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Boron aldol additions with erythrulose derivatives: dependence of stereoselectivity on the type of protecting group

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Abstract

Boron aldol additions of 1-*O*-silylated 3,4-di-*O*-benzyl- and 3,4-di-*O*-benzoyl-L-erythrulose and achiral aldehydes using dicyclohexylboron chloride have been investigated. The dibenzyl derivative gave *syn/syn* stereoisomers with high stereoselectivity, whereas the dibenzoyl derivative gave *syn/anti* stereoisomers. It is believed that, while the dibenzoyl erythrulose gives rise to the *E* enolate in the presence of dicyclohexylboron chloride, as usually observed with this reagent, only the *Z* enolate is formed in the case of the dibenzyl derivative. © 1999 Elsevier Science Ltd. All rights reserved.

The aldol reaction[1] has proved 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] We have recently reported on the enolization of silylated L-(*S*)-erythrulose acetonides **1** (R=TES, TBS, TPS) with dicyclohexylboron chloride and the addition of the resulting boron enolates to several achiral aldehydes.[3] As shown, *syn/syn* aldol[4] adducts **2** were obtained with high stereoselectivity. We have now investigated the influence of the nature of the protecting groups at O-1 and O-2 on the course of the aldol reaction with the aim of finding ways to obtain 4,5-*anti* stereoisomers. This would enhance the synthetic utility of erythrulose for its use as a chiral d^2, d^3 or d^4 synthon.[3]

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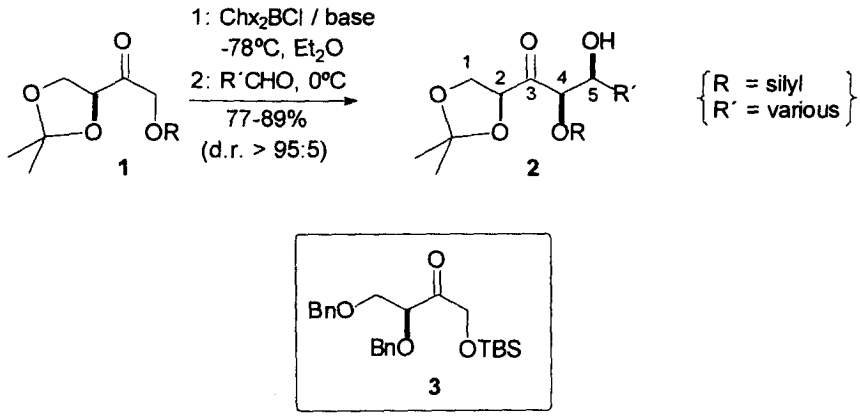
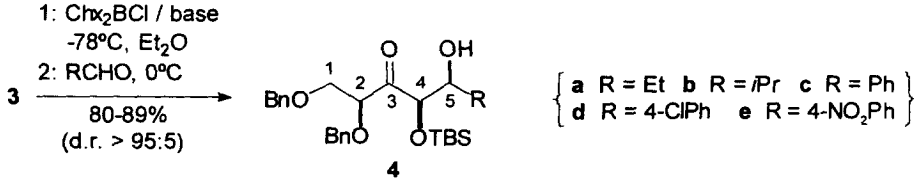
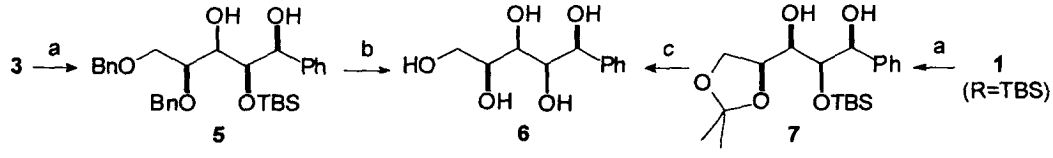


We first evaluated the 3,4-di-*O*-benzyl-L-erythrulose derivative **3**.[5] Like **1**, ketone **3** did not yield aldol products with $Sn(OTf)_2/iPr_2NEt$,[6a] $TiCl_4/iPr_2NEt$,[6b] LDA or LDA/LiCl.[1d,e,7] Either decomposition or recovery of the starting product was observed.[6c] The formation of boron enolates with dicyclohexylboron chloride (Chx_2BCl)[8,9] was then attempted. Aldol additions promoted by this reagent led to aldol adducts **4** in good chemical yields as essentially single diastereoisomers (Scheme 1).[10] The sterically hindered pivalaldehyde was the only aldehyde tested which did not react under the conditions described. The stereochemical course of the reaction was the same as with acetonides **1**, with only the *syn/syn* stereoisomer being formed.



Scheme 1.

The absolute configuration of aldols **4** was unequivocally established by chemical correlation with the previously described acetonide aldols.[3] Scheme 2 illustrates the procedure in the case of **4c**. Aldol addition of **3** with benzaldehyde, followed by in situ reduction[11] with $LiBH_4$, afforded diol **5**. Hydrogenolysis of the benzyl groups of the latter compound in the presence of 1,4-cyclohexadiene was accompanied by simultaneous desilylation to yield pentaol **6**. The same compound was obtained from erythrulose acetonide **1** (R=TBS) and benzaldehyde in two steps as indicated below.

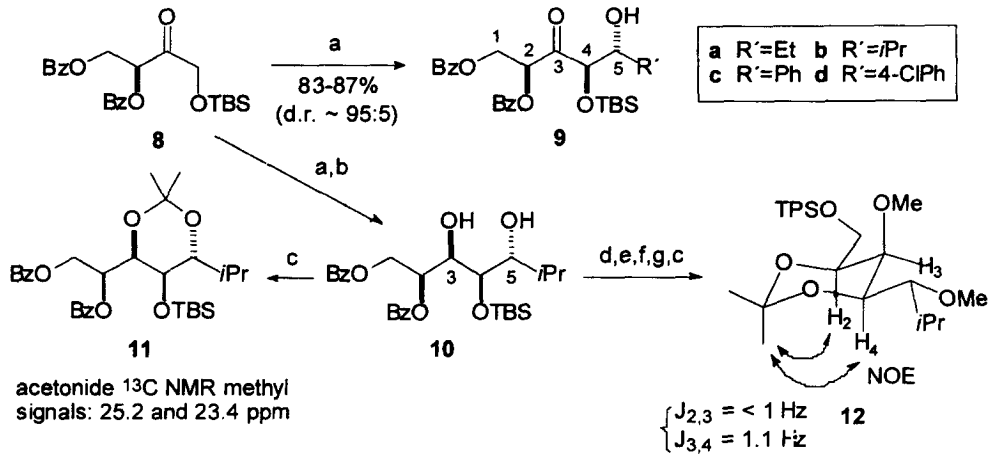


Scheme 2. Reaction conditions: (a) Chx_2BCl, Et_3N, Et_2O, −78°C, then PhCHO, −78→0°C, then $LiBH_4$, −78°C. (b) 10% Pd/C, 1,4-cyclohexadiene, EtOH, Δ. (c) PPTS, aq. MeOH, Δ

It turns out, therefore, that the replacement of the acetonide moiety by benzyl protecting groups does not change the steric course of the aldol reaction. We have previously proposed[3] that the formation of the *syn/syn* adduct is explained by participation of a *Z* enolate in a Zimmermann–Traxler chair-like transition state. Furthermore, theoretical ab initio calculations carried out in our group indicate that only the *Z* enolate satisfactorily explains the observed steric course.[12] Until our reports, however, only a single

example had been described in which dicyclohexylboron chloride promoted the formation of *syn* aldols. This example corresponds to an ethyl ketone bearing an α′-benzyloxy group.[13,14] The same authors further observed that replacement of the benzyl by a benzoyl group caused a reversal in the steric course of the reaction, *anti* aldols being formed with the benzoyl group. In view of this, we investigated aldol reactions with a dibenzoylated erythrulose.

1-*O*-*t*-Butyldimethylsilyl-3,4-di-*O*-benzoyl-L-erythrulose **8** was prepared from L-ascorbic acid according to our recently described methodology.[5,15] Under the same reaction conditions described above for **3**, ketone **8** underwent aldol additions with aldehydes and yielded *syn/anti* aldol adducts **9** with both high yield and stereoselectivity (Scheme 3). The configuration was determined through chemical reactions as depicted in Scheme 3.[15] The ^{13}C NMR signals of the acetonide moiety in **11** indicated that **10** was an *anti*-1,3-diol,[16] in contrast with the *syn* stereochemical course expected for the $LiBH_4$ reduction.[17] This established an *anti* relative configuration between C_3 and C_5 in **10**. On the other hand, NOE measurements and coupling constant values in acetonide **12** pointed to a *syn/syn* relative configuration within the C_2-C_3-C_4 segment.



8 **9** **10** **11** **12**

Scheme 3. Reaction conditions: (a) Chx_2BCl, Et_3N, Et_2O, −78°C, then RCHO, 0°C. (b) After aldol reaction with isobutyraldehyde, in situ reduction of the intermediate boron aldolate with $LiBH_4$ at −78°C. (c) 2,2-Dimethoxypropane, acetone, CSA, rt. (d) Me_3O^+ BF_4^-, proton sponge, rt. (e) KOH, aq. EtOH, rt. (f) TBAF, THF, rt. (g) TPSCl, Et_3N, CH_2Cl_2, rt

The results of these chemical reactions unambiguously indicate the absolute configuration of aldols **9** to be as depicted above. At the same time, they strongly suggest that the *E* enolate is formed predominantly from **8** in the presence of dicyclohexylboron chloride, in agreement with the usual behaviour of this reagent.[8] Computational calculations lend additional support to this idea.[12] In the case of Paterson's ethyl ketones,[13] the authors suggested that the different enolization behaviour of the benzylated versus the benzoylated ketone was due to the formation in the former compound of a five-membered chelate involving the boron, the carbonyl and α-oxygen atoms: stereoselective deprotonation of this chelate would then predominantly yield the *Z* enolate. A similar chelation should be disfavoured in the benzoylated ketone, whereby the deprotonation process would take its usual stereochemical course and afford the *E* enolate.[13] In principle, the results described here support this mechanistic interpretation but more data will be necessary to provide it with a firm basis. Efforts in this direction at both the experimental and computational level are underway in our group.

Acknowledgements

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10. The experimental procedure for the formation of boron enolates and aldol additions is the same as for acetonides **1**.[3] Chemical yields: **4a** (87%), **4b** (86%), **4c** (83%), **4d** (86%), **4e** (89%), **9a** (87%), **9b** (86%), **9c** (83%), **9d** (86%).
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14. Whether or not this behaviour in boron aldol additions constitutes a general feature of alkoxy ketones is being currently investigated within our group.
15. All experimental details about the synthetic procedures, chemical correlations, etc. are part of the Ph.D. Thesis of E.F. (University of Castellón, 1998). Complete theoretical and experimental data will be reported in due course.
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