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Dispiroketals in Synthesis (Part 12)[1]: Functionalised Dispiroketals as New Chiral Auxiliaries; the Synthesis of Dihydroxylated Dispiroketals in Optically Pure Form.

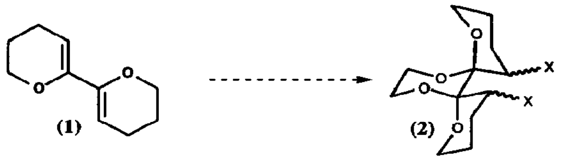
Barend C. B. Bezuidenhoudt†, Grant H. Castle and Steven V. Ley*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB1 2EW, U.K.

Abstract: A range of rigid, architecturally complex diols derived from dispiroketals have been synthesised. A bifunctional, C_2-symmetrical chiral auxiliary derived from these diols can be used in asymmetric synthesis.

The dispiroketal (**Dispoke**)[2] protecting group has been shown to be of great utility for the protection of 1,2-diols by reaction with *bis*-dihydropyrans such as (**1**). Examples include the preparation of a configurationally stable glyceraldehyde derivative,[2] many applications in the field of carbohydrates,[3] and the preparation of protected lactic acid derivatives whose enolates have been alkylated with a range of electrophiles to give the substituted adducts with moderate to excellent stereoselectivity.[4] If the *bis*-dihydropyran protecting agent bears substituents then these appended groups tend to adopt equatorial orientations which, in combination with the anomeric effects, dictates the configurations of the spirocentres. This approach has been used for chiral recognition of *trans* 1,2-diols in carbohydrates,[5] to enantioselectively protect glycerol[6] and other *meso*-polyols.[1]

It was envisaged that modification of the enol ether portions of a *bis*-dihydropyran prior to trapping with a diol would give rise to a variety of rigid, architecturally complex and diverse molecules (**2**) which may have applications in the field of asymmetric synthesis (Fig. 1).



X=OH (Oxidation or Dihydroxylation)
X=Cl, Br, I (Halogenation)
X=NR'R" (Aziridination)

Fig. 1

The preparation of enantiomerically pure materials is a crucial requirement for the modern synthetic organic chemist particularly in natural product synthesis. There has therefore been considerable interest in the exploitation of optically pure molecules which, by acting as chiral auxiliaries or modifiers, are able to influence the stereochemical outcome of chemical reactions. There is a constant need for new, cheap, low molecular weight chiral auxiliaries and chiral ligands and

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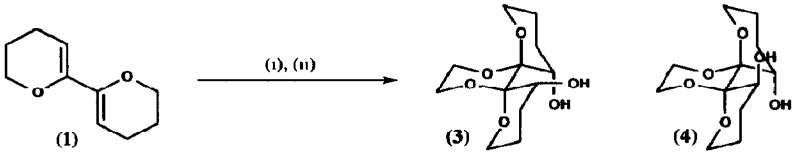
† *On study leave from the Department of Chemistry, The University of the Orange Free State, P.O. Box 339, Bloemfontein 9300, Rebublic of South Africa.*

catalysts for asymmetric synthesis which are easily obtainable in both enantiomeric forms. We considered that functionalised dispiroketals may prove useful in these respects and it was our aim to exploit these functionalised dispiroketals for asymmetric synthesis as in the following papers.

We have indeed found that treatment of *bis*-DHP (**1**) under a variety of epoxidation and dihydroxylation conditions followed by trapping with ethylene glycol under thermodynamic catalytic acidic conditions allowed the rapid formation of the easily separable diols (**3**)[7] and (**4**)[8] (Scheme 1). By changing the epoxidising or dihydroxylating agent we were able to prepare either (**3**) or (**4**) with a degree of selectivity. These results are summarised in Table 1.



(i) Epoxidation or dihydroxylation; (ii) Ethylene glycol, CSA, toluene, reflux .

Scheme 1

Epoxidation Conditions	**Overall yield**	**Ratio of (3):(4)**
Dimethyl dioxirane, -78°C	83%	2:1
Dimethyl dioxirane, 0°C	92%	1:1
*m*CPBA, DCM, 0°C	64%	1:4
Dihydroxylation Conditions	**Overall yield**	**Ratio of (3):(4)**
OsO_4. *t*BuOH, H_2O, $K_3Fe(CN)_6$, 0°C	46%	1:3

Table 1

X ray crystallographic structure determination of the two diols showed them to be fully anomerically stabilised.[9] Diol (**3**) was unsymmetrical with one hydroxyl axial and the other equatorial relative to the pyran rings. Diol (**4**) was found to be symmetrical with both hydroxyls adopting equatorial orientations.

It was envisaged that a wide range of chiral auxiliaries, (**5**), (**6**) and (**7**), may be synthesised from these diols (Figure 2).

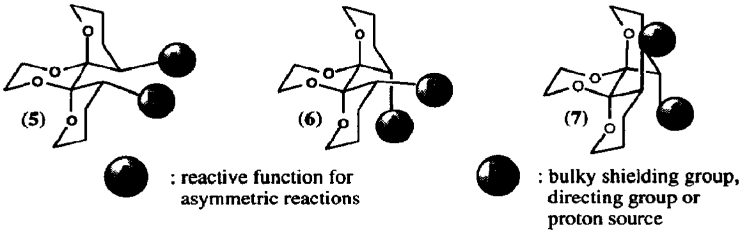
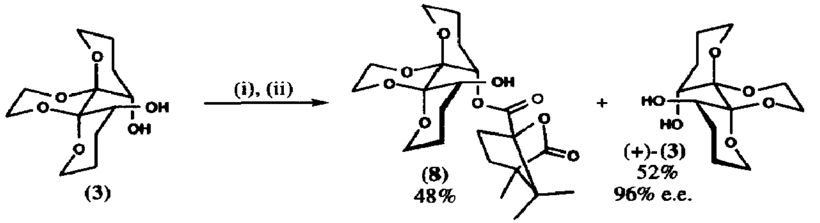


Figure 2

One important consideration is that molecules which are to act as chiral auxiliaries should be of low molecular weight since they will, by definition, be cleaved from the modified substrate at some stage during the subsequent reaction sequence. The diol (**4**) was therefore of particular interest since it would give access to a C_2- symmetrical, bifunctional chiral auxiliary such as (**7**).[10] The molecular weight of a bifunctional chiral auxiliary is effectively halved and, if viable, (**7**) would therefore constitute a very low molecular weight, rapidly obtainable, cheap, architecturally complex, chiral auxiliary.

Diol **(4)** was obtained in enantiopure form by classical resolution *via* camphanate ester formation. The dicamphanates are readily separable by flash column chromatography and subsequent basic hydrolysis furnished the optically pure diols. We are currently investigating cheaper methods to obtain this diol in optically pure form.

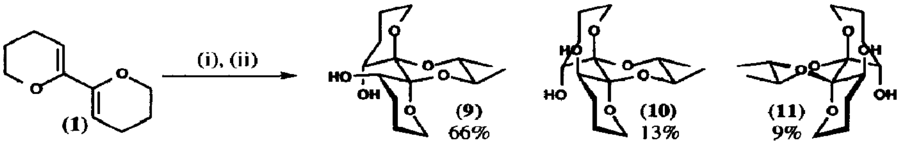
Unsymmetrical diol **(3)** was obtained *via* a tin acetal mediated kinetic resolution process. The tin acetal formed by treatment of **(3)** with dibutyltin dimethoxide[11] was in turn treated with (*s*)-(-)-camphanic chloride at 0°C. A single diastereoisomeric camphanate ester **(8)** was formed by stereoselective acylation of one enantiomeric diol (Scheme 2). The absolute stereochemistry of the camphanate ester was determined by X-ray crystalographic studies.



(i) $Bu_2Sn(OMe)_2$, benzene, Dean-Stark; (ii) (*S*)-(-)-Camphanic chloride, benzene, 0°C.

Scheme 2

Alternatively, optically pure unsymmetrical diol **(9)** may be obtained by using an optically pure diol in the original dispiroketalisation step. Epoxidation of *bis*-DHP **(1)** using dimethyl dioxirane at -78°C followed by treatment with (2*R*,3*R*) 2,3-butanediol under standard themodynamic acidic conditions resulted in the isolation of the single diastereomeric diol **(9)** along with the two diastereomeric symmetrical diols **(10)** and **(11)** (Scheme 3).



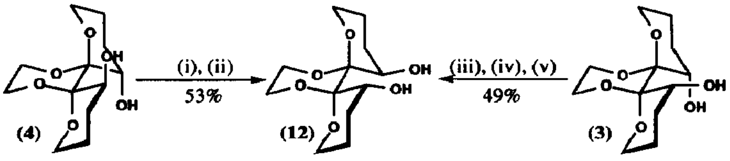
(i) Dimethyl dioxirane, 0°C; (ii) (2*R*,3*R*) 2,3-butane diol (2 eq.), CSA, toluene, 120°C.

Scheme 3

The formation of **(9)** as a single diastereoisomer can be rationalised by diastereofacial discrimination of the *meso* diepoxide precursor to **(3)** by the optically pure butane diol. The structures of **(9)**, **(10)** and **(11)** were all confirmed by X-ray structure determination. Transketalisation of **(10)** and **(11)** using ethylene glycol[6] has allowed the determination of the absolute configuration of (+)- or (-)-**4** obtained by classical resolution.

With routes to diols **3** and **4** established, we needed access to the diaxial diol **(12)**. This was accessable from **(4)** by triflation and subsequent S_N2 nucleophilic displacent using potassium superoxide® and 18-crown-6 in DMSO (Scheme 4).[12] The unsymmetrical diol **(3)** could also be converted into **(12)** *via* selective, tin acetal-mediated triflation[11] of the equatorial hydroxyl and subsequent nucleophilic displacent using potassium superoxide® and 18-crown-6 in DMSO.[12]

We have established methodology for the rapid synthesis of a variety of architecturally complex, sterically demanding, rigid diols in optically pure form. Work is ongoing to investigate their application as potential chiral auxiliaries or modifiers for asymmetric synthesis.



(i) Tf_2O, py, DCM, 0°C; (ii) KO_2, $_{18}$-C-$_6$, DMSO, rt.; (iii) $Bu_2Sn(OMe)_2$, benzene, Dean-Stark; (v) Tf_2O, py, DCM, 0°C, v. KO_2, 18-C-6, DMSO, rt.

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7. (3): m.p. 210-211°C (from toluene); ν_{max} (film)/cm^{-1} 3460 (OH), 3400 (OH), 2960, 2940, 1435, 1325, 1280, 1220, 1090, 1060, 1021, 980, 950; δ_H (270 MHz; $CDCl_3$) 1.5-2.2 (8H, 2 × H-3, 2 × H-4, 2 × H-10, and 2 × H-11), 3.4-4.1 (9H, m, 2 × H-2, 2 × H-9, H-12, 2 × H-14, and 2 × H-15), 4.39 (1H, dd, J 10.3, 5.2, Hax-5); δ_C (125 MHz; D_6-DMSO) 18.2, 24.3, 26.0, 26.3 (C-3, C-4, C-10, and C-11), 57.2 (C-2), 57.3 (C-9), 59.2 (C-5), 60.2 (C-15), 64.8 (C-14), 68.4 (C-12), 94.5 (C-7), 96.8 (C-6); *m/z* (EI) 260 $(M)^+$, 242 $(M-H_2O)^+$, 222, 189, 180, 144, 116, 99, 71, 57; Found: $(M)^+$ 260.1270. $C_{12}H_{20}O_6$ requires: *M*, 260.1260. Analysis; Found: C, 55.21%; H, 7.54%. $C_{12}H_{20}O_6$ requires C, 55.37%; H, 7.74%.
8. (4): m.p. 188°C (from toluene); ν_{max} (film)/cm^{-1} 3519 (OH), 3498 (OH), 2936, 2883, 1278, 1125, 1081, 1051, 1000, 975, 940.; δ_H (500 MHz; $CDCl_3$) 1.63-1.83 (6H, m, H_{eq}-3, 2 × H-4, H_{eq}-10, and 2 × H11), 1.83-1.92 (2H, m, H_{ax}-3 and H_{ax}-10), 3.65 (2H, m, H_{eq}-14 and H_{eq}-15), 3.35-3.75 (4H, m, 2 × H-2 and 2 × H-9), 3.90 (2H, dd, J 10.6, 5.1, H-5 and H-12), 4.13 (2H, m, H_{ax}-14 and H_{ax}-15); δ_C (67.5 MHz; $CDCl_3$) 96.9 (C-6 and C-7), 68.0 (C-14 and C-15), 60.3, 58.6 (C-2 and C-9, C-5 and C-12), 25.9, 24.5 (C-3 and C-10, C-4 and C-11); *m/z* (EI) 260 $(M)^+$, 242 $(M-H_2O)^+$, 189, 180, 171, 144, 116, 99, 71, 57, 44; Found: $(M)^+$ 260.1279. $C_{12}H_{20}O_6$ requires: *M*, 260.1260. Analysis; Found: C, 55.13%; H, 7.64%. $C_{12}H_{20}O_6$ requires: C, 55.37%; H, 7.74%.
9. We thank D.J. Williams at Imperial College and P.R. Raithby at Cambridge for X-ray structure determination.
10. See: Davies,S.G.; Mortlock, A.A.; *Tetrahedron*, **1993**, *49*, 4419 and references therein.
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