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Erythrulose As a Multifunctional Chiron: Highly Stereoselective Boron Aldol Additions

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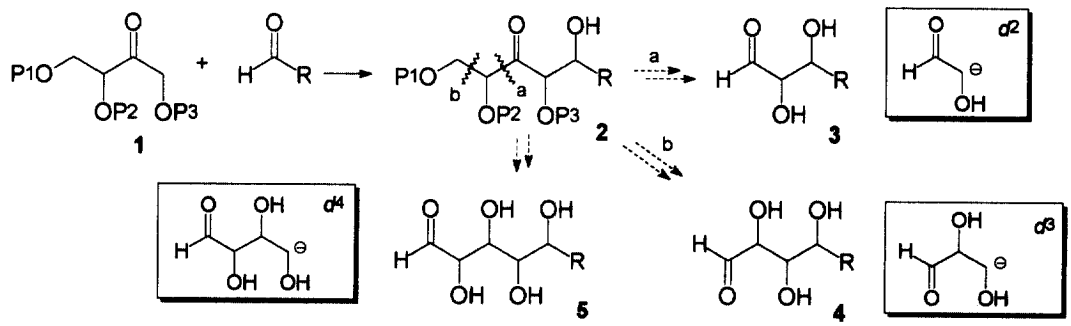
Abstract: We have investigated the formation of various metal enolates of 1-O-silylated erythrulose 3,4-acetonides. We were able to prepare boron enolates using Brown's dicyclohexylboron chloride / tertiary amine system. When these enolates were allowed to react with a range of achiral aldehydes, highly stereoselective aldol additions took place with formation of the *syn /syn* stereoisomer. This has been attributed to the exclusive formation of a Z boron enolate, which is in a sharp contrast with the usual behaviour of the aforementioned reagent.

The aldol reaction[1] has proven to be a powerful and general method for the stereocontrolled construction of carbon-carbon bonds and has relevant application in the synthesis of natural polyoxygenated molecules such as macrolide and polyether antibiotics.[2] In connection with our current interest in the development of erythrulose as an useful C_4-chiral building block for the stereocontrolled construction of polyfunctionalized structures,[3] we envisaged the enolization of protected L-(*S*)-erythrulose derivatives **1** (P^1-P^3 = protecting groups) and the subsequent addition of the resulting enolates to aldehydes. As shown below, further manipulation of the key aldol adduct **2** through prior carbonyl reduction and selective cleavage of bonds a or b would yield selectively protected α,β-dihydroxy aldehydes **3** or α,β,γ-trihydroxy aldehydes **4**, respectively. Synthetic equivalents of the d^2 synthon hydroxy acetaldehyde enolate, or its equivalent the glycolic acid enolate, have been described[4,5] but there are no counterparts for the d^3 synthon α,β-dihydroxy propanal homoenolate equivalent.[6] Furthermore, **1** could also act as an α,β,γ-trihydroxy butanal bishomoenolate equivalent (cf. **5**). In such a process, **1** would function as a hitherto unprecedented d^4 synthon type with no loss of carbon, thus maximizing atom economy.[7] The synthetic utility of erythrulose is based therefore on the fact that it may behave, according to convenience, as a C_4 chiral d^2, d^3 or d^4 synthon.



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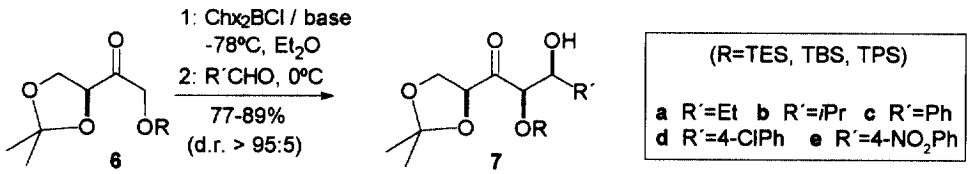
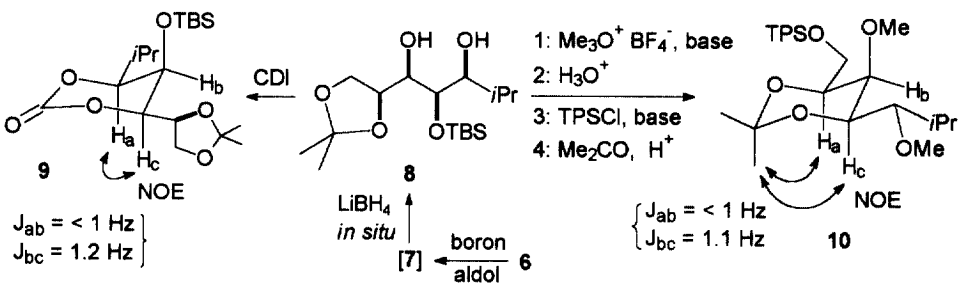
As first candidates to be evaluated we chose the L-(*S*)-erythrulose 3,4-acetonide derivatives **6** (three different silyl protecting groups, TES, TBS and TPS, were tested).[8] Treatment of **6** with $Sn(OTf)_2/iPr_2NEt$,[9a] $TiCl_4/iPr_2NEt$,[9b] $SnCl_4/iPr_2NEt$,[9c] and LDA or LDA/LiCl,[1d,e,10] followed by addition of the corresponding aldehyde, failed to yield aldol products. Except for $Sn(OTf)_2/iPr_2NEt$ (recovery of **6**), only decomposition was observed. We then directed our attention to the use of boron enolates.[11] Ketones **6** were thus allowed to react in Et_2O or CH_2Cl_2 with dicyclohexylchloroborane (Chx_2BCl),[12a] di-*n*-butylboron triflate[12b] or *n*-butyldichloroborane[12c] in the presence of a tertiary amine (Me_2NEt, Et_3N or iPr_2NEt), followed by addition of a range of achiral aliphatic and aromatic aldehydes. As a matter of fact, the two latter boron reagents failed to provide any aldol product and led only to recovery of the starting materials. In contrast, reactions promoted by Chx_2BCl led to the aldol adducts **7** in good chemical yields as an essentially single diastereomer.[13] Essentially identical results were observed with all three silyl protecting groups and all three amines. The sterically hindered pivalaldehyde was the only aldehyde tested which did not react under the conditions described.



The absolute configuration of **7d** (R=TBS) was unequivocally established by an X-ray diffraction analysis.[14] For compound **7b** (R=TBS), taken as a representative "aliphatic" adduct, the configurational assignment was effected by chemical correlations. Aldol 1,3-*syn* reduction *in situ* with lithium borohydride afforded the protected polyol **8**.[15] Treatment of **8** with carbonyl diimidazole (CDI) gave carbonate **9**, where both coupling constant values and nuclear Overhauser enhancement across the protons in a 1,3-diaxial relationship provided evidence of the relative 1,2-*syn* configuration within the newly formed stereogenic centers. Furthermore, **8** was straightforwardly transformed into acetonide **10** where, again, the relative configurations were established through NMR measurements in the same way as above. Since the acetal ring in **10** contains the initially present stereogenic centre, the relative configurations now become absolute.



An explanation of the 1,2-*syn* induction during the aldol reaction is possible within the well known Zimmermann-Traxler chair-like transition state model,[16-18] if the geometry of the formed boron enolate is assumed to be exclusively *Z*. However, the formation of a *Z* boron enolate under these conditions is rather surprising, as Chx_2BCl normally yields very predominantly or exclusively *anti* aldols through *E* enolates.[19] After a literature perusal of the synthetic uses of this reagent for aldol additions, we found only one single example, which corresponded to an ethyl ketone bearing an α′-benzyloxy group, in which a *syn* aldol was formed with

high stereoselectivity (d.r. > 9:1).[20] Whether this is a general phenomenon with α'-alkoxy ketones remains, however, to be established and is currently a topic of experimental research within our group. Furthermore, theoretical *ab initio* calculations on the enolization and aldolization steps are presently being performed in order to provide a mechanistic basis for all these facts.[21]

The aldol methodology described above can be very useful for the synthesis of polyoxygenated chiral compounds, such as higher sugars and related metabolites. Introduction of nitrogen functions through substitution of hydroxyl by amino groups further opens the way to chiral nitrogenated metabolites, such as amino polyols, amino sugars, non-natural amino acids, etc. Efforts in these directions are underway.

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13. *Optimized general procedure for formation of boron enolates and aldol additions:* To a stirred solution of Chx_2BCl (1.8 mL of a 1M hexane solution, 1.8 mMol) and Et_3N (278 μL, 2 mMol) in anhydrous Et_2O (6 mL) at -78°C was added erythrulose derivative **6** (1 mMol) in ether (6 mL). After 10 min, the reaction mixture was warmed to 0°C for 1 h and then recooled to -78°C. A solution of the aldehyde (5 mMol) in ether (6 mL) was added and after 10 min. at -78°C the reaction mixture was warmed to 0°C and stirred at this temperature for 5 h. Then pH 7 phosphate buffer (6 mL) and MeOH (6 mL) was added at 0°C followed by 30% aq H_2O_2 solution (3 mL). After stirring for 1 h at room temperature, the mixture was poured into brine and extracted with ether. Solvent removal *in vacuo* and column chromatography of the residue on silica gel (hexane-EtOAc 9:1 and then 4:1) afforded the aldol addition product **7** as essentially one diastereomer (the minor diastereomers were almost undetectable by NMR of the crude reaction mixture). Chemical yields: R=TES, **7a** (85%), **7b** (77%), **7c** (80%), **7d** (87%); R=TBS, **7a** (87%), **7b** (86%), **7c** (83%), **7d** (86%), **7e** (89%); R=TPS, **7b** (85%), **7c** (78%).
14. The X-ray diffraction study was actually performed on the *enantiomer* of **7d** (R=TBS), prepared from the appropriate D-erythrulose derivative.[8] The crystallographic data have been deposited in the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K., and may be requested from the Director of this Centre.
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17. An open transition state seems not to be operative in the present case. This conclusion is supported by an study of the influence of the proportion of Chx_2BCl on the stereoselectivity of the process. Addition of less than 1.5 equiv. of reagent caused a much too slow reaction. Within the range of 1.7-2.5 equiv. of reagent, only the *syn-syn* aldol was formed with the same yield and diastereomeric proportion reported in the text. When 3 or more equiv. were added, extensive decomposition was observed. See: Walker, M.A.; Heathcock, C.H. *J.Org.Chem.* **1991**, *56*, 5747-5750.
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21. The computational calculations are being performed by Dr. J. Murga. The experimental results presented here are part of the projected Ph.D. Thesis of E.F. Complete theoretical and experimental data will be published in due course.