COMMUNICATION

Rapid assembly of *anti*,*anti*-1,2,3-triol motifs *via* stereoselective addition of organometallics to aldehydes obtained from (*R*′,*R*′,*S*,*R*)-2,3-butane diacetal protected butanetetraol derivatives

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A predictable stereoselective method for the synthesis of enantiopure *anti*,*anti*-1,2,3-triols through the addition of organometallic reagents to the axially disposed aldehyde derived from (*R*′,*R*′,*S*,*R*)-2,3-butane diacetal protected butanetetraol is described.

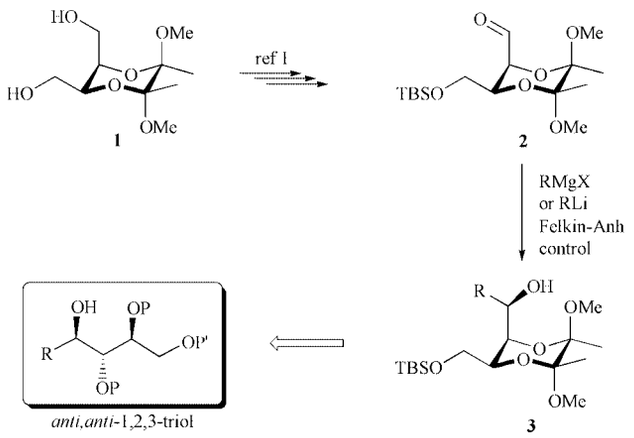
Owing to the general lack of good methods for the production of *enantiopure anti*-1,2-diols, we introduced (*R*′,*R*′,*S*,*R*)-2,3-butane diacetal (BDA) protected butanetetraol **1** as a four carbon building block to access these important motifs.[1] This work was initiated and further developed for a project aimed at the total synthesis of the annonaceous acetogenin muricatetrocin C.[2] Since then, this four carbon building block, containing the embedded *anti*-1,2-diol unit, not only has served its purpose in the above synthesis but also has proven useful in a short total synthesis of the polyhydroxylated macrolactone aspicilin.[3]

Although this unit was principally designed to prepare *isolated anti*-1,2-diols, its application to stereodefined 1,2,3-triol motifs, found in other natural products, was also of considerable interest. It was hoped that carbon–carbon bond formation through addition of carbon-centred nucleophiles to an aldehyde[4] functionality attached to the dioxane ring would lead to high levels of stereoinduction at the newly formed asymmetric centre.[5] This idea was attractive since the 2,3-butane diacetal group would be acting as a protecting group, a chiral memory and a stereodirecting group.[6] Since both axially and equatorially disposed aldehyde functionalities are readily available, additions of carbon-centred nucleophiles to each would produce differing contiguous polyol arrangements.

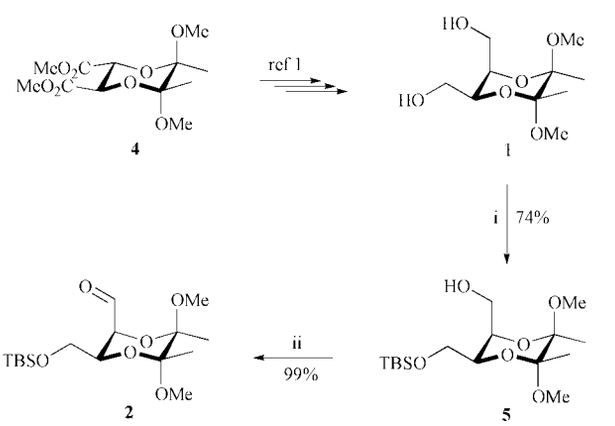
Molecular modeling calculations[7] combined with analysis of single crystal X-ray crystallographic data of related compounds indicated that additions of organometallic reagents to aldehyde **2**, in which the carbonyl group adopts an axial disposition on the dioxolane ring, should occur with high levels of diastereoselectivity. It was believed that the neighbouring axial methoxy group would act as an effective steric block to the approach of the nucleophiles over the dioxane ring and, if Felkin–Anh control was in operation, a high degree of selectivity towards attack at the *Re*-face was anticipated. As a consequence of this opportunity we wish to describe here our initial findings on the stereoselective carbon–carbon bond formation to the axial aldehyde **2** (Scheme 1).

The desired aldehyde starting material **2** was readily prepared on multigram scale through an efficient two step procedure from diol **1**, which in turn was prepared from BDA protected (*R*,*R*)-dimethyl tartrate[8] **4** following our recently reported chiral memory protocol.[9] Selective silylation of the equatorial hydroxymethyl group using *tert*-butyldimethylsilyl chloride and imidazole in THF afforded alcohol **5**.[1] Oxidation of this material by the standard Swern protocol[10] then gave the desired aldehyde **2** in quantitative yield. This material was used crude throughout the course of these studies and was found to be stable indefinitely when stored at −23 °C (Scheme 2).

In order to assess the utility of **2** as a building block for polyol production it was first treated with a range of commercially available[11] or readily prepared Grignard reagents.



Scheme 1



Scheme 2 *Reagents and conditions*: i, imidazole (1.5 eq.), TBSCl (1.0 eq.), THF, RT, 2 h; ii, $(COCl)_2$ (1.3 eq.), DMSO (2.6 eq.), CH_2Cl_2, −78 °C then Et_3N (3.5 eq.), −78 °C–rt over 1 hour.

The reactions were carried out in each case by dissolving the aldehyde in THF, cooling to −78 °C and then adding excess organometallic reagent dropwise *via* syringe. The reaction mixtures were either kept at −78 °C until complete or, as in the sluggish cases, warmed slowly towards 0 °C until TLC analysis showed completion of the reaction. All of the reactions were quenched with pH 7.2 buffer and a simple aqueous work-up gave the crude reaction product which was analysed by high field ^{1}H NMR spectroscopy to determine the diastereomeric ratio of the reaction products. Separation of the diastereoisomeric products by silica gel chromatography was straightforward in all of the examples studied (Scheme 3, Table 1).[12]

In all cases the major product was formed by attack of the Grignard reagent to the *Re*-face as anticipated.[13] The reaction selectivity varied from a moderate 67% de (5 : 1 dr, entry 7) with phenylmagnesium bromide to an excellent 97% de (60 : 1 dr, entry 3) with isopropylmagnesium chloride. It can be seen from Table 1 that the highest levels of stereoinduction were observed

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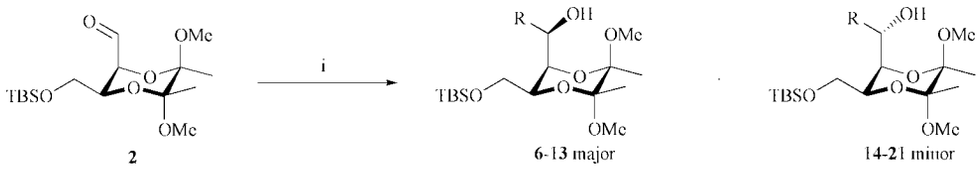
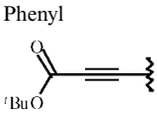
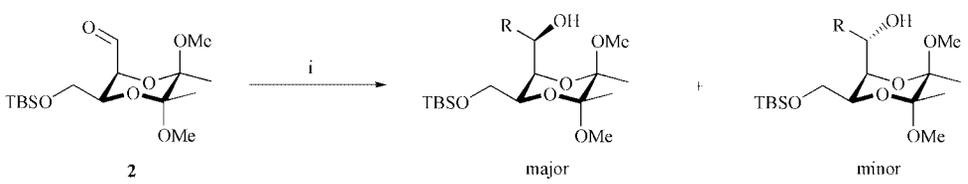


Scheme 3 *Reagents and conditions*: i, RMgX.

Table 1 Results of addition reactions of Grignard reagents to aldehyde **2**

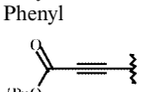
Entry	R	Solvent	Temperature/°C	Time/min	Reaction yield (%)	Reaction dr[a]	Major	Minor
1	Methyl	THF	−78	240	94	45 : 1	**6**	**14**
2	Ethyl	THF	−78 ⟶ 0	150	65	27 : 1	**7**	**15**
3	Isopropyl[b]	THF	−78 ⟶ 0	150	22[c]	60 : 1	**8**	**16**
4		THF	−78 ⟶ 0	210	71	25 : 1	**9**	**17**
5	Allyl	THF	−78	30	77	6 : 1	**10**	**18**
6		Et_2O	−78 ⟶ −10	150	86	9 : 1	**11**	**19**
7	Phenyl	THF	−78 ⟶ −30	30	84	5 : 1	**12**	**20**
8		THF	−78 ⟶ −10	120	75	12 : 1	**13**	**21**

[a] Determined by crude ^{1}H NMR spectroscopy. [b] ^{i}PrMgCl was used. [c] Compound **5** was also isolated in 76% yield.



Scheme 4 *Reagents and conditions*: i, RLi.

Table 2 Results of addition reactions of organolithium reagents to aldehyde **2**

Entry	R	Solvent	Temperature/°C	Time/min	Reaction yield (%)	Reaction dr[a]	Major	Minor
1	Methyl	THF	−78 ⟶ rt	480	77	10 : 1	**6**	**14**
2	Butyl	THF	−78 ⟶ 0	150	41	7 : 1	**22**	**23**
3	Phenyl	THF	−78 ⟶ −10	150	82	3 : 1	**12**	**20**
4		THF	−78 ⟶ −10	120	93	2 : 1	**13**	**21**

[a] Determined by crude ^{1}H NMR spectroscopy.

with sp^3 hybridised Grignard reagents but this, in some cases, was at the expense of the reaction yields[14] which otherwise were good to excellent.

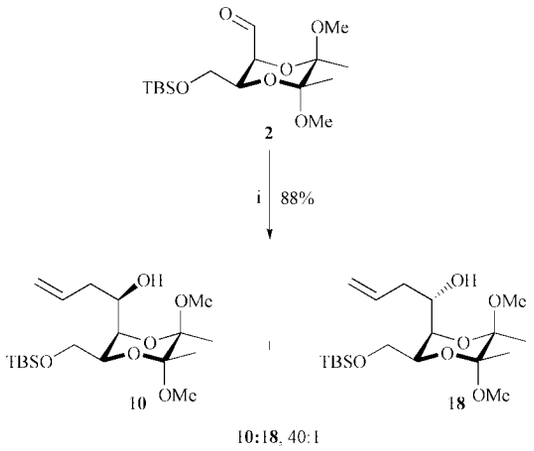
As a direct comparison, axial aldehyde **2** was treated with a range of commercially available or readily prepared organolithium reagents in an analogous fashion to the previous study (Scheme 4, Table 2).

As with the Grignard additions the major product in each case was formed by attack at the *Re*-face. The diastereoselectivities were, on the whole, lower, however, as with the Grignard additions, the highest selectivities were observed with sp^3 derived organolithium reagents. For example, with methyllithium an 81% de was observed (10 : 1 dr, entry 1). The reaction yields were in general good to excellent except with butyllithium[14] (41%, entry 2) and in all cases the major and minor diastereoisomeric products were separable by silica gel chromatography.

When one compares Table 1 with Table 2, it is clear that the best selectivities in the addition of carbon-centred nucleophiles to the axially disposed aldehyde occur with the more coordinating magnesium counter ion over the lithium. This suggests chelation of the aldehyde oxygen to the counter cation attached to the dioxolane ring oxygen is occurring during attack and the observed selectivity arises through the 1,3-related methoxy group blocking the approach to the *Si*-face.

To support this simplistic idea a Lewis acid mediated allylation of **2** was performed using allyltributyltin and zinc chloride in diethyl ether at room temperature. The reaction produced two diastereoisomers **10** and **18** in the ratio of 40 : 1 (95% de) and with a yield of 88%. The major diastereoisomer **10** was identical in every respect to the major diastereoisomer produced in the addition of allylmagnesium bromide and confirmed that chelation controlled addition was indeed occurring in both the nucleophilic additions and the Lewis acid mediated additions (Scheme 5).

In conclusion, building block **2** offers a general and reliable route to the production of enantiopure and diastereomerically pure *anti*,*anti*-1,2,3-triol motifs through addition of organometallic reagents. In general, Grignard reagents give rise to higher diastereoselectivities than the corresponding lithium reagents and reaction yields are good unless the nucleophile is sp^3 hybridized and possesses β-hydrogens.



Scheme 5 *Reagents and conditions*: i, $ZnCl_2$ (3 eq.), Et_2O, 0 °C, 30 min then $Bu_3SnCH_2CHCH_2$ (3 eq.), 0 °C to rt, 36 hours.

Acknowledgements

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Notes and references

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9 D. J. Dixon, A. C. Foster, S. V. Ley and D. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1631.
10 K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651.
11 Purchased from Aldrich Chemical Company.
12 Representative procedure for the addition of organometallic reagents to aldehyde **2**: to a solution of aldehyde **2** (50 mg, 0.143 mmol) in THF (1 ml) at −78 °C under argon was added methylmagnesium bromide (3.0 M in THF, 143 μl, 0.430 mmol). The reaction mixture was stirred for 4 h at −78 °C and then quenched with phosphate buffer (pH = 7.4, 5 ml) at −78 °C, extracted with ether (3 × 5 ml), washed with brine (5 ml), reextracted with ether (5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil. Analysis of this material indicated that the reaction had produced two diastereoisomers in a ratio of 45 : 1. Purification by flash column chromatography (ether–petroleum ether (40–60 °C) 1 : 3, 1% TEA) gave the isomerically pure alcohol **6** (49 mg, 94%) as a colourless liquid. R_f = 0.26 (ether–petroleum ether (40–60 °C) 1 : 3); $[\alpha]_D^{27}$ = −90.6 (*c* = 1.0, CH_2Cl_2); ν_{max}(thin film)/cm^{-1}: 3505br w, 2952m, 2857w, 1463w, 1373w, 1255w, 1116s, 1039m, 1016m, 837m, 778w; δ_H (400 MHz, $CDCl_3$): 4.16 (2H, m, O*H* + CH_2CH), 4.01 (2H, m, C*H*OH and C*H*H), 3.79 (1H, dd, *J* 5.0 and 10.5, CH*H*), 3.75 (1H, t, *J* 4.5, C*H*CHOH), 3.33 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 1.31 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.25 (3H, d, *J* 6.6, CH_3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.093 (3H, s, $SiCH_3$), 0.090 (3H, s, $SiCH_3$); δ_C (100.6 MHz, $CDCl_3$): 99.5, 98.8, 75.2, 71.4, 69.2, 62.4, 49.1, 47.9, 25.8, 20.3, 18.4, 18.2, 18.2, −5.5, −5.6; found: C 56.36, H 9.82. $C_{17}H_{36}O_6Si$ requires: C 56.01, H 9.95%; *m*/*z* (EI) 365 (MH^+, 90%), 331 (20), 275 (40), 215 (90), 159 (100), MH^+: found: 365.2356. $C_{17}H_{36}O_6Si$ requires: 365.2359.
13 Stereochemistry was determined following the method of Mosher: J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
14 The major side product was alcohol **5** formed by β-hydride reduction.