity (Scheme 1).[10] An alternative sequence for the generation of **8** entailed alkylation of **5** with 1-chloro-3-(triphenylphosphoranylidene)-2-propanone,[11] followed by Wittig olefination[12] and hydrogenation. Whilst this sequence was realised for analogues of **8** bearing thiophenyl anomeric groups, the hydrogenation reactions of the Wittig products in the thiopyridyl sequences were unviably sluggish.[13]



Reagents and conditions: (i) PySSPy, *n*-Bu_3P, CH_2Cl_2, 0°C→rt; (ii) Method A: **5** + **6**, CH_2Cl_2, 50% aq NaOH, *n*-Bu_4NI, rt; Method B: **5** + **6** + *n*-Bu_4NI + DMF added to NaH, rt; (iii) O_3, CH_2Cl_2, -78°C; PPh_3, rt; (iv) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C→rt.

Scheme 1

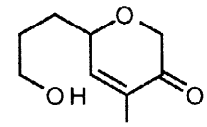
As in our earlier work, treatment of cooled dichloromethane solutions of **3** containing activated 4Å molecular sieves with silver triflate caused formation of a beige precipitate. Work-up after several hours gave bicyclic *C*-glycosides **9** and **10**, and in some cases **11** in good combined yields, with the cis-fused diastereomer **9** bearing the β-configured side-chain predominating in all cases (Scheme 2).

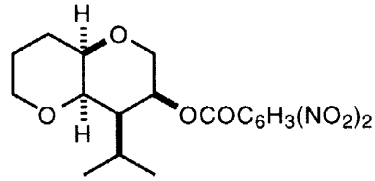


[a]Reaction carried out at -20°C; [b]reaction carried out at -40°C; [c]reaction carried out at 0°C; [d]ratio not determined (see text).

Scheme 2

In the case of substrate **3d**, four products were formed; these compounds were found to undergo interconversion on silica gel, perhaps as a consequence of facile enolisation–ring-opening–ring-closure processes. Indeed, treatment of the product mixture in this case with either TFA or Et_3N gave material showing a ^1H nmr signal at 6.98 ppm, strongly suggestive of an enone β-proton as in **12**, and we speculate that the facility of this transformation arises from the additional conjugation provided by the phenyl substituent. The assignment of cis-fusion to the cyclisation products **9** and **10** followed both from inference from our previous work,[3] and from the characteristically small ^1H nmr coupling constants observed for the signals corresponding to H-1 and H-6, indicative of their mutual syn relationship. In contrast, the trans-fused isomers **11** typically exhibited H-6 signals as double doublets with two large (ca. 9 Hz) *J*-values, indicating the anti-periplanar relationship of H-1 and H-6, and of H-5 and H-6. The predominance of **9** over **10** was established by carrying out some simple derivatisation experiments. Thus, treatment of a 2.8:1 mixture of





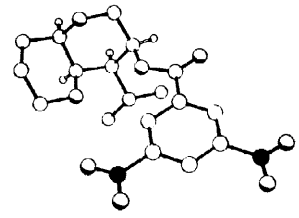
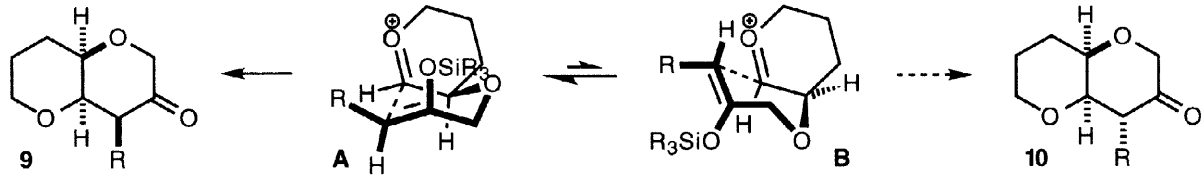


Figure
X-Ray crystal structure of **13**

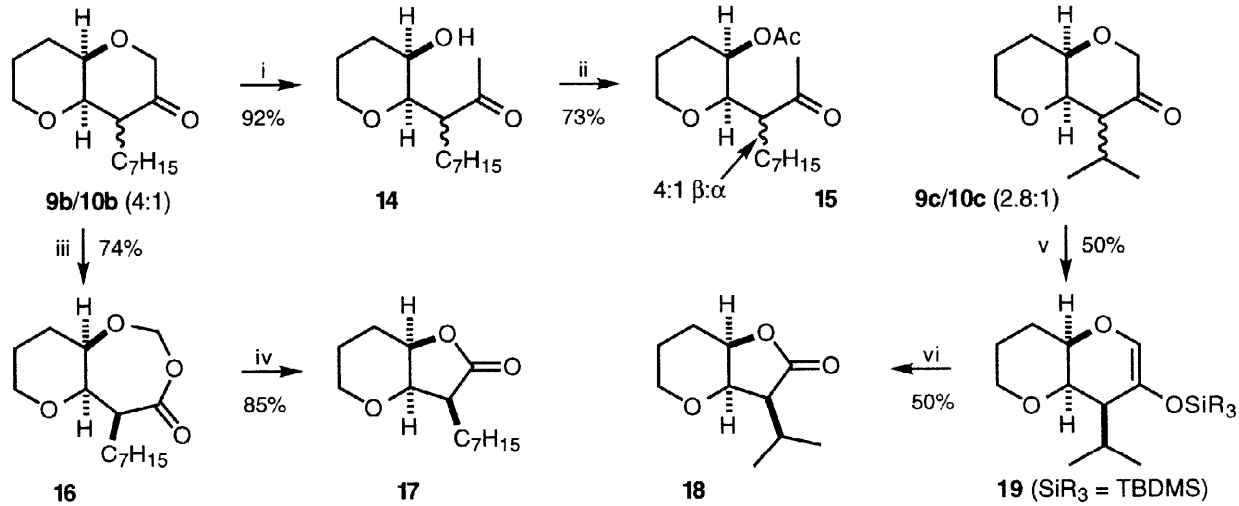
ketones **9c** and **10c**[14] with L-Selectride® in THF at -78°C gave a single secondary alcohol in 40% yield, consistent with it being a product of reduction of **9c**, and not of **10c**. 3,5-Dinitrobenzoylation of this gave the ester **13**, whose X-ray crystal structure confirmed its stereochemistry, and therefore that of **9c** (Figure).

The predominant formation of the cis-fused isomers **9** rather than **10** may be indicative of the preferred adoption of reactive conformation **A** over conformation **B** in the cyclisation reaction. In the former orientation an axial nucleophilic side-chain both allows anchimeric stabilisation of the anomeric cation by the tether ether oxygen atom, and enables closer mutual approach of the increasingly δ-positive silicon atom to the increasingly electron-rich template ring oxygen during cyclisation (Scheme 4).



Scheme 4

Ketones **9** and **10** are bicyclic *C*-glycosides, and we sought methods for their conversion into the monocyclic products of overall intermolecular *C*-glycosidation. Reaction of a 4:1 mixture[15] of **9b/10b** with samarium(II) iodide in THF–MeOH[16] resulted in clean reductive cleavage of the tether C–O bond to give hydroxyketones **14**, which existed predominantly as the cyclic ketol tautomers. These could be acetylated in the ring-opened form to give acetoxyketones **15**. Alternatively, Baeyer–Villiger oxidation of the same diastereomeric mixture of **9b** and **10b** using *m*-CPBA in dichloromethane gave in high yield a separable 5:1 mixture of the acetal-lactone **16**[17] (74%) and its C-6 epimer (15%). Treatment of **16** with concentrated sulfuric acid in methanol effected smooth conversion into the γ-lactone **17**.[18] Interestingly, the more hindered ketones **9c/10c** were completely inert to *m*-CPBA and a range of other peracids. Ketones **9c/10c** could be derivatised instead by silyl enol etherification; treatment of the 2.8:1 mixture of ketones **9c/10c** with TBDMSOTf–Et_3N gave a separable ca. 5:2:1 mixture of enol ethers.[19] Exposure of the major component **19**[20] to ruthenium(VIII) oxide generated in situ, followed by sequential treatment of the crude product with K_2CO_3–MeOH and conc. sulfuric acid–MeOH gave γ-lactone **18**. The derivatisation reactions of **9** and **10** are depicted in Scheme 5.



Reagents and conditions: (i) SmI_2, 3:1 THF–MeOH, -40°C; (ii) Ac_2O, DMAP, pyridine, rt; (iii) *m*-CPBA (2 equiv), CH_2Cl_2, rt; (iv) conc H_2SO_4 (cat), MeOH, rt; (v) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C→rt; (vi) $NaIO_4$, $RuCl_3{\cdot}nH_2O$, CCl_4–MeCN–H_2O, rt, then K_2CO_3, MeOH, then conc H_2SO_4 (cat), MeOH, rt.

Scheme 5

In summary, we have demonstrated that template-directed intramolecular *C*-glycosidation is an effective and efficient strategy for the synthesis of bicyclic, and ultimately monocyclic *C*-glycosides. It is worth noting that compounds **14/15** are the formal products of stereoselective *inter*molecular delivery of the more substituted, thermodynamic enolate of 2-decanone to an anomeric cation syn with respect to the C-2 hydroxyl group, whilst

bicycles **17** and **18** are the lactonised products of the analogous process using ester enolates. We have explored also the utility of this approach for the stereoselective synthesis of the central, sugar-derived fragment of the elfamycin antibiotic aurodox; the results of this investigation will be published elsewhere.

ACKNOWLEDGEMENTS

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7. Generation of the anion of **5** using NaH–DMF, followed by addition of **6** consistently gave substantial quantities of the product of S_N2 reaction of **6** with the conjugate base of 2-mercaptopyridine.
8. Compounds **7**, **8** and **3** typically were obtained as ca. 8:1 mixtures of anti:syn thioglycoside anomers.
9. The geometry of **3** was established by ^{1}H nmr n.O.e. studies; we thank Mr Dick Sheppard and Mr Paul Hammerton of this Department for these experiments.
10. Silyl enol etherification of the more sterically hindered ketones **8b** and **8c** gave small (≈5%) amounts of the alternative regioisomers.
11. Chopard, P. A.; Hudson, R. F. *J. Org. Chem.* **1963**, *28*, 2446-2447.
12. Heathcock, C. H.; Hecker, S. J. *J. Org. Chem.* **1985**, *50*, 5159-5166.
13. We speculate that the nitrogen and/or sulfur atom of the PyS group acts as a catalyst poison.
14. This ratio of ketones **9c** and **10c** was obtained when cyclisation of **3c** was carried out at -20°C.
15. This ratio of ketones **9b** and **10b** was obtained when cyclisation of **3b** was carried out at 25°C.
16. For a review on the uses of SmI_2 in organic synthesis, see Kagan, H. B.; Namy, J. *Tetrahedron* **1986**, *42*, 6584-6614.
17. [1*R**,6*S**,7*R**]-6-Heptyl-5-oxo-2,4,8-trioxabicyclo[5.4.0]undecane **16**: δ_H ($CDCl_3$, 270 MHz) 5.37 and 5.29 (both 1H, d, J 18.5 Hz, AB quartet, OCH_2O), 4.11-4.04 (1H, m, H-9eq), 3.79-3.75 (1H, m, H-1), 3.49-3.38 (2H, m, H-9ax + H-7), 2.82 (1H, t, J 6.5 Hz, H-6), 2.17-1.91, 1.81-1.55 and 1.49-1.20 (16H, 3 x m, H-10, H-11 and $(CH_2)_6CH_3$), 0.90 (3H, t, J 7.0 Hz, CH_3).
18. [1*R**,6*R**,7*S**]-9-Heptyl-8-oxo-2,7-dioxabicyclo[4.3.0]nonane **17**: δ_H ($CDCl_3$, 300 MHz) 4.25 (1H, m, H-6), 4.09 (1H, dd, J 4.0, 2.0 Hz, H-1), 3.93 (1H, m, H-3eq), 3.37 (1H, td, J 12.0, 2.0 Hz, H-3ax), 2.53 (1H, dt, J 9.5, 4.0 Hz, H-9), 2.35-2.29 (1H, m, 1 x H-4 or H-5), 1.95-1.60 and 1.52-1.20 (15H, 2 x m, 1 x H-4 + 2 x H-5, or 2 x H-4 + 1 x H-5, and $(CH_2)_6CH_3$), 0.89 (3H, t, J 7.0 Hz, CH_3).
19. The second most abundant product (20%) was the corresponding enol ether derived from **10c**. The minor product (10%) was the isomeric tetrasubstituted silyl enol ether. The total yield was 80%.
20. [1*R**,5*S**,6*R**]-4-*tert*-Butyldimethylsilyloxy-5-isopropyl-2,7-dioxabicyclo[4.4.0]dec-3-ene **19**:δ_H ($CDCl_3$, 270 MHz) 6.25 (1H, d, J 2.5 Hz, H-3), 4.08-4.01 (1H, m, H-8eq), 3.67 (1H, m, H-1), 3.60 (1H, dt J 2.5 Hz, H-6), 3.41 (1H, td, J 12.0, 2.5 Hz, H-8ax), 2.41-2.35 (1H, m, H-5), 2.13 (1H, octet, J 5.0 Hz, $CH(CH_3)_2$), 2.05-1.92, 1.70-1.59 and 1.40-1.28 (4H, m, H-9 + H-10), 1.06 and 1.02 (both 3H, d, J 7.0 Hz, $CH(CH_3)_2$), 0.91 (9H, s, *t*-Bu), 0.13 and 0.11 (both, 3H, s, $Si(CH_3)_2$).
21. ZENECA in the U.K. is part of ZENECA Limited.