

# Enantiopure 2-Substituted Glyceraldehyde Derivatives by Aza-Claisen Rearrangement or C-Alkylation of Enamines

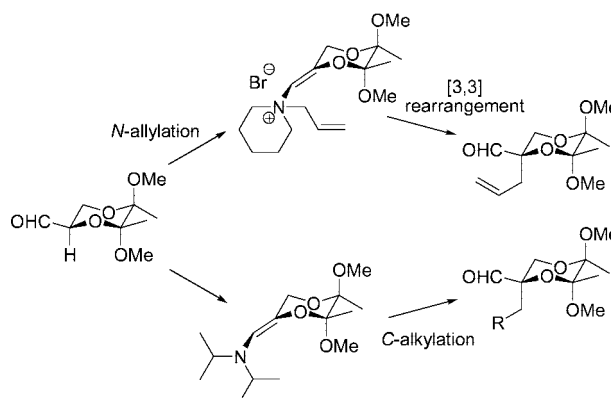
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## ABSTRACT



2-Alkyl derivatives of butane-2,3-diacetal (BDA) protected glyceraldehyde were stereoselectively prepared by aza-Claisen rearrangement of *N*-allyl-enammonium ions or C-alkylation of enamines. This allows rapid and convenient access to densely functionalized chiral building blocks.

The selective construction of fully substituted stereocenters remains an important challenge for synthetic chemists.<sup>1</sup> Among the most successful methods for the stereoselective introduction of highly substituted carbon centers have been rearrangements and cycloadditions which proceed by concerted cyclic transition states. While the Claisen rearrangement and its numerous variants have found widespread application in natural product synthesis,<sup>2</sup> there are relatively

few examples for aza-Claisen rearrangements of allyl-enamines with highly functionalized substrates, due to the high temperatures (>200 °C) necessary.<sup>3a</sup> Although it has been known for some time that the rearrangement of allyl-enammonium salts proceeds at much lower temperatures (20–100 °C) to give rise to fully substituted carbon centers,<sup>3b</sup> the reaction has not received much attention.<sup>4</sup>

The C-alkylation of enamines (Stork enamine synthesis) has been used extensively in synthesis because it reliably affords monoalkylation in the  $\alpha$ -position to the carbonyl

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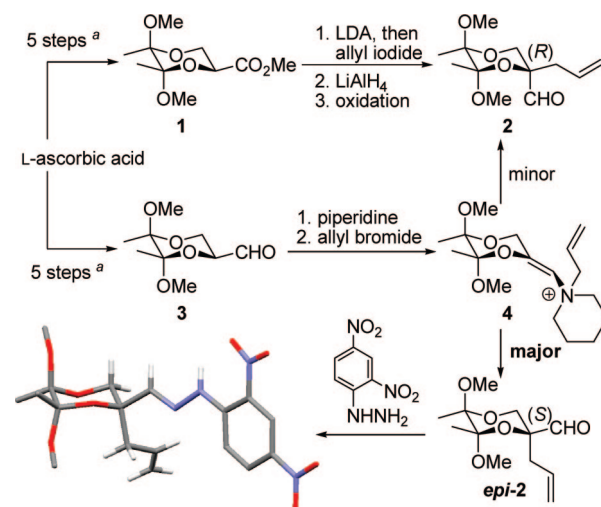
group of an aldehyde or ketone without the risk of over-alkylation.<sup>5</sup> Accordingly, the introduction of fully substituted carbons by means of enamine alkylation is much less well preceded.<sup>3,6</sup>

Butane-2,3-diacetal (BDA) protected diols have been applied as chiral building blocks in several natural product syntheses.<sup>7</sup> Most recently, we have employed BDA-protected diols as convenient chiral starting materials in the synthesis of bicyclic acetals,<sup>8</sup> and we disclosed a new protocol for the removal of BDA protecting groups under mild conditions.<sup>9</sup> A particularly attractive feature of BDA building blocks is that the diacetal moiety can preserve stereochemical information during a reaction sequence. Such chiral memory protocols have been successfully implemented in the stereo-selective alkylation of BDA-protected glycolic acid,<sup>10</sup> in the desymmetrization of *meso*-tartrate<sup>11</sup> and in the alkylation of BDA-protected methyl glycerate.<sup>12</sup> In addition, BDA-protected glyceraldehyde has been introduced as a stable alternative to glyceraldehyde acetonide.<sup>13</sup>

Here we report the first use of enamines derived from BDA-protected glyceraldehyde as substrates for aza-Claisen rearrangements and C-alkylation reactions.<sup>14</sup>

For a future natural product synthesis program, reliable access to allylated aldehyde **2** was required (Scheme 1). The

**Scheme 1.** Alternative Routes to Allylated Glyceraldehyde **2**<sup>a</sup>



<sup>a</sup>Ref 13.

initial synthetic plan was based on the selective allylation of the lithium enolate of ester **1**, which allowed intermediate **2** to be prepared in eight steps from L-ascorbic acid with an overall yield of 9.6%.<sup>12,15</sup> To shorten this sequence, we decided to investigate whether aldehyde **2** could be efficiently accessed by an aza-Claisen rearrangement of enammonium ion **4**.

Reaction of BDA-protected glyceraldehyde **3**<sup>13b</sup> with a secondary amine would lead to an enamine in which the original stereogenic center of glyceraldehyde has been removed; however, the chiral information is retained in the diacetal backbone. After N-allylation, we expected the aza-Claisen rearrangement to proceed stereoselectively with the allyl group approaching from an equatorial trajectory as had been previously observed in the allylation of the related ester enolate.<sup>12</sup> The resulting iminium ion would be easily hydrolyzed upon workup to form the desired aldehyde.

In the event, we found that treatment of aldehyde **3** with piperidine afforded an enamine as a single isomer in quantitative yield.<sup>16</sup> Subsequent reaction with allyl bromide in refluxing acetonitrile for 12 h led, after aqueous workup, to a 4:1 diastereomeric mixture of the rearranged product (Scheme 1). Surprisingly, analysis of the <sup>1</sup>H NMR spectrum revealed that the desired diastereomer **2** was the minor component of this mixture. The crystal structure of the 2,4-dinitrophenyl hydrazone of the major diastereomer confirmed it to be epimeric aldehyde *epi-2*. Despite the modest isolated yield of 40%, we decided to further explore this reaction sequence, since starting from the enantiomeric aldehyde *ent-3*, which is available in two steps from D-mannitol,<sup>13a</sup> would

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(16) The Z-geometry of the enamine double bond was established by <sup>1</sup>H NMR spectroscopy through the observation of an nOe between the exocyclic enamine proton and the methylene group of the dioxane ring. This assignment was subsequently confirmed by the crystal structure of the corresponding N-(2-methylallyl)enammonium bromide *ent-4b* (see Supporting Information).

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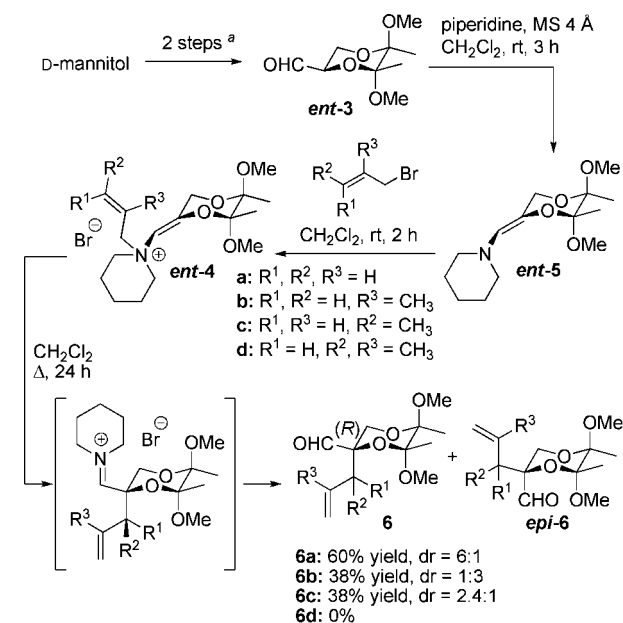
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(14) A related imine, derived from BDA-glyceraldehyde **4**, was recently employed in the synthesis of β-lactams by [2 + 2] cycloaddition: Carrasco, E.; Light, M. E.; Santos, M.; Plumet, J. *Synlett* **2007**, 3180–3182.

allow us to obtain **6a** ( $\equiv$  *ent-epi-2*) with the required (*R*)-configuration at C-2 for the total synthesis project (Scheme 2).

**Scheme 2.** N-Allylation Aza-Claisen Rearrangement Sequence<sup>a</sup>

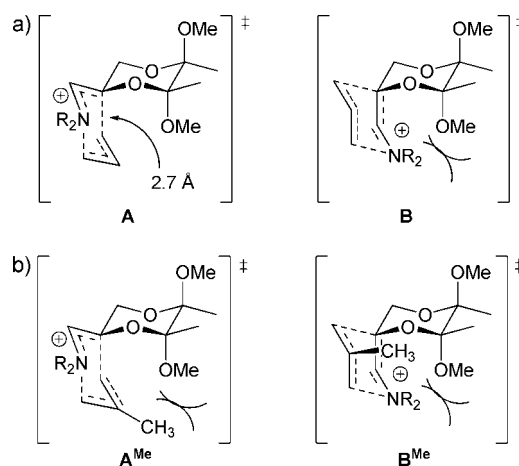


We briefly investigated the influence of the secondary amine on the stereoselectivity of the rearrangement. While replacement of piperidine with diethylamine left the diastereomeric ratio unchanged, the use of pyrrolidine as the amine component led to a decrease in diastereoselectivity.<sup>17a</sup> We next changed the solvent to  $\text{CH}_2\text{Cl}_2$ , thus lowering the reaction temperature from 80 to 40 °C. Under these conditions, a diastereomeric ratio of 6:1 was observed. We attribute this mainly to a temperature and not a solvent effect, since raising the reaction temperature in a closed vessel decreased the diastereoselectivity.<sup>17b</sup> Using  $\text{CH}_2\text{Cl}_2$  as the solvent for enamine formation, allylation, and rearrangement, we were able to carry out a one-pot procedure, which reproducibly gave yields of 50–60% with a dr of 6:1 on a 25 g scale.

The rearrangement of enammonium ions with further substitution of the allyl group led to lower yields and diminished diastereoselectivities. When 2-methylallylbromide was used as the allylating agent, aldehyde **6b** was obtained after rearrangement and hydrolysis in 38% yield with a reversed dr of 1:3. Treatment of **5** with *trans*-crotylbromide and subsequent rearrangement gave aldehyde **6c** in 38% yield with a dr of 2.4:1 (Scheme 2).<sup>18,19</sup>

Attempts to induce the rearrangement of gem-dimethylated allyl-enammonium ion **3d** were met with failure. Despite this limited substrate scope, the reaction allows rapid access to a densely functionalized chiral building block. Thus, aldehyde **6a** is available in three steps from D-mannitol in 27% overall yield.<sup>20</sup>

The unexpected stereochemical outcome of the aza-Claisen rearrangement prompted us to carry out DFT calculations to better understand the origin of the selectivity.<sup>21</sup> The computational results agree qualitatively with the experimental observation as the transition state **A** leading to the equatorial aldehyde product **6a** is favored over the alternative transition state **B** leading to the epimeric product. This can be explained in terms of a loose transition state for the aza-Claisen rearrangement, in which the dioxane ring assumes a chair conformation. The newly forming C–C bond is particularly long (2.7 Å),<sup>22</sup> thus sterically less demanding than the existing C–C bond, and therefore assumes the sterically more demanding axial position (Figure 1a). The



**Figure 1.** Schematic representation of transition states for the aza-Claisen rearrangement. Transition state **A** has been found and fully characterized, while the competing transition state, **B**, was not isolated.

reversal of stereoselectivity for **6b** is the result of an unfavorable steric interaction between the allylic methyl group and the axial methoxy group, which increases the energy of transition state **A**<sup>Me</sup>.

(17) (a) These reactions were performed on aldehyde **3**. Influence of the secondary amine used for enamine formation on the diastereoselectivity of the aza-Claisen rearrangement:  $\text{CH}_3\text{CN}$ , 80 °C, piperidine: dr 4:1, diethylamine: dr 4:1, pyrrolidine: dr 2.3:1.  $\text{CH}_2\text{Cl}_2$ , 40 °C, piperidine: dr 6:1, morpholine: 5.2:1. (b) These reactions were performed on *ent-3*. Influence of temperature on the diastereoselectivity of the aza-Claisen rearrangement:  $\text{CH}_2\text{Cl}_2$ , piperidine, 100 °C: dr 4:1, 120 °C: dr 4:1.

(18) The stereochemistry of the major components from **6b** and **6c** was determined by analogy to **6a**.

(19) **6c** was isolated as a 6:1 inseparable mixture of diastereomers at the allylic center: see Supporting Information for full experimental details and spectra.

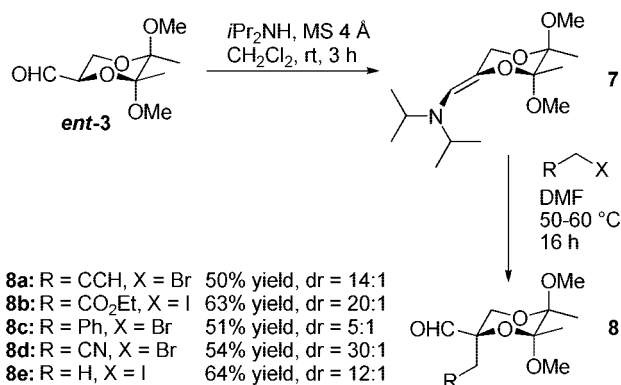
(20) The enammonium salt of **4b** was isolated and subsequently subjected to rearrangement conditions, which gave identical results to the one-pot procedure. This provides strong evidence for an N-allylation/[3,3]-rearrangement process and not direct C-alkylation. Additionally, no reaction was observed in the case of **4d**. If the direct C-alkylation process was operative, we would expect some product formation.

(21) Jaguar (version 7.0) was used (Schrodinger LLC: New York, 2007) and the 6-31G\* basis set (Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986) with the the B3LYP functional: Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648–5652. Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785–789.

Since the scope of the aza-Claisen rearrangement is essentially limited to introduction of an allyl substituent, we decided to explore whether C-alkylation of a suitable enamine would allow us to introduce other synthetically useful substituents. While there are examples for the C-alkylation of 2,2-dialkyl-substituted enamines,<sup>6</sup> the C-alkylation of 2-oxy-substituted enamines to the best of our knowledge has not been described.

Gratifyingly, we found after some experimentation that C-alkylation of diisopropyl enamine **7** could be achieved with reactive alkylating agents in DMF at 40–60 °C. The resulting aldehydes **8a–e** were obtained in 50–63% yield and diastereomeric ratios between 5:1 and 30:1 (Scheme 3). A

**Scheme 3.** C-Alkylation of BDA-Protected Glyceraldehyde Enamine **7**



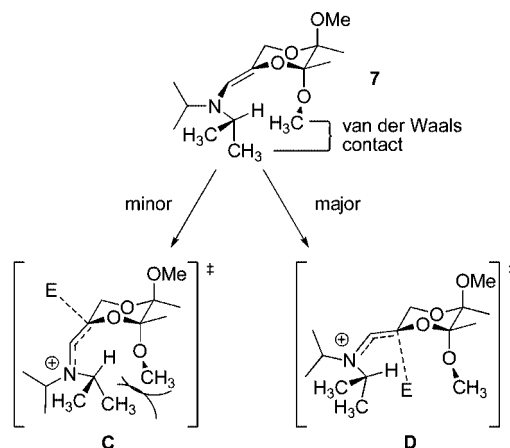
variety of functional groups such as a nitrile, ester, or alkyne were introduced into the BDA-protected glyceraldehyde core, which might serve as versatile and highly functionalized intermediates in natural product synthesis. With less reactive electrophiles such as ethyl iodide, no alkylation was observed.

Interestingly, the stereoselectivity of the alkylation reaction is identical to the aza-Claisen rearrangement, placing the substituent in an axial position of the BDA ring. The ground-state conformation of enamine **7** was calculated using DFT methods, which suggests steric factors are responsible for the observed stereoselectivity. The nitrogen atom and its substituents form an almost trigonal planar arrangement, which is coplanar with the enamine double bond.<sup>23</sup> One of the isopropyl groups is in close contact with the methoxy substituent. An electrophile approaching via an equatorial trajectory would force the isopropyl and methoxy groups closer together. The steric clash in transition state **C** disfavors this reaction pathway. However, if the electrophile approaches from the sterically more hindered axial face of the

(22) For comparison, the C–C bond of the transition state is 2.1 Å for the Claisen rearrangement of H<sub>2</sub>CCHCH<sub>2</sub>C(Me)<sub>2</sub>CHCH<sub>2</sub>, and it is 2.5 Å for the Claisen rearrangement of H<sub>2</sub>CCHCH<sub>2</sub>N<sup>+</sup>(Me)<sub>2</sub>CHCH<sub>2</sub>. This long bond appears to be a feature of the aza-Claisen reaction.

enamine (**D**), the isopropyl groups are forced into a sterically unencumbered equatorial position (Scheme 4). Not only is

**Scheme 4.** Selectivity of C-Alkylation<sup>a</sup>



<sup>a</sup>Schematic representations of the ground-state conformation of **7** and transition states of the C-alkylation.

this selectivity complementary to the previously developed enolate alkylation<sup>12</sup> but also the equatorial orientation of the aldehyde group maintains its reactivity allowing straightforward addition of nucleophiles to the carbonyl group.

In conclusion, the use of BDA-protected glyceraldehyde derived enamines in aza-Claisen rearrangements and C-alkylation reactions provides convenient and rapid access to densely functionalized chiral building blocks in satisfactory yields and good diastereoselectivities. Furthermore, these reactions are the first examples for the C-alkylation of heteroatom-substituted enamines. Future work will be directed toward application of the highly functionalized products as intermediates in the synthesis of complex target molecules.

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**Supporting Information Available:** Experimental procedures, characterization of new compounds, crystal structure data, and details of calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(23) Enamine **7** can have an almost planar nitrogen atom, with good overlap between the nitrogen lone pair and the double bond  $\pi$ -orbitals, but at the cost of steric interactions between the isopropyl groups and the rest of the molecule. Twisting around the C–N bond reduces the steric interactions, but reduces the lone pair double bond overlap. The energy change for this rotation is small (less than 1 kcal/mol) until the lone pair is at about 45° to the double bond, when the energy increases rapidly. The most reactive conformation, with the lone pair perfectly aligned with the double bond orbitals, is similar in energy to the minimum energy conformation.