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

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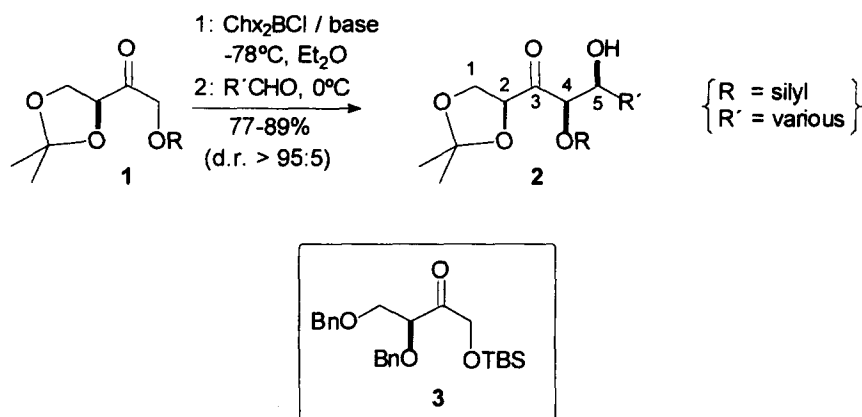
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### Abstract

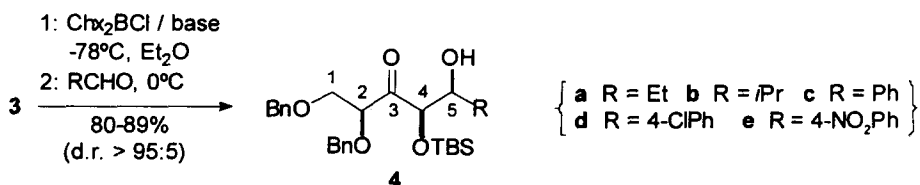
Boron aldol additions of 1-*O*-silylated 3,4-di-*O*-benzyl- and 3,4-di-*O*-benzoyl-L-erythrulose and achiral aldehydes using dicyclohexylboron chloride have been investigated. The dibenzyl derivative gave *syn/syn* stereoisomers with high stereoselectivity, whereas the dibenzoyl derivative gave *syn/anti* 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<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> As shown, *syn/syn* aldol<sup>4</sup> 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*<sup>2</sup>, *d*<sup>3</sup> or *d*<sup>4</sup> synthon.<sup>3</sup>

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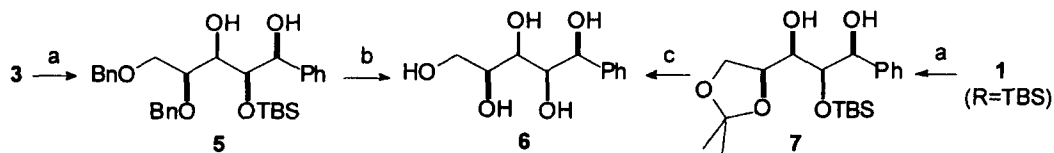


We first evaluated the 3,4-di-*O*-benzyl-L-erythrulose derivative **3**.<sup>5</sup> Like **1**, ketone **3** did not yield aldol products with  $\text{Sn}(\text{OTf})_2/\text{iPr}_2\text{NEt}$ ,<sup>6a</sup>  $\text{TiCl}_4/\text{iPr}_2\text{NEt}$ ,<sup>6b</sup> LDA or LDA/LiCl.<sup>1d,e,7</sup> Either decomposition or recovery of the starting product was observed.<sup>6c</sup> The formation of boron enolates with dicyclohexylboron chloride ( $\text{Chx}_2\text{BCl}$ )<sup>8,9</sup> was then attempted. Aldol additions promoted by this reagent led to aldol adducts **4** in good chemical yields as essentially single diastereoisomers (Scheme 1).<sup>10</sup> 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.<sup>3</sup> Scheme 2 illustrates the procedure in the case of **4c**. Aldol addition of **3** with benzaldehyde, followed by in situ reduction<sup>11</sup> with  $\text{LiBH}_4$ , 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** ( $\text{R}=\text{TBS}$ ) and benzaldehyde in two steps as indicated below.

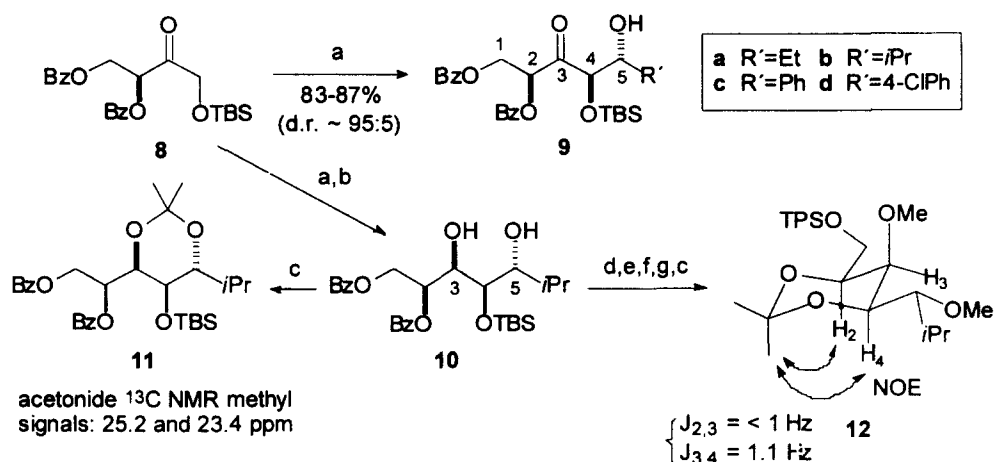


Scheme 2. Reaction conditions: (a)  $\text{Chx}_2\text{BCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , then  $\text{PhCHO}$ ,  $-78 \rightarrow 0^\circ\text{C}$ , then  $\text{LiBH}_4$ ,  $-78^\circ\text{C}$ . (b) 10%  $\text{Pd/C}$ , 1,4-cyclohexadiene,  $\text{EtOH}$ ,  $\Delta$ . (c) PPTS, aq.  $\text{MeOH}$ ,  $\Delta$

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<sup>3</sup> that the formation of the *syn/syn* adduct is explained by participation of a *Z* enolate in a Zimmerman–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.<sup>12</sup> 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  $\alpha'$ -benzyloxy group.<sup>13,14</sup> 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.<sup>5,15</sup> 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.<sup>15</sup> The <sup>13</sup>C NMR signals of the acetonide moiety in **11** indicated that **10** was an *anti*-1,3-diol,<sup>16</sup> in contrast with the *syn* stereochemical course expected for the LiBH<sub>4</sub> reduction.<sup>17</sup> This established an *anti* relative configuration between C<sub>3</sub> and C<sub>5</sub> 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<sub>2</sub>-C<sub>3</sub>-C<sub>4</sub> segment.



Scheme 3. Reaction conditions: (a) Chx<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, -78°C, then RCHO, 0°C. (b) After aldol reaction with isobutyraldehyde, in situ reduction of the intermediate boron aldolate with LiBH<sub>4</sub> at -78°C. (c) 2,2-Dimethoxypropane, acetone, CSA, rt. (d) Me<sub>3</sub>O<sup>+</sup> BF<sub>4</sub><sup>-</sup>, proton sponge, rt. (e) KOH, aq. EtOH, rt. (f) TBAF, THF, rt. (g) TPSCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 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.<sup>8</sup> Computational calculations lend additional support to this idea.<sup>12</sup> In the case of Paterson's ethyl ketones,<sup>13</sup> 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  $\alpha$ -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.<sup>13</sup> 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.

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- The experimental procedure for the formation of boron enolates and aldol additions is the same as for acetonides **1**.<sup>3</sup> Chemical yields: **4a** (87%), **4b** (86%), **4c** (83%), **4d** (86%), **4e** (89%), **9a** (87%), **9b** (86%), **9c** (83%), **9d** (86%).
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