Template-Directed Intramolecular *C*-Glycosidation. Synthesis of the Central Tetrahydrofuran Fragment of the Elfamycin Antibiotic Aurodox

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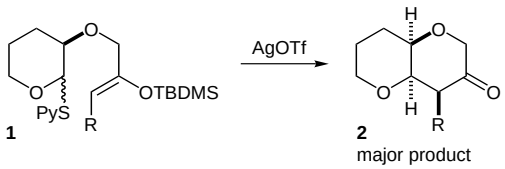
Abstract: A 14-step synthesis of the central tetrahydrofuran portion **4** of the elfamycin antibiotic aurodox is described, starting from the D-lyxose derivative **5**. The key steps are template-directed intramolecular *C*-glycosidation by cation-mediated cyclisation of thioglycoside **6**, and chelation-controlled addition of ethynylmagnesium bromide to aldehyde **8**.

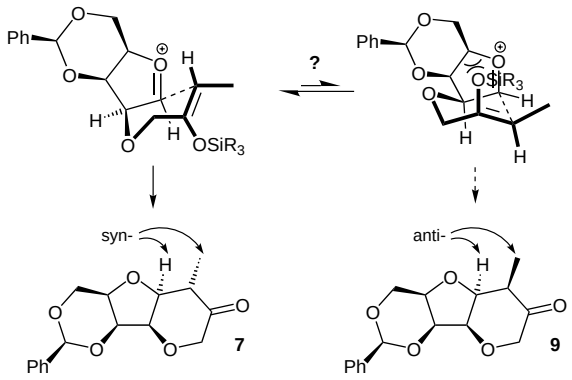
As part of our programme to develop template-directed cyclisation reactions for *C*-glycoside synthesis,[1] we recently described[2] the silver(I) triflate-mediated conversion of thioglycosidic silyl enol ethers **1** into bicyclic *C*-glycosides **2** (Scheme 1). These transformations proceeded in good yields and with good diastereoselectivities; further synthetic elaboration gave the products (or their derivatives) of overall in*ter*molecular delivery of nucleophilic carbon functionality to the anomeric centre, syn- with respect to the neighbouring hydroxyl group.



Scheme 1

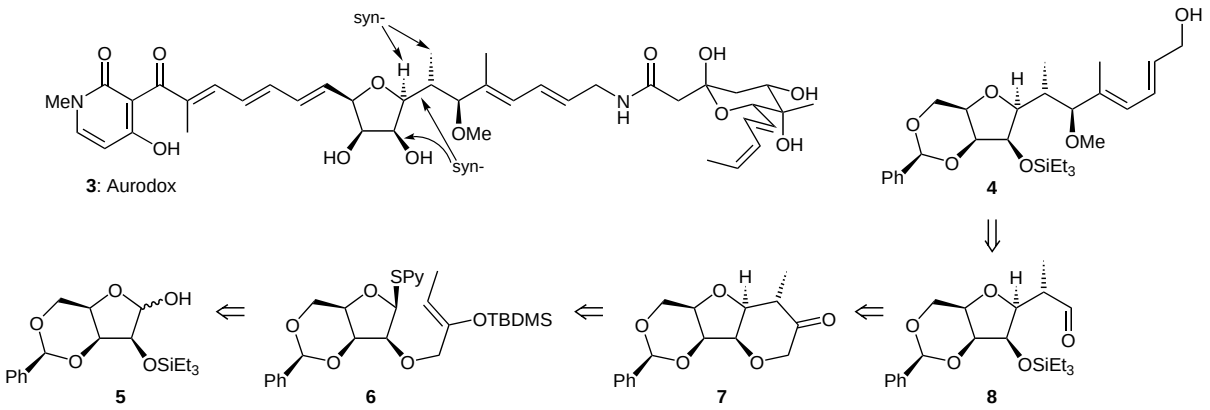
We became interested in the application of this methodology to target-oriented synthesis, and chose fragment **4** corresponding to the central tetrahydrofuran portion of the elfamycin antibiotic aurodox **3**[3] as an appropriate candidate. The retrosynthetic analysis is shown in Scheme 2; our plan was to introduce the dienyl side-chain by chelation-controlled addition of an appropriate organometallic nucleophile to the aldehyde **8**, which would be made from the product **7** of cyclisation of substrate **6**, in turn derived from D-lyxose derivative **5**.

Compound **4** was a compelling goal for several reasons. Firstly, it possesses a syn-relationship between the anomeric C–C bond and the neighbouring oxygen atom on the five-membered ring, and as such seemed an ideal target molecule to exemplify our intramolecular delivery-based approach.[4] Secondly, it contains a fully oxygenated five-membered sugar-derived template; we considered that the crowded environment created by the all-β disposition of the oxygenated substituents, and the potentially destabilising effect of these substituents on the anomeric cationic intermediate would provide a stern test for our strategy. Finally, unlike the major products **2** of the previous cyclisation reactions on six-membered templates, compound **4** bears a syn relationship between the ex-anomeric hydrogen atom and the substituent on the vicinal exocyclic stereocentre. Inspection of our pictorial model for the cyclisation process led us to believe that the anti-selectivity observed previously would be reversed on account of the crowded nature of the substrate β-face, favouring **7** over **9** (Scheme 3), and we were keen to test this hypothesis. This Letter reports the results of these investigations.



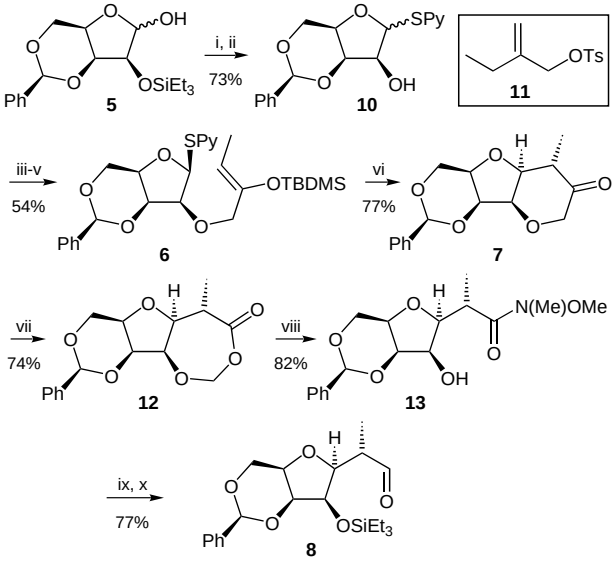
Scheme 3

Target substrate **6** (Scheme 2) was readily assembled from protected D-lyxose **5**[5] according to the route used in our methodological studies.[6] Thus, thioglycosidation[7] of **5** and desilylation gave thioglycosidic alcohol **10**, whose sodium salt was alkylated with tosylate **11**.[8] The resulting ether was subjected to ozonolysis, followed by silyl enol



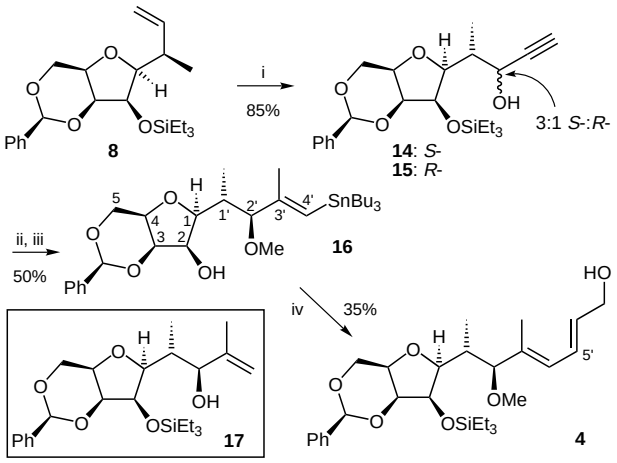
Scheme 2

etherification to give the *Z*- enol ether **6** in good overall yield as a single regioisomer. Addition of a solution of **6** to silver(I) triflate in CH_2Cl_2 resulted in clean formation of a single product, which was identified as **7** on the basis of n.O.e.s between H-1 and H-6 (11%), and H-5 and the benzylidene ortho-proton (2%).[9] Next, compound **7** was subjected to regioselective Baeyer–Villiger reaction in the presence of buffered peracetic acid containing TFA and $MgSO_4$ as a drying agent; the expected structure of the resulting crystalline lactone–acetal **12** was confirmed by X-ray crystallography.[10] Treatment of **12** with HN(Me)OMe·HCl–Me_3Al[11] resulted in smooth ring-opening to give the crystalline *N*-methoxyamide **13**, which was silylated, and reduced using $LiAlH_4$–THF[12] to give the aldehyde **8** (Scheme 4).



Scheme 4: (i) PySSPy, *n*-Bu_3P, CH_2Cl_2, 0°C; (ii) *n*-Bu_4NF, CH_2Cl_2, 0°C; (iii) **10** + **11** + *n*-Bu_4NI in DMF added to NaH, 0°C; (iv) O_3, CH_2Cl_2, -78°C, then PPh_3, -78°C→rt; (v) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C→rt; (vi) AgOTf (2 equiv), 4Å mol sieves, CH_2Cl_2, -20°C, 5 h; (vii) CH_3CO_3H, NaOAc, TFA (cat.), $MgSO_4$, CH_2Cl_2; (viii) *i*-PrMgCl, MeONHMe·HCl, THF, -20°C; (ix) Et_3SiOTf, Py, CH_2Cl_2, 0°C; (x) $LiAlH_4$, Et_2O, 0°C.

The final stages of our synthesis of **4** involved introduction of the *E*,*E*-configured 1,3-diene-containing side-chain. Our plan was to effect syn-carbometallation of an ethynyl group and then chain-extend this by coupling with a suitable hydroxy-containing iodoalkene. It was anticipated that the correct stereochemistry adjacent to the requisite terminal alkyne would be secured by delivery of acetylide anion in a chelation-controlled fashion to the re- face of the carbonyl function in silyloxyaldehyde **8**. In the event, addition of ethynylmagnesium bromide to **8** resulted in the high-yielding formation of two diastereomeric secondary alcohols **14** and **15** in a ca. 3:1 ratio. Assignment of *S*-configuration to the newly-formed stereocentre in the major compound followed from the observation of its CF_3 resonance 120 Hz upfield from that of the minor, *R*-isomer in the ^{19}F nmr spectrum (376.5 MHz) of the derived Mosher's esters.[13] Also, the major product **17** of addition of isopropenylmagnesium bromide to **8** was shown by X-ray crystallographic analysis[10] to have the *S*-configuration at this centre. Separation of **14** and **15** could be achieved by reversed-phase HPLC, but it was found to be more convenient to process these as a mixture. Thus, methylation of **14**/**15** under standard conditions, followed by stannylcupration[14] using $Bu_3Sn(Bu)CuCNLi_2$[15] and quenching with iodomethane gave **16** in 50% yield, together with ca. 20% of the minor diastereomer; the isomers were now readily separated by flash column chromatography.[16] Finally, coupling of **16** with *E*-3-iodo-2-propen-1-ol[17] mediated by copper(I) thiophene-2-carboxylate[18] gave the target compound **4** in an unoptimised yield of 35%.[19] The completion of the synthesis of **4** is shown in Scheme 5.[20]



Scheme 5: (i) HCCMgBr, THF, 0°C; (ii) NaH, MeI, DMF, 0°C→rt; (iii) *n*-$Bu_3Sn(Bu)CuCNLi_2$ (4 equiv), MeI (20 equiv), THF–DMPU (10:1), -78°C→rt; (iv) copper(I) thienyl-2-carboxylate, *E*-3-iodo-2-propen-1-ol, *N*-methylpyrrolidone, rt.

In summary, we have demonstrated that template-directed intramolecular *C*-glycosidation is an effective strategy for the assembly of a stereochemically complex *C*-glycoside, with good to excellent stereoselectivity. We are investigating also the application of this approach to the synthesis of *C*-disaccharides, and the results of these studies will be published in due course.

Acknowledgements

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References and Notes

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4. Martin and co-workers have reported extensively on intramolecular *C*-arylation of glycosides using cation-mediated transformations. See: Martin, O. R.; Hendricks, C. A. V.; Deshpande, P. P.; Cutler, A. B.; Kane, S. A.; Rao, S. P. *Carbohydr. Res.* **1990**, *196*, 1-58 and references therein.
5. D-Lyxonolactone was protected as the benzylidene acetal, triethylsilylated and reduced with DIBAL-H to give **5**.
6. All yields cited herein are of isolated, purified materials which gave satisfactory ^1H, ^{13}C nmr and IR spectra, and which showed low-resolution MS and either elemental combustion analysis or

high-resolution MS characteristics in accord with the assigned structures.

7. Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289-4296. *S*-Glycosidation of **5** resulted in the formation of a ca. 7:2 β:α anomeric mixture, together with a small amount of the *N*-glycoside.[1(i)] Separation of the isomers was carried out after desilylation; only the β-anomer was taken through the rest of the sequence.
8. The alcohol precursor of **11** was made by CuI-mediated addition of ethylmagnesium bromide to propargyl alcohol: Duboudin, J. G.; Jousseaume, B. *J. Organometal. Chem.* **1979**, *168*, 1-11.
9. We thank Mr Dick Sheppard and Mr Paul Hammerton of this department for these determinations.
10. We thank Professor David J. Williams and Dr Andrew J. P. White of this department for these determinations.
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16. The yield of **16** cited is that obtained from the mixture of **14** and **15**. Compound **16**: $[\alpha]_D^{25}$ -16.3 (*c* 0.55, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz) 7.53-7.48 (2H, m, ortho-Ph), 7.37-7.28 (3H, m, meta- and para-Ph), 5.75 (1H, s, H-4'), 5.51 (1H, s, PhC*H*), 4.62-4.51 (2H, m, H-2 + H-1 or H-3), 4.40 (1H, d, J 13.0 Hz, H-5), 4.18-4.05 (2H, m, H-5 + H-2'), 3.58 (1H, br s, H-4), 3.49 (1H, t, J 10.5 Hz, H-3 or H-1), 3.22 (3H, s, OCH_3), 1.90-1.82 (1H, m, H-1'), 1.63 (3H, s, C-3' CH_3), 1.50 (6H, m, 3 x Bu_3Sn CH_2), 1.30 (6H, m, 3 x Bu_3Sn CH_2), 1.00-0.84 (27H, C-1' CH_3 + $SiEt_3$ CH_3 + 3 x Bu_3Sn CH_2 + Bu_3Sn CH_3), 0.59 (6H, q, J 8.0 Hz, $SiEt_3$ CH_2); δ_C ($CDCl_3$, 75 MHz) 151.8, 138.5, 129.0, 128.6, 128.0, 126.5, 99.6, 91.7, 79.1, 76.6, 75.1, 70.8, 67.5, 56.1, 35.6, 29.4, 27.4, 17.7, 13.8, 11.5, 10.2, 6.8, 4.8.
17. *E*-3-Iodo-2-propen-1-ol was made by DIBAL-H reduction of methyl *E*-3-iodo-2-propenoate, which was prepared according to a literature procedure: Biougne, J.; Théron, F.; Normant, M. H. *Comptes Rendus Acad. Sci. C* **1971**, *272*, 858-861.
18. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.
19. Yield based on recovered stannane (30% recovery).
20. Compound **4**: $[\alpha]_D^{25}$ -36.8 (*c* 0.75, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz) 7.50-7.45 (2H, m, ortho-Ph), 7.35-7.29 (3H, m, meta- and para-Ph), 6.52 (1H, dd, J 15.0, 10.5 Hz, H-5') 6.02 (1H, d, J 10.5 Hz, H-4'), 5.82 (1H, dt, J 15.0, 6.0 Hz, H-6'), 5.48 (1H, s, PhC*H*), 4.61 (1H, dd, J 9.0, 5.0 Hz, H-2), 4.55 (1H, dd, J 9.0, 1.0 Hz, H-1 or H-3), 4.41 (1H, d, J 13.0 Hz, H-5), 4.21 (2H, d, J 6.0 Hz, H-7'), 4.18-4.10 (2H, m, H-3 or H-1 + H-5), 3.57 (1H, br s, H-4), 3.47 (1H, d, J 10.5 Hz, H-2'), 3.18 (3H, s, OCH_3), 1.98-1.89 (1H, m, H-1'), 1.65 (3H, s, C-3' CH_3), 1.00-0.81 (12H, m, C-1' CH_3 + $SiEt_3$ CH_3), 0.57 (6H, q, J 8.0 Hz, $SiEt_3$ CH_2); δ_C ($CDCl_3$, 100 MHz) 138.4, 137.2, 131.5, 128.7, 128.6, 128.0, 127.5, 127.2, 126.4, 99.5, 89.2, 78.9, 76.4, 75.0, 70.7, 67.4, 63.7, 56.1, 35.8, 11.5, 10.5, 6.7, 4.7; *m*/*z* (CI) 473 $[M - OCH_3]^+$, 455 $[M - OCH_3 - H_2O]^+$, 341, 323, 282, 250, 141, 132, 121 (Found: $[M - OCH_3]^+$, 473.2724; $C_{28}H_{44}O_6Si$ requires $[M - OCH_3]^+$, 473.2723).
21. ZENECA in the U.K. is part of ZENECA Limited.