

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 dispiroketal, 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

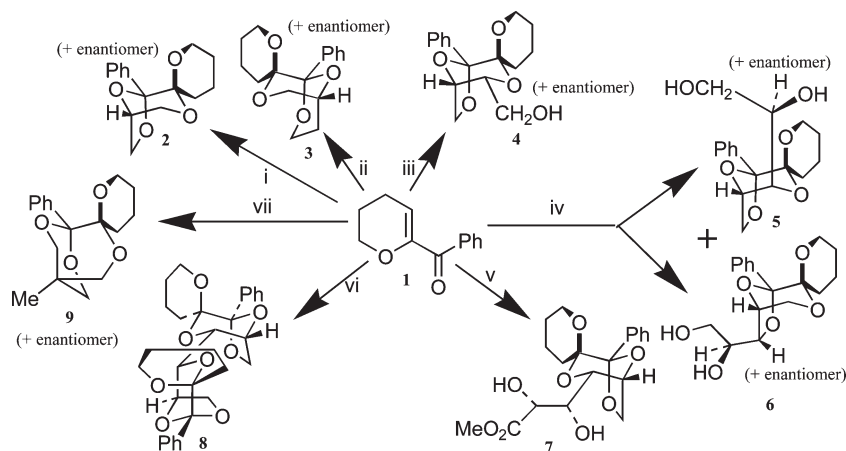
tuning effect between that of the corresponding benzylated and benzoylated systems.⁵

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 $-20\text{ }^{\circ}\text{C}$ forms the vinyl anion. Cooling to $-78\text{ }^{\circ}\text{C}$ 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/> *bjr2@le.ac.uk



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%).

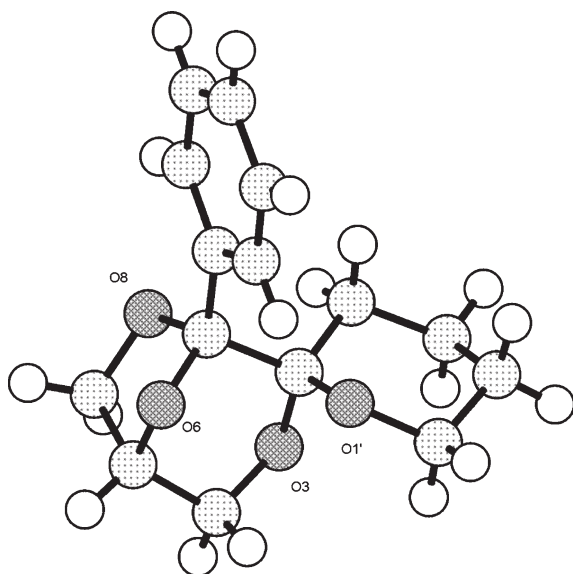


Fig. 1 X-Ray structure of 2.

Reaction of **1** with 1,2,4-butanetriol 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 (PPh₃, CBr₄), 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

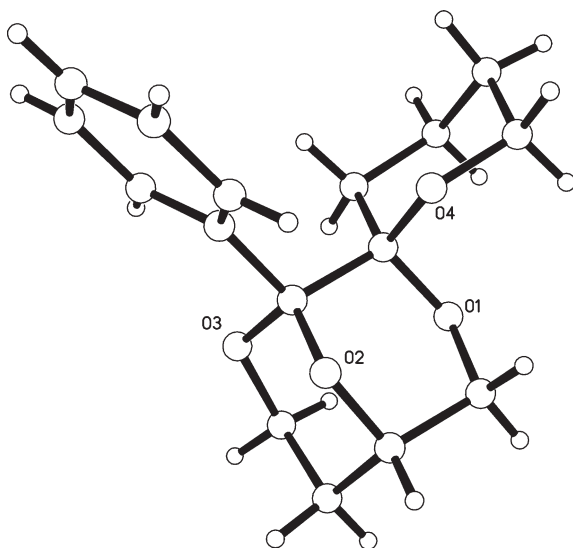


Fig. 2 X-Ray structure of 3.

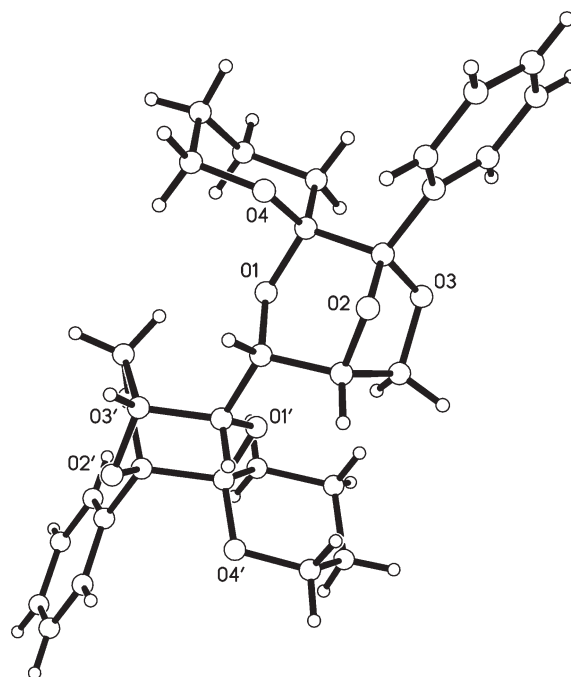


Fig. 3 X-Ray structure of 8.

CSA led to the recovery of erythritol (as the tetraacetate) in 75% yield.

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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