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THE ALKYLATION OF A NOVEL ACETAL DERIVED FROM (2*R*,3*R*)-(+)-TARTARIC ACID: AN UNEXPECTED REARRANGEMENT

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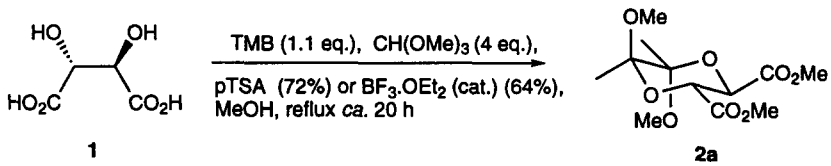
Abstract: The novel chiral *bis*-acetal dioxane **2a** derived from (2*R*,3*R*)-(+)-tartaric acid was shown to undergo an unexpected rearrangement upon treatment with lithium amide base to give the chiral dioxolane **3a** in optically active form. Alkylation and aldol studies were performed on the diisopropyl ester of this dioxolane **3b**.

Tartaric acid is a chiral building block, useful for the asymmetric synthesis of natural products,[1] the synthesis of ligands for asymmetric catalysis[2] and the synthesis of inclusion complex host molecules.[3] Recently we have prepared a novel C_2 symmetric chiral *bis*-acetal compound **2a**, namely dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate derived from (*L*)-(+)-tartaric acid **1**. It was prepared in good yield using an acetal exchange reaction with 2,2,3,3-tetramethoxybutane (TMB) a reagent recently used extensively as a protecting group for vicinal diols particularly in cyclic systems.[4]



1 **2a**

Scheme 1

Compound **2a** is a highly crystalline substance at normal temperatures, with a rigid conformation which is controlled by a double anomeric effect, making it a potentially useful substrate for various stereoselective transformations. Seebach and Naef[5] have previously shown that the enolate of dimethyl (2*R*,3*R*)-*O*-isopropylidene-*L*-tartrate could be successfully deprotonated with LDA and subsequently quenched with several electrophiles to give alkylated and hydroxyalkylated products in good yields and with high diastereoselectivity. Later, Evans and coworkers[6] demonstrated that the silyl ketene acetal of di-*tert*-butyl (2*S*,3*S*)-*O*-cyclopentylidene-*D*-tartrate undergoes a variety of highly diastereoselective Mukaiyama type aldol reactions with various prochiral aldehydes and activated ketones. Prompted by these literature reports we were interested in examining the propensity of compound **2a** to form lithium enolates and dienolates and to trap these with various electrophiles in an attempt to mono and dialkylate the molecule. However, initial lithium amide deprotonation/ reprotonation experiments showed that a mixture of three compounds was obtained, which were identified as the unusual dioxolane **3a**[7] and the dimethoxydioxane diastereomers **4a** and **5a**, respectively (Scheme 2). These latter compounds correspond to the protected forms of *D*- and *meso*-tartaric acid respectively. This interesting[8] reaction was explored further and the results are outlined in the Table. The configurations of compounds **4a** and **5a** have been unambiguously assigned by X-ray crystallographic analysis.

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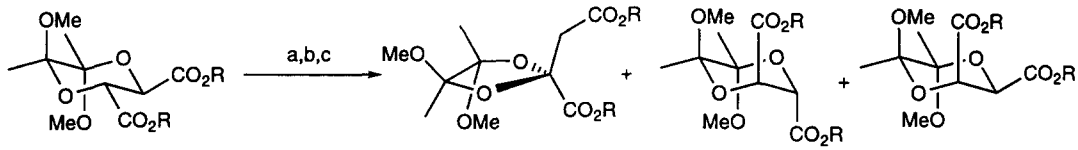
Dioxolane **3a** was found to be optically active {$[\alpha]_D^{21}$ -129.7 (*c* 1.42, $CHCl_3$)} thus confirming the *trans* disposition of the ring methoxyl groups, indicating that chirality has been transferred from the tartaric acid backbone to that of the dioxolane. A mechanism is proposed (Scheme 3) which also accounts for the formation of the optically active dioxolane species **3a**. It is thought that the mono-enolate that results from treatment of **2a** with LDA, β-eliminates forming a dimethyl maleate anionic species **7** which closes in a 5-*exo*-trig manner *via* an intra-molecular Michael addition to afford the dioxolane **3a** after protonation of the intermediate enolate **9**.

Scheme 2



2a R = Me
2b R = ^{i}Pr

3a
3b

4a
4b

5a
5b

(a) LDA, THF, -100°C to -70°C; (b) MeOH, -100°C to -70°C; (c) 10% NH_4Cl(aq.) -70°C to r.t.

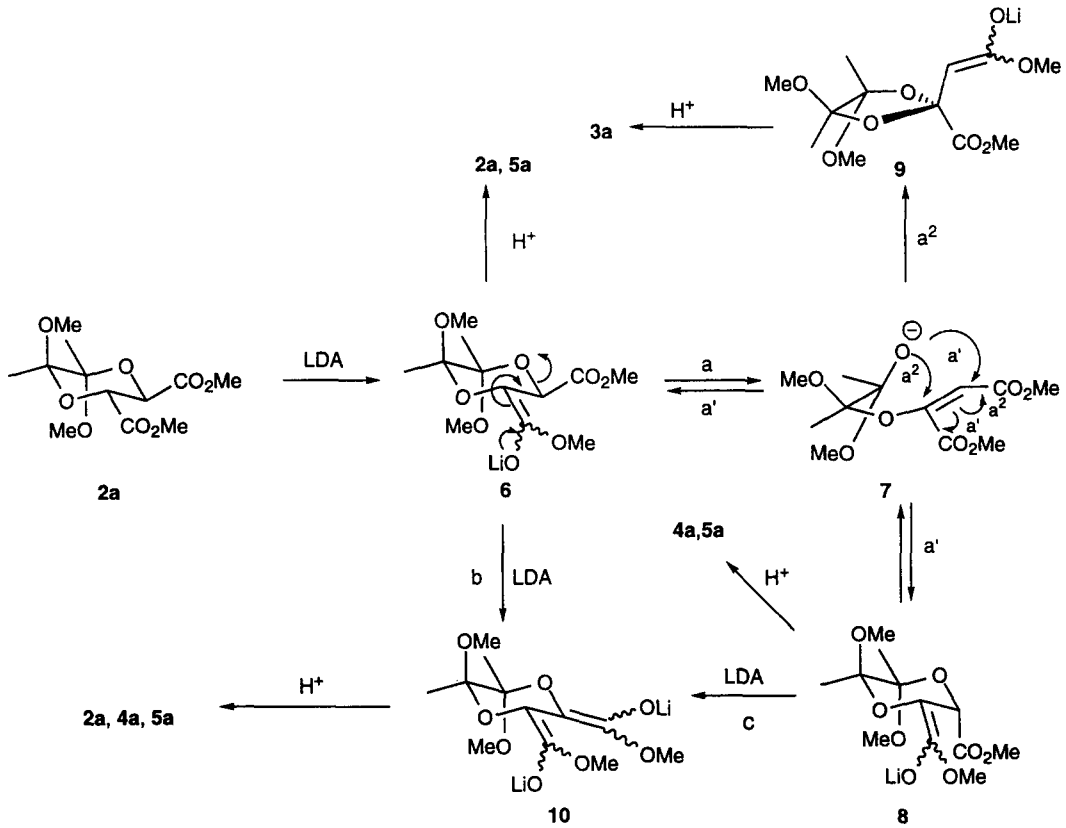
Table: Deprotonation/Reprotonation of Compound **2a**

LDA (equivs)	Reaction Time (mins)	Proton Source	Products[a]			
			5a (%)	**4a** (%)	**3a** (%)	**2a**(%)
1.0	5	MeOH	7	6	50	12
1.0	18	MeOH	11	8	44	8
1.0	40	MeOH	10	9	51	5
1.0	60	MeOH	9	7	56	5
2.1	5	MeOH	24	18	41	0
2.1	18	MeOH	29	14	44	0
2.1	60	MeOH	22	18	37	0

[a] Product distribution established by ^{1}H nmr analysis

This reaction is an example where the 5-*exo*-trig ring closure mode seems to be preferred over 6-*Endo*-Trig ring closure. The use of two equivalents of base gave no recovered starting material and this was compensated for by enhancement of the yields of dioxanes **4a** and **5a**, respectively. At the present the reason for this has not been determined but may be due to dianion formation. The yield of rearrangement product **3a** was slightly better in most of the cases where one equivalent of LDA was used. The mechanistic possiblities for this rearrangement are indicated in Scheme 3. The formation of the *trans*-diaxial isomer **4a** can be explained in two ways: either by formation of the monoenolate **8** and protonation of the same or by protonation of the dienolate **10** formed from **6** or **8**. That dienolate formation occurred has been established by deuteration experiments. A sample of **2a** was treated with 1 equivalent of LDA and quenched with MeOD. From the integration values measured on the ^{1}H nmr spectrum of the crude product and from mass spectroscopic analysis

of a purified sample of **4a**, it was established that there was dideuterated **4a** present and that the proportion of di- to monodeuterated **4a** was *ca.* 1:1. Compound **5a** is postulated to be formed by either protonation of monoenolates **6** and **8** or of the dienolate **10**. That the transformation **7** to **8** is reversible was established when compound **5b** was shown to give a mixture of **3b** (34%), **2b** (3%), **5b** (23%) and **4b** (6%) upon treatment with 1.3 equivalents of LDA for 35 min. That step a^2 was not reversible was demonstrated when dioxolane **3a** was treated with LDA (1.5 eq.). After a 30 min enolate formation time, reprotonation afforded only recovered **3a**. That none of the protonated maleate diester species **7** was isolated from any of these experiments would seem to infer that ring closure is very fast.



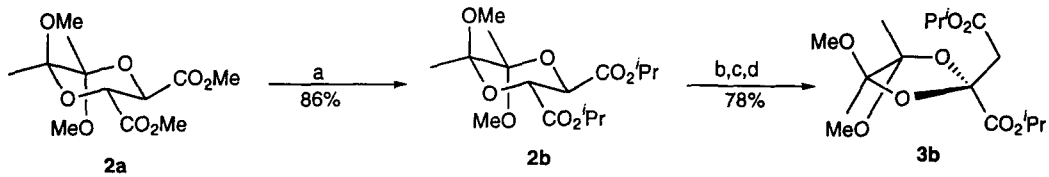
Scheme 3

Compound **3a** proved difficult to isolate in a pure state owing to its tendancy to eluate with the diaxial isomer **4a** during chromatographic separation attempts and thus it became necessary to look to other ester derivatives. The dioxalane derivative **3b** {$[\alpha]_D^{20}$ -108.79 (*c* 4.66, $CHCl_3$)}was synthesised in good yield *via* the diisopropyl ester derivative **2b** (Scheme 4). Two equivalents of LDA were routinely used since purification was simpler and good yields of the dioxolane **3b** were thus obtained.

Alkylation studies upon **3b** have only been moderately fruitful thus far. The two best electrophiles to-date being methyl iodide and benzaldehyde. Attempted alkylations using electrophiles such as benzyl bromide, allyl bromide and ethyl iodide gave only starting material and decomposition products. Alkylation with methyl iodide gave the dioxolane derivative **11** as a mixture of two diastereomers in 40% yield and in a 2:1 ratio,

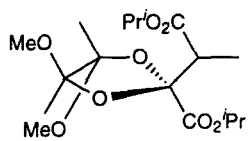
whilst aldol reaction with benzaldehyde gave compound **12** in 70% yield as a 4:1 mixture of only two diastereomers.

Scheme 4



a) $Ti(O^iPr)_4$, (0.1 eq.), 2-propanol, reflux; b) LDA (2.1eq.), THF, -78°C, 15 min; c) MeOH (4 eq.), -78°C; d) NH_4Cl (aq.), -78°C to r.t.

In conclusion, a potentially useful chiral dioxane derivative has been easily prepared in good yield from readily available and cheap *L*-(+)-tartaric acid. It was found that compound **2a** undergoes an unusual, base induced rearrangement to give a chiral dioxolane compound in which the chirality has been transfered from the tartaric acid precursor onto the resulting dioxolane ring. Preliminary studies indicate that **2a** and its rearrangement product **3b** have potential as substrates for asymmetric synthesis and studies are continuing in this respect.



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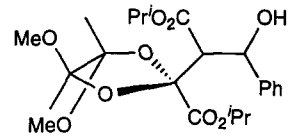

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