ChemComm

Practical radical cyclisations leading to the construction of near-stereopure quaternary carbon stereogenic centres

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Received (in Liverpool, UK) 12th October 1998, Accepted 2nd November 1998

The 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl auxiliary is effective in directing bromopropargyloxy additions to the olefinic bonds of vinylogous esters/carbonates; in the presence of AIBN and 1-ethylpiperidinium hypophosphite, the adducts undergo highly stereoselective reductive radical cyclisations in which quaternary carbon stereogenic centres are generated.

The control of the absolute stereochemical outcome of reactions that generate quaternary carbon stereogenic centres is an important requirement in synthesis which is receiving much attention.[1] For radical methodology to provide a contribution, it is necessary to effect stereoselective additions of tertiary carbon radicals to carbon-based radical acceptors or of carbon radicals to tertiary olefinic acceptors. The ability to direct such radical additions by the use of temporarily attached auxiliaries† would offer notable synthetic versatility. To date, however, very few examples of such processes have been reported.[2]

Recently, we have shown that vinylogous esters/carbonates bearing the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl auxiliary react with NBS and primary alcohols with excellent regioselectivity, high *anti* stereoselectivity and reasonable facial selectivity.[3] For example, in reactions involving PrOH, the olefins **1a–c** gave rise to *ca*. 6:1 mixtures of the bromopropoxy derivatives **2a–c** and **3a–c** (Scheme 1), from which the major products **2a–c** could be isolated in near-stereopure states and satisfactory yields by fractional crystallisation. Seeking to stereoselectively replace the bromine atoms by functional carbon substituents, we have studied the radical reactivity of bromides of type **4**. We now report our findings.

As outlined in Scheme 2, it was envisaged that, in the presence of a radical reducing agent, bromides of type **4** would afford tertiary radicals of type **5** which would undergo 5-*exo*-*dig* cyclisations and acceptance of hydrogen atoms to give products of types **6** and/or **7**. In an initial experiment, it was found that the vinylogous ester **1a** was converted into a 4:1 mixture of the requisite bromide **4a** and a diastereomer by the action of NBS and propargyl alcohol; fractional crystallisation provided **4a**,‡ mp 169–170 °C, $[\alpha]_D$ −68 (*c* 0.54, CH_2Cl_2), in 54% yield. When heated in toluene under reflux with AIBN and Bu_3SnH, **4a** was transformed into one major product (35% yield after chromatography and crystallisation), mp 94–95 °C, $[\alpha]_D$ −23 (*c* 0.25, CH_2Cl_2), that clearly possessed the structure **6a** or **7a** on the basis of its analytical and spectral properties.

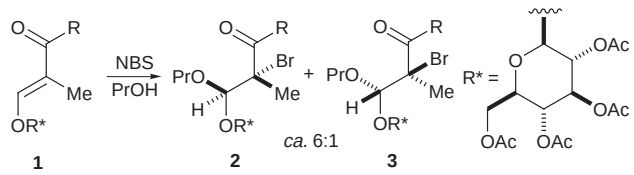
That the radical cyclisation product possessed the stereostructure **6a** was established by an X-ray crystallographic analysis of a derivative. Thus, catalytic hydrogenation (H_2, 5% Pd–C, EtOAc) afforded a 3:1 mixture of dihydro derivatives, from which the major diastereomer, mp 151–152 °C, $[\alpha]_D$ +40 (*c* 0.25, CH_2Cl_2), was isolated by fractional crystallisation. The product possessed the stereostructure **8** on the basis of the X-ray analysis§ (Fig. 1). Clearly, the radical **5a** had undergone a reductive cyclisation to give **6a** rather than **7a**. Moreover, there was a preference for hydrogen addition to **6a** to occur *syn* to the acyl group. Finally, the presumed stereochemical outcome of the initial bromopropargyloxylation reaction was substantiated.

Numerous attempts were made to improve the efficiency of the **4a**→**6a** transformation and to avoid the handling of toxic tin-based reagents. The use of AIBN and tris(trimethylsilyl)-silane[4] in toluene under reflux provided a cleaner raw product but chromatography was still required to remove impurities; **6a** was then isolated in 65% yield. However the best result was achieved when **4a** was heated with AIBN and 1-ethylpiperidinium hypophosphite[5] in toluene under reflux; the crude product, obtained in essentially quantitative yield after work-up, was very largely **6a**.

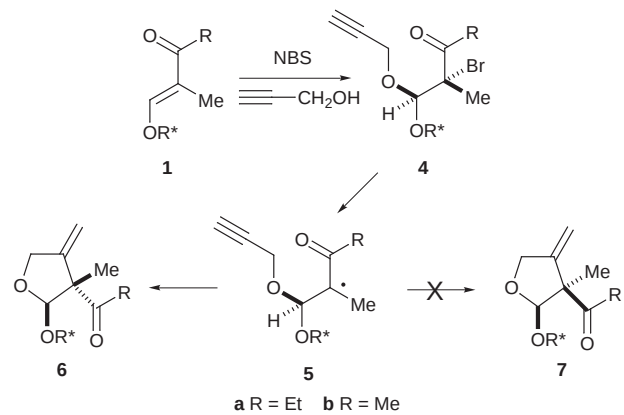
The effectiveness of the overall technology was demonstrated further by its application to the vinylogous ester **1b**. Thus, subjection of **1b** to the action of NBS and propargyl alcohol gave **4b**‡ (47% yield after crystallisation), mp 133–134 °C, $[\alpha]_D$ −82 (*c* 0.25, CH_2Cl_2), which underwent the hypophosphite-induced reductive radical cyclisation to give largely **6b** almost quantitatively; crystallisation provided **6b**,‡¶ mp 133–134 °C, $[\alpha]_D$ −28 (*c* 0.28, CH_2Cl_2), in 61% yield.

The excellent stereoselectivity observed in the aforecited radical cyclisations can be accommodated by an extension of a stereoinduction model proposed by Giese.[6] Thus, it is envisaged that the cyclisation occurs by way of the conformer **9** in which the acetal hydrogen atom is *syn* to the olefinic bond of the delocalised radical. A prediction of this model is that the stereochemical outcome is determined solely by the acetal configuration and that the auxiliary plays no direct role in the stereoinduction process.

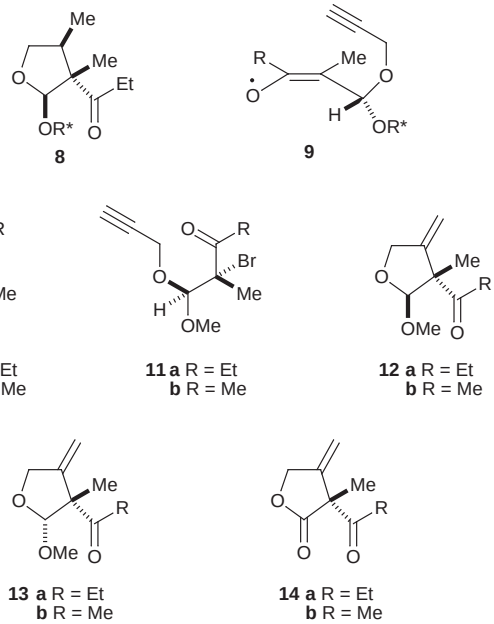
The vinylogous ester **10a**‖ was converted into the acetylenic bromide *rac*-**11a**‡ (73% yield after chromatography) which



Scheme 1



Scheme 2



underwent radical cyclisation to give compound *rac*-**12a**‡ (77% yield after chromatography) [a comparative NOE difference spectroscopic study on *rac*-**12a** and *rac*-**13a** (obtained by equilibration of *rac*-**12a** using TsOH and MeOH) left little doubt about the stereochemical assignments]. Similarly, **11b**‡ (obtained in 78% yield after chromatography by bromopropargyloxylation of **10b**‖) afforded *rac*-**12b**‡ (74% yield after chromatography). Clearly, the configuration of the acetal stereocentre of the reactants *rac*-**11a** and *rac*-**11b** determines the configuration of the quaternary carbon stereocentre of the products *rac*-**12a** and *rac*-**12b**, providing strong support for the stereoinduction model **9**.

To complete the study, it was appropriate to remove the sugar auxiliary from **6a** and **6b** and to determine the enantiomeric purities of the products. In preliminary experiments, it was shown that *rac*-**12a** and *rac*-**12b** could be oxidised (CrO_3, H_2SO_4, Me_2CO, ultrasound)[7] to the γ-lactones *rac*-**14a** and *rac*-**14b**,** the enantiomers of which were separable by GC.††

Under methanolysis conditions (TsOH, MeOH), **6a** was transformed into a 1:1 mixture of the methoxy derivatives **12a** and **13a**‡ (84% yield after chromatography), $[\alpha]_D$ −110 (*c* 0.16, CH_2Cl_2), whereas **6b** afforded a 3:1 mixture of the methoxy derivatives **12b** and **13b**‡ (79% yield after chromatography), $[\alpha]_D$ −142 (*c* 0.30, CH_2Cl_2). Following Jones' oxidation of the mixtures, the γ-lactones **14a** and **14b**** were isolated, each with 96% ee. Since the ee analyses were conducted on products that had been obtained from raw samples of **6a** and **6b**, it is clear that the hypophosphite-induced radical cyclisations displayed excellent stereoselectivities; moreover, the diastereomeric purities of the precursors **4a** and **4b** were high. When a crystallised sample of **6b** was employed, the derived γ-lactone **14b** possessed an ee of >99%.

The aforecited findings are significant in the following respects. In the presence of AIBN, 1-ethylpiperidinium hypophosphite offers marked advantages over Bu_3SnH or tris(trimethylsilyl)silane in effecting 5-*exo*-*dig* reductive radical cyclisations‡‡ of acetylenic bromides. The high stereoselectivities observed in the radical cyclisations are striking; they can be accommodated by a simple stereoinduction model dictated by allylic strain considerations. As well as providing a further illustration of the versatility of vinylogous esters/carbonates of type **1** in asymmetric synthesis, the technology enables units featuring quaternary carbon stereogenic centres with three functional arms to be assembled in multigram quantities.

We thank the DTI and EPSRC for subsidisation of a studentship (to D. S. W.) under the Link Asymmetric Synthesis Programme. We are also grateful to P. D. Tiffin for relevant preliminary studies and to Dr G. Potter for helpful advice.

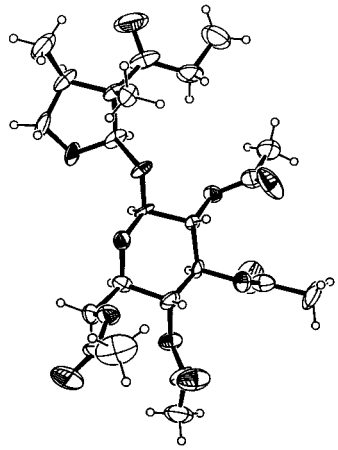


Fig. 1 Molecular structure of **8**.

Notes and references

† For examples of the use of chiral auxiliaries in radical reactions, see ref. 8.

‡ This compound displayed analytical and spectral properties that supported its assigned structure.

§ *Crystal data* for **8**: $C_{23}H_{34}O_{12}$, M = 502.5, monoclinic, space group $P2_1$, a = 6.425(6), b = 23.566(7), c = 17.545(7) Å, β = 90.36(4)°, Z = 4 (2 molecules per asymmetric unit), D_c = 1.256 g cm^{-3}, $F(000)$ = 1072, μ(Mo–Kα) = 1.05 cm^{-1}, crystal size 0.30 × 0.25 × 0.25 mm. A total of 4328 reflections were measured, 4315 of which were unique (R_{int} = 0.067), on a Siemens R3m/V diffractometer using the $\omega/2\theta$ scan method (λ = 0.71073 Å) at 293(2) K. The structure was solved by direct methods and refined by full-matrix least-squares based on F^2, with all non-hydrogen atoms anisotropic and hydrogen atoms constrained in calculated positions. The final cycle converged to R = 0.1280 and wR^2 = 0.2431. CCDC 182/1081. The crystallographic data is available as a .cif file; see http://www.rsc.org/suppdata/cc/1998/2691

¶ A solution of **4b** (5.61 g, 10 mmol), 1-ethylpiperidinium hypophosphite (8.99 g, 50 mmol) and AIBN (0.34 g, 2.0 mmol) in toluene (150 cm^3) was heated under reflux for 1 h. The resulting olive-green mixture was concentrated and the residue was dissolved in CH_2Cl_2. The solution was filtered through a pad of Celite and the filtrate washed with water (×2) and brine. Evaporation of the dried ($MgSO_4$) organic phase left a white solid (5.05 g) which was largely **6b**. After crystallisation from Pr^{i}OH, **6b** (2.99 g, 61%) was isolated in a pure state.

‖ Compounds **10a** and **10b** were prepared by methylation (MeOTs, Me_2SO) of the corresponding sodium enolates [obtained by the method of Kaushal *et al*. (ref. 9)].

** The yields of these products were low (10–18%).

†† The enantiomers were separated on a Chiraldex γ-cyclodextrin trifluoroacetyl column (heated from 100 to 160 °C at a rate of 1.5 °C min^{-1}).

‡‡ This appears to be the first report of the use of 1-ethylpiperidinium hypophosphite to effect such reactions.

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Communication 8/07930G