C-Furanoside Synthesis *via* Radical Cyclisation of β-Alkoxyacrylates

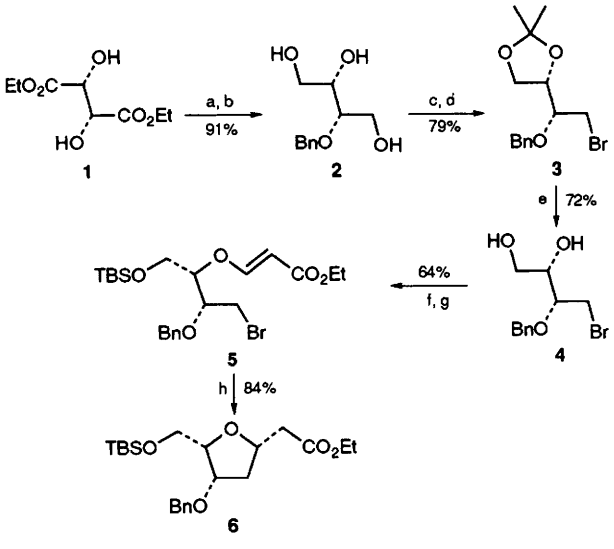
Eun Lee* and Cheol Min Park

Department of Chemistry, Seoul National University, Seoul 151-742, Korea

Stereoselective synthesis of *C*-furanosides is accomplished *via* tributylstannane-mediated radical cyclisation of β-alkoxyacrylates.

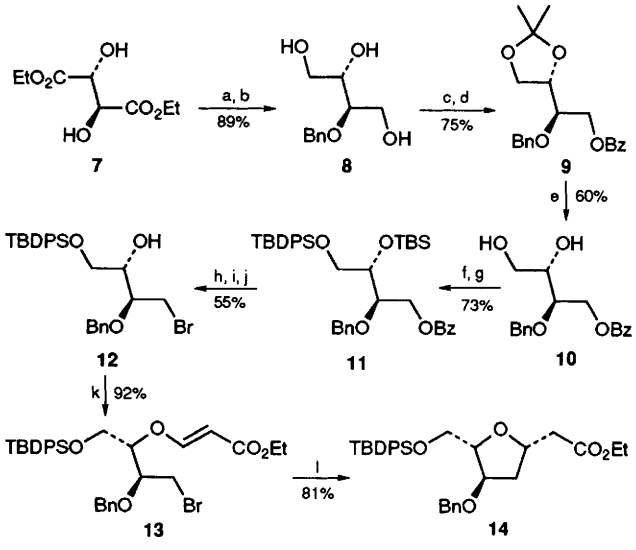
C-Furanosides are an important class of compounds as precursors to *C*-nucleoside antibiotics and other more complex natural products. Generally these are made from reducing sugars *via* Wittig reaction with stabilised ylides and intramolecular Michael addition of the hydroxy group.[1] This method generally yields mixtures of stereoisomers at the 'anomeric' carbon centre. Similar problems are frequently encountered in reactions involving radical[2] and ionic[3] intermediates. We reported recently that the β-alkoxyacrylate moiety is an excellent radical acceptor in intramolecular cyclisation reactions producing (tetrahydrofuranyl)- and (tetrahydropyranyl)-acetate ring systems in high yield.[4] The most notable feature of this type of reaction is the high stereoselectivity: *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans were obtained exclusively. This selectivity can be explained on conformational analysis grounds in that the s-*trans* conformation of the β-alkoxyacrylate C–O bond is more stable than the alternative s-*cis* conformation which should be destabilised by $A^{1,3}$ type allylic strain.[5]

We now report that the strategy can be applied successfully in *C*-furanoside synthesis using appropriately functionalised polyhydroxy compounds generated from tartaric acids. Ethyl (*R*,*R*)-tartrate **1** was converted into the corresponding benzaldehyde acetal which was reduced by a mixed hydride reagent to afford the benzyl ether **2**.[6] The bromide **3** was obtained *via* acetonide protection and bromide substitution of the primary hydroxy group. Deprotection led to the isolation of the diol **4**, which was treated with ethyl propiolate in the presence of *N*-methylmorpholine[7] to give the β-alkoxyacrylate **5** after selective protection of the primary hydroxy group. The substrate **5** was subjected to standard radical generating conditions in the presence of tributylstannane and the product **6** was isolated in good yield (Scheme 1). No other products were isolated.

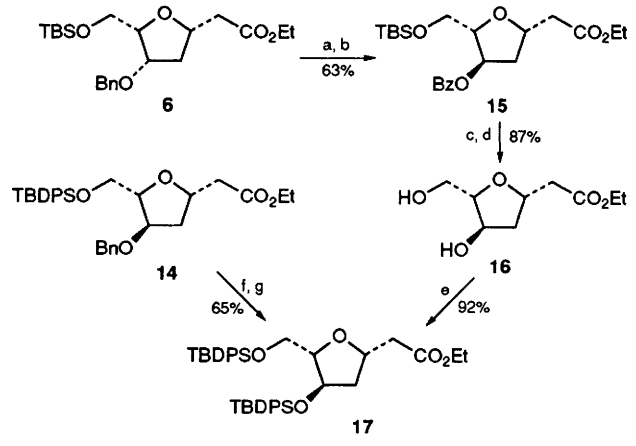


Scheme 1 *Reagents and conditions*: (a) PhCHO, cat. TsOH, benzene, reflux; (b) $LiAlH_4$–$AlCl_3$ (1:1), Et_2O–CH_2Cl_2 (1:1), reflux; (c) $Me_2C(OMe)_2$, cat. TsOH, benzene, reflux; (d) CBr_4, PPh_3, pyridine; (e) cat. TsOH, MeOH; (f) TBSCl, imidazole, CH_2Cl_2; (g) $HCCCO_2Et$, NMM, CH_2Cl_2; (h) Bu_3SnH, cat. AIBN, benzene, reflux (Ts = *p*-$MeC_6H_4SO_2$; TBSCl = Bu^tMe_2SiCl; NMM = *N*-methylmorpholine; AIBN = azoisobutyronitrile; Bn = benzyl)

The diastereoisomeric *C*-furanoside derivative **14** was synthesized from ethyl *meso*-tartrate **7**. The benzyl ether **8** obtained from **7** was converted into the benzoate **9**. Deprotection of **9** led to the diol **10**, which was sequentially treated with TBDPSCl and TBSCl to give the differentially protected tetrahydroxybutane **11**. Hydrolysis of the benzoate moiety and bromide substitution followed by boron trifluoride deprotection of the TBS ether group afforded the bromoalcohol **12**.† The *C*-furanoside product **14** was obtained in good yield from the corresponding β-alkoxyacrylate **13** (Scheme 2). Again, no other products were isolated.



Scheme 2 *Reagents and conditions*: (a)–(c) as Scheme 1; (d) BzCl, pyridine, CH_2Cl_2; (e) cat. TsOH, MeOH; (f) TBDPSCl, imidazole, CH_2Cl_2; (g) TBSCl, imidazole, CH_2Cl_2; (h) K_2CO_3, MeOH; (i) CBr_4, PPh_3, pyridine; (j) BF_3·OEt_2, $CHCl_3$; (k) $HCCCO_2Et$, NMM, CH_2Cl_2; (l) Bu_3SnH, cat. AIBN, benzene, reflux (Bz = benzoyl; TBDPSCl = Bu^tPh_2SiCl)



Scheme 3 *Reagents and conditions*: (a) H_2, Pd/C, EtOH; (b) PPh_3, DEAD, $PhCO_2H$, benzene; (c) TsOH, EtOH, reflux; (d) NaOEt, EtOH; (e) TBDPSCl, imidazole, CH_2Cl_2; (f) H_2, $Pd(OH)_2$, EtOH; (g) TBDPSCl, imidazole, DMAP, CH_2Cl_2 (DEAD = diethyl azodicarboxylate; DMAP = 4-dimethylaminopyridine)

The structural assignment of **6** and **14** was confirmed by correlation with the known *C*-furanoside derivative **17**.[8] In the event, hydrogenolysis and Mitsunobu conversion of **6** afforded the benzoate **15**, which was deprotected to give the diol **16**. Derivatisation of **16** with TBDPSCl led to the isolation of **17** as the sole product. The conversion of **14** into **17** was accomplished uneventfully (Scheme 3).

In the reactions described above, the '2,5-*cis*' principle held invariably, regardless of the stereochemistry of additional substituents. We believe that this stereoselectivity is unique in radical cyclisations involving β-alkoxyacrylate and further application of this type of reaction in the synthesis of more complex molecules will the subject of our future investigations.

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Footnote

† The detour involving benzoate was necessary because deprotection of the bromide corresponding to **9** resulted mainly in the formation of the tetrahydrofuran derivative in this case.

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5 The s-*cis* conformation of methyl vinyl ether is known to be more stable than the s-*trans* conformation. See D. Bond and P. v. R. Schleyer, *J. Org. Chem.*, 1990, **55**, 1003. In this case, the substrates are *sec*-alkyl vinyl ethers, and steric effects are obviously more important.
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8 M. A. Bernstein, H. E. Morton and Y. Guindon, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1155. ^{1}H NMR data for the final product **17** matched exactly with the reported values.