Dispiroketals in Synthesis: Preparation of a Stable, Sterically Demanding Glyceraldehyde Ketal and Diastereoselective Reactions with Simple Organometallic Reagents

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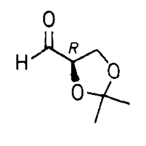
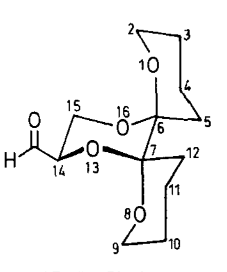
A preparation of the novel dispiroketal of D-glyceraldehyde is described. The diastereoselective addition of various organometallic reagents proceeds with *anti* selectivity due to the large steric bulk of the dispiroketal.

The preparation of small, highly oxygenated intermediates in enantiomerically pure form is of pivotal importance in organic synthesis. The use of derivatives of D-glyceraldehyde, an important C_3 synthon, has been widespread and continues to be an area of great synthetic interest.[1] Many authors have investigated the addition of nucleophiles to isopropylideneglyceraldehyde and have found that whilst *anti* selectivity is predominant, the addition of simple organometallic species (e.g., alkyllithiums, Grignard reagents) is usually only poorly *anti* selective. Due to the abundance of stereogenic centres bearing methyl groups in natural products, methods for the stereocontrolled addition of methyl reagents to simple precursors are of great importance. The stereoselective introduction of methyl groups into isopropylideneglyceraldehyde is very difficult.[2]



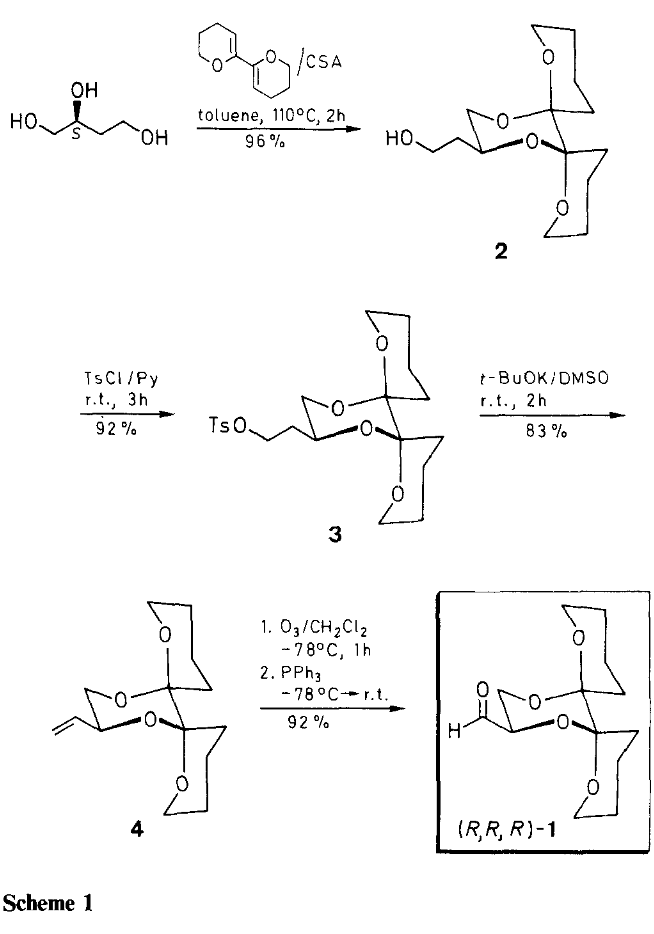
2,3-O-Isopropylidene-D-glyceraldehyde



(R, R, R)-1

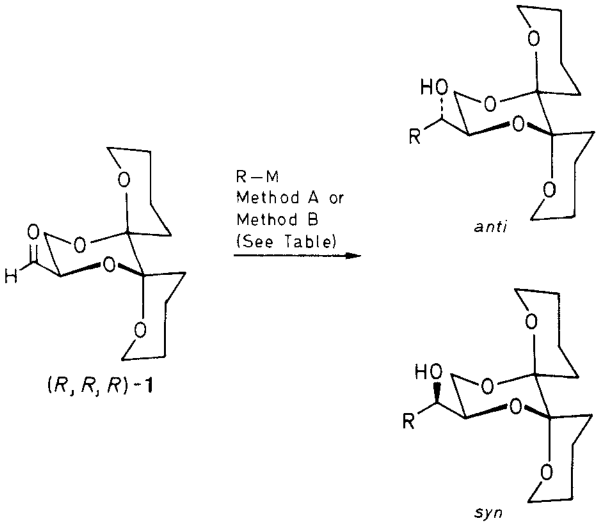
The 1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane (dispiroketal) moiety provides a novel, rigid, and sterically demanding alternative protecting group for vicinal diols. Due to the domination of anomeric effects, only one stereoisomer of the dispiroketal is formed.[3] In the case of substituted vicinal diols the product is a single diastereomer, the substituent being solely in the equatorial orientation. The stereochemistry of the ketal centres is induced by that of the substituent. Because of the contiguous nature of the spirocentres and the controlling anomeric effects, the two ketal centres are formed with the same absolute stereochemistry and in a predictable manner. This leads from a vicinal diol with one chiral centre to a dispiroketal containing three chiral centres, a process of *chirality multiplication through anomeric effects.*

Reaction of 3,3′,4,4′-tetrahydro-6,6′-bi-2*H*-pyran[4] (bis-DHP) with (*S*)-(−)-1,2,4-butanetriol in toluene with catalytic camphorsulphonic acid gave the hydroxyethyl compound **2** as a single diastereoisomer in 96% yield. This demonstrates the thermodynamic control of the reaction and selective protection of a vicinal diol in the presence of a 1,3-diol, a notable feature of dispiroketals. The tosylate **3** was prepared under standard conditions in 92% yield (the structure of which was confirmed by single crystal X-ray). Elimination with potassium *tert*-butoxide gave the ethenyl compound **4** in 83% yield. Ozonolysis in dichloromethane, followed by addition of triphenylphosphine and chromatography on silica gel afforded the formyl derivative (*R*,*R*,*R*)-**1** in 92% yield (Scheme 1). In contrast to isopropylideneglyceraldehyde, **1** is stable at room temperature and may be stored for prolonged periods. As a consequence of the geometry of the dioxan ring, epimerisation is unlikely to occur as this would lead to an axially orientated formyl group experiencing considerable steric interactions.



Scheme 1

The course of nucleophilic addition to glyceraldehyde derivatives has been the subject of intensive research interest over recent years.[1,5] Whilst high *syn* selectivity *can* be induced via α-chelation controlled processes, the selectivity of *anti* addition is a consequence of the natural steric bias of the system and the delicate balance of α-coordination (*pro syn*) and β- or α,β-coordination (both *pro anti*). In the case of isopropylideneglyceraldehyde the exact mode of coordination, and hence selectivity, may be ambiguous. For example the use of a strongly coordinating reagent *may* still give rise to variable *anti*/*syn* ratios. The preparation of benzyl and silyl ethers has led to some improvement[6] in *anti* selectivity, however these derivatives are not chemically equivalent to the isopropylideneglyceraldehyde. The dispiroketal derivative, (*R,R,R*)-**1**, has the advantage of improved stability and yet is chemically equivalent to the widely used isopropylideneglyceraldehyde derivative, deprotection being achieved under acidic conditions.[7] Additions of various organometallic reagents to aldehyde **1** have been studied. (Scheme 2) The results are shown in the Table 1.



Scheme 2

Entries 1, 3, 4, and 6 show a consistent selectivity, which appears to be independent of reagent choice. The titanium reagent (entry 7) gives excellent *anti* selectivity, comparable to that achieved with the 2,3-dibenzyl or 2-benzyl-3-*tert*-butyldimethylsilyl ethers.[6] Addition of ethenylmagnesium bromide (entry 8) gives good *anti* selectivity in contrast to previous reported work.[8] Interestingly the ethynyl Grignard shows an opposite selectivity with **1** compared to isopropylideneglyceraldehyde where a slight *syn* preference was observed.[9]

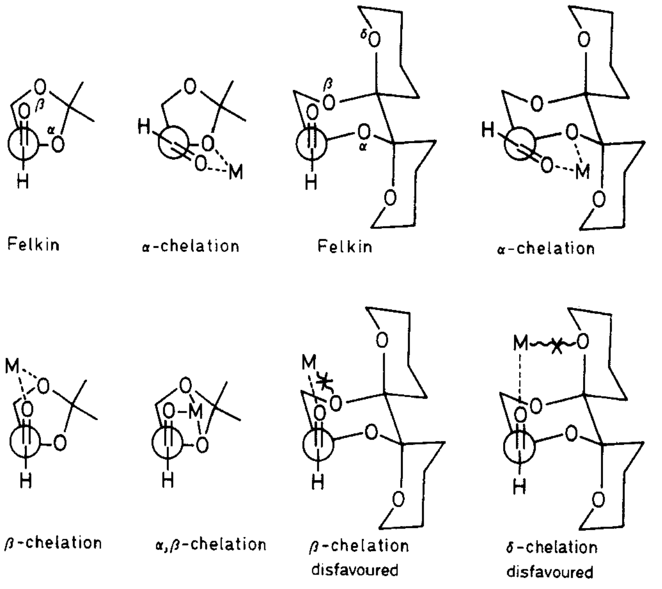
It can be seen that the addition of most reagents to **1** leads to *anti* adducts as predicted by Felkin's non-chelation controlled model[10] and the β or α,β coordination models proposed for isopropylideneglyceraldehyde.[11] In **1**, the rigidly defined geometry of the dioxan ring is likely to negate the possibility of β coordination, due to the greatly increased interatomic distances between the carbonyl oxygen and the β oxygen, relative to those in isopropylideneglyceraldehyde. Molecular modelling studies indicate that, although the axially disposed δ oxygen is in a suitable position to form a chelated complex, this would introduce considerable ring strain in the dispiroketal moiety. These considerations allow the hypothesis that the *anti* selectivity shown by the aldehyde **1** is mainly due to the steric bulk of the dispiroketal group (Scheme 3).

We are at present investigating further the effects of chelation and non-chelation control in additions to **1** and further applications of dispiroketals to synthesis. These

Table. Additions of Organometallic Reagents to the Aldehyde **1**[g]

Entry	Reagent	Conditions, Solvent, Temp., Time, Method	Yield (%)[a]	anti/syn Ratio	Lit. *anti/syn* Ratio[b]
1	MeLi	Et_2O/THF, −78 °C, 22 h, A	82	82 : 18[c]	60 : 40
2	MeLi	Et_2O/THF, 25 °C, 12 h, A	78	67 : 33[c]	–
3	MeMgCl	THF, −78 °C, 24 h, A	92	81 : 19[c]	–
4	MeMgBr	THF, −78 °C, 22 h, A	62	79 : 21[c]	73 : 27
5	$Me_2CuLiMe_2S$	Et_2O, −78 °C, 20 h, B	69	12 : 88[c]	18 : 82
6	$MeCuMgBrMe_2S$	Et_2O, −78 °C, 20 h, B	85	82 : 18[c]	65 : 35
7	MeTi(O-*i*-Pr)$_3$	Et_2O/hexane, −40 °C, 20 h, B	87	93 : 7[c]	70 : 30
8	$CH_2{=}CHMgBr$	THF, −78 °C, 4 h, A	56	91 : 9[d]	60 : 40[f]
9	$(CH_2{=}CH)_2Zn$	THF, 25 °C, 48 h, A	84	67 : 33[d]	–
10	HC≡CMgBr	THF, −78 °C, 5 h, A	65	89 : 11[d]	44 : 56
11	allylMgBr	THF, −78 °C, 18 h, A	89	68 : 32[c]	60 : 40
12	EtMgBr	THF, −78 °C, 6 h, A	62	73 : 27[e]	–

[a] Yield corrected for unreacted starting material.
[b] Literature ratio obtained for addition to 2,3-*O*-isopropylidene-D-glyceraldehyde.
[c] Yield and ratio by gas chromatography of crude material.
[d] Yield of isolated product, ratio by high field NMR.
[e] Yield of isolated product, ratio by gas chromatography on acetylated product.
[f] Vinylmagnesium chloride at 20–60 °C.
[g] All products have been characterised by ^1H NMR, IR and MS analysis. The absolute stereochemistry of the ethenyl derivative was unambiguously established by conversion to *meso*-tetra-*O*-benzylerythritol. The stereochemistry of the methyl, ethynyl, allyl, and ethyl adducts was established by correlation of common derivatives obtained from the ethenyl adduct.



Scheme 3

include the protection of sugars and direct preparation of (*R,R,R*)-**1** from mannitol. New bis-DHP derivatives are also being investigated as possible chiral auxiliaries.

Addition of Organometallic Reagents to 1; General Procedures:

Method A: To a stirred solution of **1** ((1 equiv), in the indicated solvent (Table 1), cooled to $-78\,^\circ C$, under argon, was added, dropwise, a solution of the organometallic reagent (10–20 equiv) and the resulting mixture was kept at $-78\,^\circ C$, by addition of sat. aq NH_4Cl solution. Et_2O was added and the organic phase was washed twice with brine and dried (anhydr. $MgSO_4$) and concentrated in vacuo. The crude compounds were purified by flash chromatography (silica gel, eluent: Et_2O/petroleum ether (bp 40–60 °C) 1:1).

Method B: To a stirred solution of the organometallic reagent (10–20 equiv) cooled to $-78\,^\circ C$, under argon, was added, dropwise, a solution of **1** (1 equiv), and the resulting mixture was kept at $-78\,^\circ C$ for 5–24 h. The isolation procedure was the same as that given above for Method A.

(6*R*,7*R*,14*S*)-14-(2-Hydroxyethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane (2):

To a solution of (*S*)-1,2,4-butanetriol (2.55 g, 24 mmol) in dry distilled toluene (30 mL) was added 10-camphorsulphonic acid (105 mg, 0.4 mmol). The solution was heated at reflux, under argon, for 2 h, allowed to cool to r.t. and quenched by addition of sat. aq $NaHCO_3$ solution (20 mL). The solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined extracts were dried (anhydr. $MgSO_4$), filtered and concentrated in vacuo to give a brown oil. Purification by flash chromatography on silica gel (Merck 9385) eluting with Et_2O/petroleum ether (bp 40–60 °C) (3:1) afforded the product as a colourless oil, yield: 2.37 g (96 %); $[\alpha]_D^{20}$ $-133°$ (c = 1.09, $CHCl_3$).

IR (film): ν = 3440, 2948, 2869, 1439, 1352, 1272, 1209, 1178, 1070, 1040, 992 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.48–1.82 (m, 14 H), 2.3 (m, 1 H exchangeable with D_2O, OH), 3.43 (dd, 1 H, J = 2.9, 11.2 Hz, H-15_{eq}), 3.66–3.75 (m, 5 H), 3.82 (dd, 2 H, J = 5.4, 6.6 Hz, H-18), 4.12–4.21 (m, 1 H, H-14).

MS: m/z (%) = 272 (M^+), 0.1), 223 (0.6), 201 ($C_{10}H_{17}O_4^+$, 3.4), 101 ($C_5H_9O_2^+$, 100).

HRMS: calc. for $C_{14}H_{24}O_5$ 272.1624; found 272.1621.

(6*R*,7*R*,14*S*)-14-[2-(4-Methylphenylsulphonyl)ethyl]-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane (3):

To a stirred solution of **2** (11.2 g, 61 mmol) in pyridine (30 mL) under argon was added at 0 °C a solution of TsCl (11.7 g, 61.5 mmol) in pyridine (7 mL). After completion of the addition, the reaction mixture was allowed to warm to r.t. After 3 h the reaction was quenched by addition of water (100 mL)and then extracted with CH_2Cl_2 (300 mL). The organic extracts were washed with 10 % HCl (3 × 100 mL) and water (3 × 100 mL), dried (anhydr. $MgSO_4$), filtered and concentrated in vacuo to give **3** as an off-white crystalline solid; yield: 16.04 g, (92 %); mp 104–105 °C (Et_2O); $[\alpha]_D^{20}$ $-45°$ (c = 0.83, $CHCl_3$).

IR (film): ν = 2945, 2868, 1439, 1359, 1209, 1188, 1176, 1070, 1039, 1000, 934 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.2–1.78 (m, 14 H), 2.44 (s, 3 H, CH_3), 3.39 (dd, 1 H, J = 11.3, 3.2 Hz, H-15_{eq}), 3.44–3.67 (m, 5 H), 3.87–4.04 (m, 1 H, H-14), 4.06–4.2 (m, 1 H, H-18), 4.25–4.34, (m, 1 H, H-18), 7.33 (d, 2 H, J = 8.4 Hz, *m*-tolyl), 7.79 (d, 2 H, J = 8.4 Hz, *o*-tolyl).

MS: m/z (%) = 426 (M^+, 0.1), 368 (0.3), 326 (5.6), 297 (2.9), 226 (9.4), 155 ($C_7H_7SO_2^+$, 62), 101 ($C_5H_9O_2^+$, 100), 91 ($C_7H_7^+$, 31), 54 (99).

HRMS: calc. for $C_{21}H_{30}SO_7$ 426.1712; found 426.1707

(6*R*,7*R*,14*S*)-14-Ethenyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane (4):

To **3** (1.6 g, 38 mmol) at r.t. were added *t*-BuOK (5.06 g, 45 mmol) and DMSO (25 mL) and the solution was stirred for 2 h. The resultant red-brown solution was added to sat. aq $NaHCO_3$ (30 mL) and extracted with Et_2O (30 mL). The ethereal extract was washed with water (2 × 30 mL) and dried (anhydr. $MgSO_4$), filtered, concentrated in vacuo and the residue purified by flash chromatography on silica gel (Merck 9385) eluting with Et_2O/petroleum ether (bp 40–60 °C) (1:1) to give **4** as a colourless oil; yield: 1.06 g, (83 %); $[\alpha]_D^{20}$ $-123°$ (c = 1.05, $CHCl_3$).

IR (film): ν = 2945, 2869, 1439, 1352, 1285, 1270, 1029, 1190, 1178, 1178, 1164, 1132, 1104, 1072, 1038, 1016, 991, 936, 892 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.46–1.85 (m, 12 H), 3.44–3.52 (dd, 1 H, J = 3-2. 11 Hz, H-15_{eq}), 3.63–3.72 (m, 5 H, 2 × H-9, H-15_{ax}), 4.40–4.48 (m, 1 H, H-14), 5.21 (dt, 1 H, J = , 2 Hz, H-18_{trans}), 5.36 (dt, 1 H, J = 17.5, 2 Hz, H-18_{cis}), 5.78 (ddd, 1 H, J = 17.5, 10.5, 6 Hz, H-17).

MS: m/z (%) = 255 (MH^+, 0.2), 253 (M-H^+, 0.1), 223 (0.3), 201 ($C_{10}H_{17}O_4^+$, 3.0), 167 (6.1), 157 (8.7), 101 ($C_5H_9O_2^+$, 100), 83 (5.7), 71 (6.6), 57 (17.4), 55 (15.5), 54 (10.6), 28 (19.6).

HRMS: calc. for $C_{10}H_{17}O_4$ (MH^+ $-C_4H_6$) 201.1127; found 201.1131.

(6*R*,7*R*,14*R*)-14-Formyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane (1):

Ozone was bubbled into a stirred solution **4** (0.42 g, 1.65 mmol) in CH_2Cl_2 (30 mL) at $-78\,^\circ C$ for 1 h. Ph_3P (0.61 g, 2.34 mmol) was added and the solution was allowed to warm to r.t. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica gel (Merck 9385) eluting with Et_2O/petroleum ether (bp 40–60 °C) (3:1) to give **1** as a colourless oil; yield: 0.388 g (92 %); $[\alpha]_D^{20}$ $-88°$ (c = 1.445, $CHCl_3$).

IR (film): ν = 2943, 2870, 1732 ($\nu_{C=O}$), 1439, 1353, 1286, 1272, 1210, 1190, 1161, 1099, 1070, 1040, 991, 966 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.40–1.92 (m, 14 H), 3.54–3.84 (m, 6 H, 2 × H-2, 2 × H-9), 2 × H-15), 4.39 (dd, 1 H, J = 4.5, 10.3 Hz, H-14), 9.70 (s, 1 H, CHO).

MS: m/z (%) = 257 (MH^+, 0.9), 227 (MH^+ $-CH_2O$, 0.9), 167 (6.8), 156 (13.2), 101 ($C_5H_9O_2^+$, 100).

HRMS: calc. for $C_{12}H_{19}O_4$ (MH^+ $-CH_2O$) 227.1283; found 227.1279.

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