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# Chelation Control in the Aldol Reaction of Tetronic Acid. Application to the Synthesis of Pentoses, Arabitol and Ribitol

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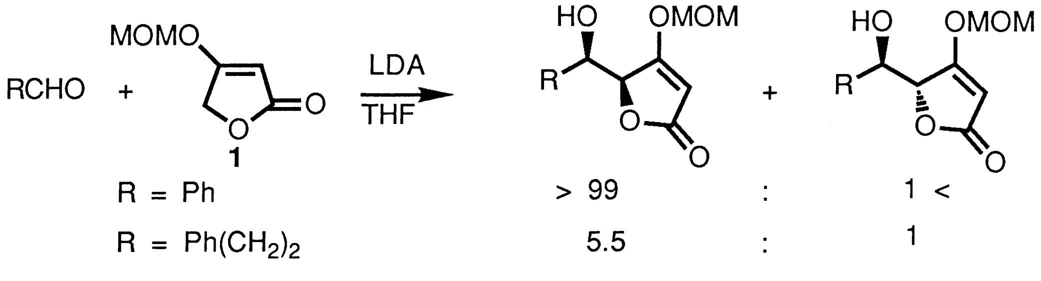
The aldol reaction of lithium enolates of tetronates with (R)-2,3-*O*-cyclohexylideneglyceraldehyde afforded the chelation controlled products stereoselectively. The conversion of the aldol products into arabitol and ribitol was also described.

Recently, we reported[1)] the aldol reaction of dianion of tetronic acid with 20-oxosteroid to give rise carbon-carbon bond formation products stereo- and site-selectively, where a six-membered chelated intermediate plays an important role to control the stereochemistry of the products. In this paper, we would like to report further results obtained by the reaction of lithium enolates of tetronates with aldehydes involving the seven-membered chelated intermediates, although a similar aldol reaction employing dianion of tetronic acid was not successful under the various reaction conditions attempted.

In 1987, Pelter published[2)] the aldol reaction of lithium enolate of methyl tetronate with aldehydes, however the detailed study has not been made on the stereochemical behaviour. We, therefore, initially reinvestigated the reaction of lithium enolate of methoxymethyl tetronate (**1**) with benzaldehyde and found that the isolated product was only the *threo* isomer in 87.8% yield when this reaction was performed in THF by slow addition of benzaldehyde to the enolate at - 78 °C. The treatment of **1** with dihydrocinnamaldehyde under the same reaction conditions also



furnished the *threo* isomer as a major aldol product in 83.9% yield in a ratio of 5.5 : 1, although Pelter reported that a similar reaction yielded the mixture of *threo* and *erythro* isomers in a ratio of ca. 1 : 1. This stereoselectivity was rationalized by assuming the well-established chelation control in the reaction of *E*-enolate[3] with aldehyde as shown in Fig.1, where the transition state leading to the *threo* isomer was superior to another transition state in terms of steric hindrance.[4]

In order to extend the synthetic utility of the present reaction, the aldol reaction of **1** with (R)-2,3-*O*-cyclohexylideneglyceraldehyde (**2**) was then

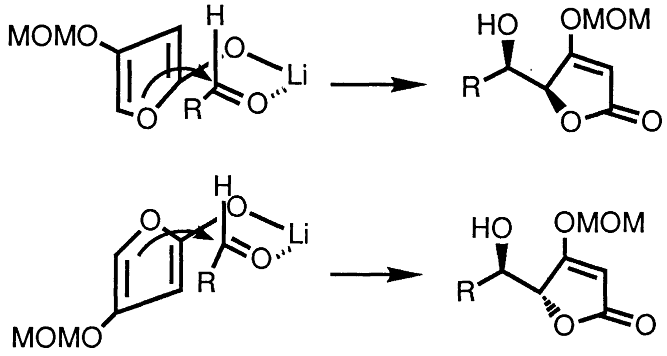
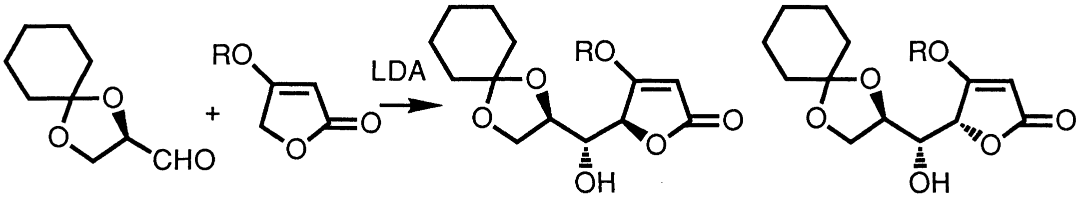


Fig. 1.

Table 1. The Aldol Reaction of Lithium Enolates of Tetronates with (R)-2,3-*O*-Cyclohexylideneglyceraldehyde (**2**)

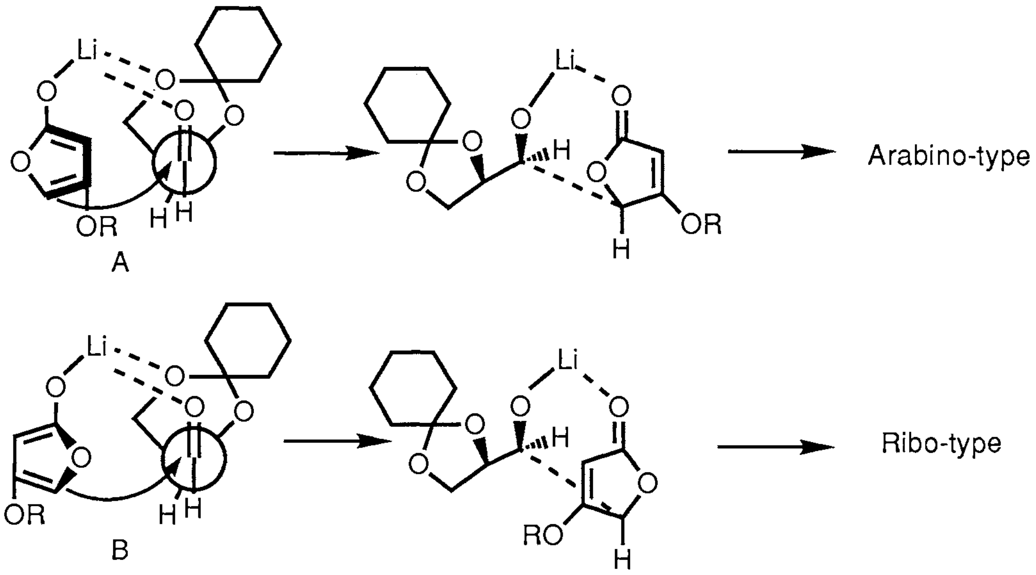


**2** Arabino Ribo

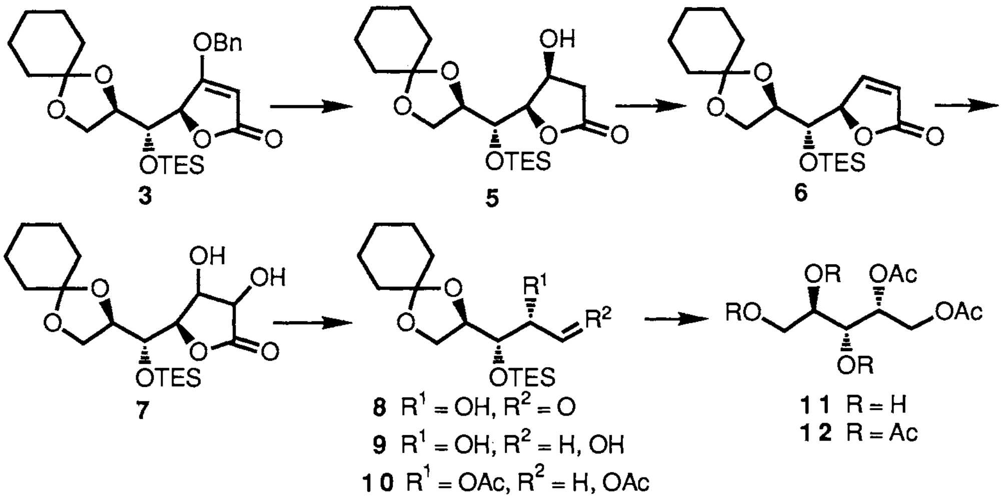
| Protecting group (R) | Products ( Arabino : Ribo) | Yield / % |
|---|---|---|
| Methoxymethyl | 4.2 : 1 | 81.1 |
| Methylthiomethyl | 5 : 1 | 51.2 |
| Benzyloxymethyl | 3.3 : 1 | 57.5 |
| Methyl | 3.8 : 1 | 83.9 |
| Benzyl | 1.7 : 1 | 37.7 |

investigated and found that the reaction provides arabino- and ribo-type compounds in a ratio of 4.2 : 1 (81.1% yield).

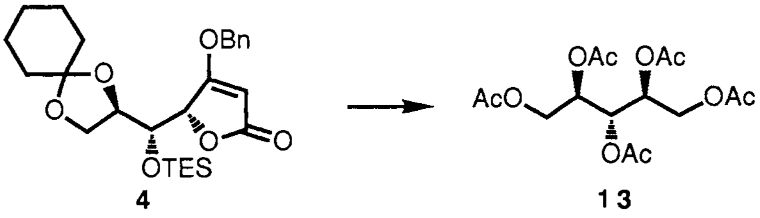
This stereoselectivity can also be rationalized by assuming that this reaction proceeded through the sterically less interacted chelation model (A) as a transition state to give arabino-type compound rather than the transition state (B) leading to the formation of ribo-type compound, where the C$_3$-oxygen of glyceraldehyde played an important role in the chelation formation. The results of the aldol reaction of lithium enolates of the tetronates with **2** were summarized in Table 1, which shows that the bulky protecting group, such as benzyl group was not suitable protecting group because of the decrease in the conversion yield and stereoselectivity.



The stereochemistries of the arabino- and ribo- compounds were unambiguously determined by their conversion into the penta-acetates of arabitol and ribitol, respectively. Thus the reaction of lithium enolate of benzyl tetronate with **2** in THF at -78 °C, followed by addition of triethylsilyl chloride afforded **3** and **4** in a ratio of 1.7 : 1 as shown in Table 1. Catalytic reduction of **3** over rhodium on alumina in ethyl acetate under $H_2$ (7 atm) gave the lactone **5** in 86.6% yield. Mesylation of **5** in dichloromethane in the presence of triethylamine afforded the olefin **6** in one step, which on treatment with potassium permanganate5) in dichloromethane in the presence of dicyclohexano-18-crown-6 furnished the diol **7**. Oxidative cleavage of **7** with $HIO_4$, followed by reduction of the resulting aldehyde **8** with sodium borohydride gave the alcohol **9** in 83.5% yield. Acetylation of **9** afforded the diacetate **10**, which on acid treatment brought about deprotection of the acetal and the silyl groups to give **11**. Finally, acetylation of **11** provided the penta-acetate **12** which was identical with an authentic sample prepared from arabitol by acetylation.



Similarly, the minor aldol product **4** was converted into the penta-acetate **13** identical with a sample derived from ribitol by acetylation.



This strategy would widely be applicable to the synthesis of polyhydroxy-compounds and such an application is under investigation in this laboratory.

References

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