Triol protection with 6-benzoyl-3,4-dihydro-(2*H*)-pyran†

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6-Benzoyl-3,4-dihydro-(2*H*)-pyran will protect 1,2,3-triols such as glycerol as their corresponding spiro-[5-phenyl-3,6,8-trioxabicyclo[3.2.1]octane-4,2′-tetrahydropyran]s and 1,2,4-triols (less efficiently) as the corresponding trioxabicyclo[3.2.2]nonanes; the hexol mannitol is converted into the corresponding bis-protected product.

Ketones (or gem-dimethoxyalkanes) can react with 1,2 or 1,3-diols with acid catalysis to form acetals, and dihydropyrans react with alcohols under similar conditions to form tetrahydropyrans. Ley and co-workers recently introduced bis-dihydropyrans to protect a wide range of 1,2-diols as their dispiroketals, the products being formed were those with maximum anomeric stabilisation at newly formed centres.[1] The Ley group has exploited the rigid architecture of these 'bispoke' derivatives in subsequent asymmetric reactions,[2] and exploited the bispoke derivatives of vicinal equatorial carbohydrate diols to tune glycoside reactivity.[3] Ley and co-workers have also developed 1,2-diketones (as 1,1,2,2-tetramethoxy derivatives) as 1,2-diol protecting groups, forming in acidic methanol the corresponding 2,3-dimethoxy-1,4-dioxane.[4] Reaction with glycerol gave triol protection resulting in 2-methoxy-3,7,8-trioxabicyclo[3.2.1]octane. Reaction with vicinal equatorial carbohydrate diols resulted in a glycosidation reactivity tuning effect between that of the corresponding benzylated and benzoylated systems.[5]

In contrast to that of diols, the protection of triols has been neglected. In this paper, we combine the protecting capability of dihydropyran and a carbonyl group in a single molecule to protect triols.

6-Benzoyl-3,4-dihydro-(2*H*)-pyran **1** can be conveniently prepared in large multigramme quantities.[6] Addition of *tert*-butyl lithium (34 mmol) to 3,4-dihydro-(2*H*)-pyran (33 mmol) at −20 °C forms the vinyl anion. Cooling to −78 °C followed by addition of *N*,*N*-dimethylbenzamide (31 mmol) and warming to room temperature gave a crude product (>95% pure) that was adequate for subsequent reactions, and could be kept in the fridge for weeks.

Initial experiments involved the reaction of **1** with glycerol and camphorsulfonic acid (CSA) in toluene under Dean and Stark conditions which gave two products, the expected trioxabicyclo-[3.2.1]octane **2**,[7] and a second compound whose spectral characteristics were consistent with a 2,5,7-trioxabicyclo[2,2,2]-octane. However reaction of glycerol (2.7 mmol), CSA (5.5 mmol), trimethylorthoformate (5.5 mmol) and **1** (5.5 mmol) in refluxing (12 h) methanol ('orthoformate' conditions) rapidly formed a single racemic crystalline triol protected product (1*R*,4(2′)*S*,5*S*)-spiro[5-phenyl-3,6,8-trioxabicyclo[3.2.1]octane-4,2′-tetrahydropyran] **2** in good yield (42%) (Scheme 1). In the product, **2**, the tetrahydropyranyl oxygen is axial relative to the 1,4-dioxane chair due to the anomeric effect, as shown in the X-ray structure (Fig. 1). Refluxing **2** in aqueous acid led to the recovery of **1**.

† Electronic supplementary information (ESI) available: experimental and X-ray diffraction data. See http://www.rsc.org/suppdata/cc/b4/b418035f/

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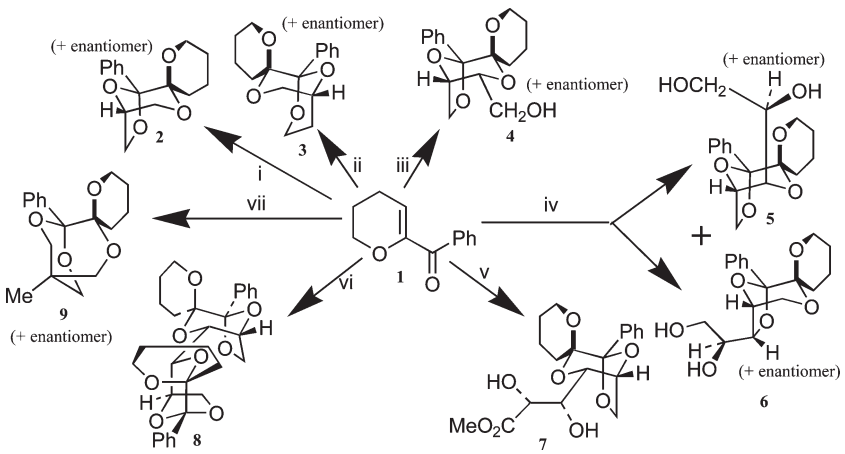

Scheme 1 Reaction of 6-benzoyl-3,4-dihydro-(2*H*)-pyran with trihydroxy-containing compounds in refluxing methanol containing trimethylorthoformate and catalytic camphorsulfonic acid (with yields). (i) Glycerol (42%), (ii) *racemic* butane-1,2,4-triol (6.5%), (iii) erythritol (68%), (iv) xylitol (**5** + **6** 37%), (v) δ-gluconolactone (48%), (vi) mannitol (39%), and (vii) 1,1,1-tris(hydroxymethyl)ethane (5%).

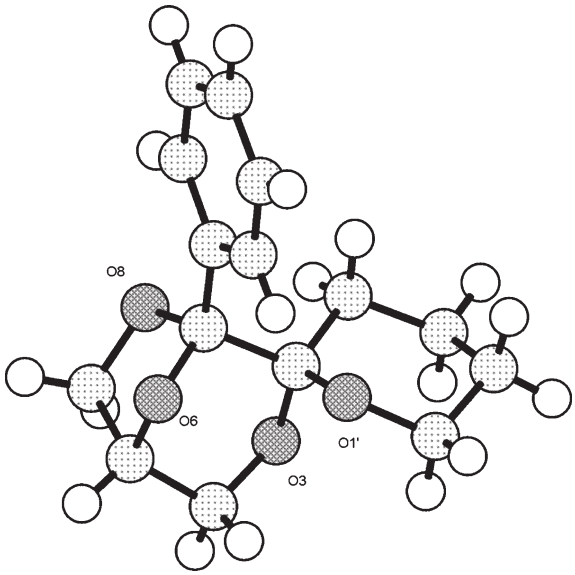

Fig. 1 X-Ray structure of **2**.

Reaction of **1** with 1,2,4-butantriol under 'orthoformate' conditions led to the isolation of crystalline *racemic*-(1*R*,5*R*,8(2′)*R*)-spiro[1-phenyl-2,7,9-trioxabicyclo[3.3.1]nonane-8,2′-tetrahydropyran] **3** in low yield (6%) (Scheme 1, Fig. 2).

Reaction with *meso*-erythritol under orthoformate conditions gave one major racemic product **4** which was readily separable by flash chromatography from a second minor isomer. Derivatisation of the major isomer to the 4-nitrobenzoate and analysis by X-ray crystallography showed that the remaining hydroxymethyl group was attached to C-2. This equatorial hydroxymethyl group could be converted into the corresponding bromide (PPh_3, CBr_4), or oxidised (Swern conditions) to the aldehyde and reacted with Grignard or Wittig reagents, or the alcohol converted into an alkene in one pot using manganese dioxide and the Wittig reagent.[8] Refluxing **4** in water–THF with CSA led to the recovery of erythritol (as the tetraacetate) in 75% yield.

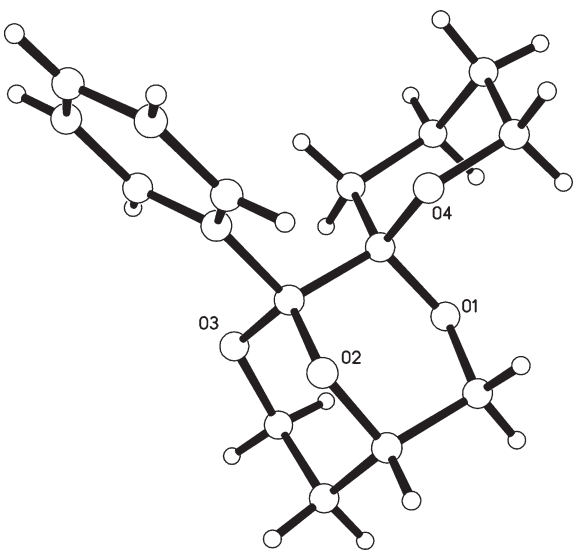

Fig. 2 X-Ray structure of **3**.

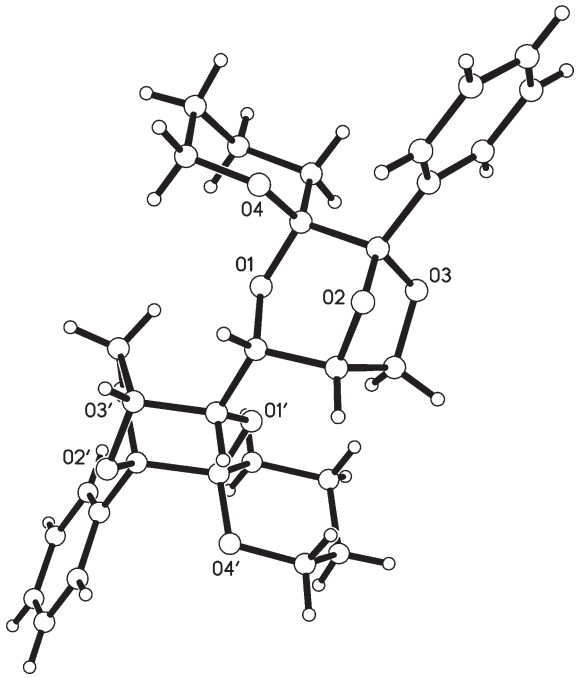

Fig. 3 X-Ray structure of **8**.

Reaction of **1** with the *meso*-pentol xylitol under the orthoformate conditions gave two isomeric products **5** and **6**. Derivatisation of the isomer **6** to the bis-4-nitrobenzoate followed by X-ray crystallography showed that **6** had the residual 1,2-dihydroxyethyl group attached to C-7.

X-Ray analysis of the bis-4-nitrobenzoate derivative of **7** showed that reaction of **1** with δ-gluconolactone gave methoxycarbonyl **7**, where reaction had occurred on the three terminal hydroxyl groups of the open chain form.

The reaction with D-(+)-mannitol under 'orthoformate' conditions gave the fully protected highly crystalline product **8** in 40% yield (Fig. 3).

Reaction with the 5-epimer of mannitol, D-sorbitol, gave a complex mixture, as did reactions attempted with molecules only containing secondary alcohols. However, reaction with 1,1,1-tris(hydroxymethyl)ethane gave a product (5%) whose spectral characteristics were consistent with the expected trioxabicyclo[3.2.2]nonane **9**.

In these preliminary studies, a convenient procedure for the protection of triols has been developed, that should prove valuable in synthesis of highly functionalised polyhydroxylated natural products, desymmetrisation of meso-polyols and the synthesis of isotopically labelled compounds.

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Notes and references

1 S. V. Ley, R. Downham, P. J. Edwards, J. E. Innes and M. Woods, *Contemp. Org. Synth.*, 1995, **2**, 365.

2 R. Downham, P. J. Edwards, D. A. Entwistle, A. B. Hughes, K. S. Kim and S. V. Ley, *Tetrahedron: Asymmetry*, 1995, **6**, 2403; S. V. Ley, S. Mio and B. Meseguer, *Synlett*, **1996**, 787; S. V. Ley, S. Mio and B. Meseguer, *Synlett*, 1996, 791; D. Lainé, M. Fujita and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1639; D. Lainé, M. Fujita and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1647.

3 G-J. Boons, P. Grice, R. Leslie, S. V. Ley and L. L. Yeung, *Tetrahedron Lett.*, 1993, **34**, 8523.

4 S. V. Ley, H. W. M. Priepke and S. L. Warriner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2290; R. Lenz, S. V. Ley, D. R. Owen and S. L. Warriner, *Tetrahedron: Asymmetry*, 1998, 2471; J. S. Barlow, D. J. Dixon, A. C. Foster, S. V. Ley and D. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1627.

5 P. Grice, S. V. Ley, J. Pietruszka, H. M. I. Osborn, H. W. M. Priepke and S. L. Warriner, *Chem.–Eur. J.*, 1997, **3**, 431; M-K. Cheung, N. L. Douglas, B. Hinzen, S. V. Ley and X. Pannecoucke, *Synlett*, 1997, 257; L. Green, B. Hinzen, S. J. Ince, P. Langer, S. V. Ley and S. L. Warriner, *Synlett*, 1998, 440.

6 R. K. Boeckman, Jr. and K. J. Bruza, *Tetrahedron Lett.*, 1981, **37**, 3997.

7 A 3,6,8-trioxabicyclo[3.2.1]octane has been reported previously: P. Calinaud and J. Gelas, *Can. J. Chem.*, 1978, **56**, 2292.

8 L. Blackburn, X. Wei and R.J. K. Taylor, *Chem. Commun.*, 1999, 1337; X. Wei and R. J. K. Taylor, *J. Org. Chem.*, 2000, **65**, 616.