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Stereo- and Enantioselective Synthesis of Acetylenic 2-Amino-1,3-diol Stereotriads

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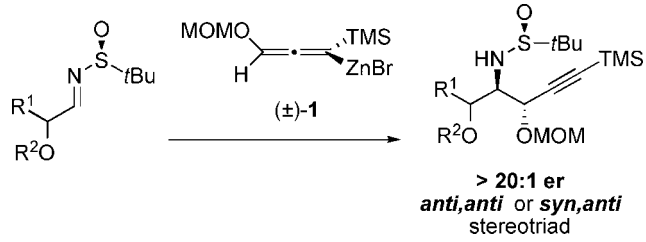
ABSTRACT



The high-yielding and highly efficient stereoselective synthesis of enantiopure *anti,anti* and *syn,anti* acetylenic 2-amino-1,3-diol stereotriads from α-alkoxy-*tert*-butanesulfinylimines bearing a stereocenter α to the imino group is reported. The stereoselectivity of the reaction of these *tert*-butanesulfinyl (*t*BS)-imines with allenylzinc (±)-1 was found to be controlled only by the configuration of the *t*BS group. An excellent kinetic resolution of the racemic allenylzinc species was observed, allowing a high stereocontrol no matter what the configuration or the protecting group of the α-alkoxy group.

2-Amino-1,3-diol subunits constitute an important stereotriad pattern found in many natural molecules of biological interest, such as indolizidine and pyrrolizidine alkaloids.[1] A straightforward synthetic approach to these alkaloids could involve the construction of the bicyclic skeleton from properly functionalized enantiopure acetylenic 2-amino-1,3-diols presenting an *anti*,*anti* or a *syn*,*anti* relationship (Figure 1). In this context, we have recently shown[2] that allenylzinc

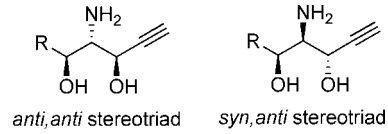


Figure 1. Acetylenic 2-amino-1,3-diol stereotriads.

species are highly valuable reagents to prepare acetylenic *anti*- or *syn*-β-amino alcohols[3] (from the corresponding acetylenic aziridines[4−6]) and *anti*- or *syn*-acetylenic aminoethers.[2,7]

The reaction of reagent (±)-**1** derived from 3-methoxymethyl-1-trimethylsilyl-1-propyne with enantiopure *t*BS-imines gives the corresponding enantiopure acetylenic

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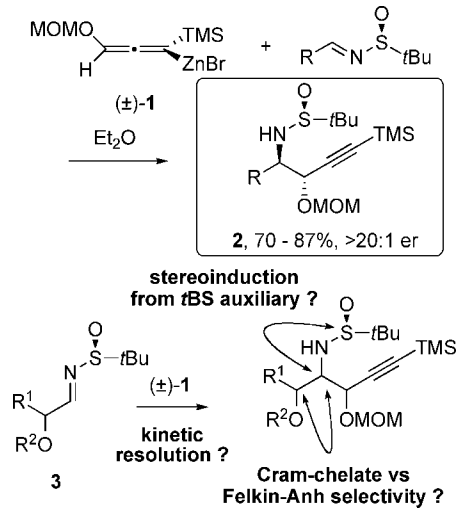
anti amino ethers **2** (Scheme 1).[3b,8] The key to these results is the highly efficient kinetic resolution of the racemic

Scheme 1. Synthesis of Acetylenic Amino Ethers and Approach to Acetylenic Stereotriads



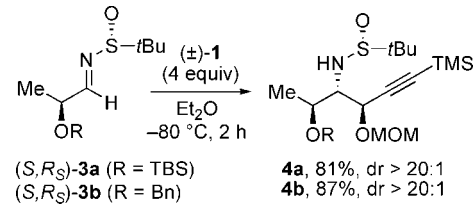
allenylzinc reagent brought about by the excellent stereocontrol of the *tert*-butanesulfinyl (*t*BS) moiety for the addition onto the imine. The synthetic potential of this approach has been exploited recently for the enantiocontrolled synthesis of (−)-α-conhydrine[9] and for the formal total synthesis of the two quinolizidinyl alkaloids (−)-epiquinamide and (−)-homopumiliotoxine 223G.[10] In order to obtain acetylenic 2-amino-1,3-diols and thus access to the corresponding (O,N,O) stereotriads, we envisioned applying this method to α-alkoxy *t*BS-imines **3** (Scheme 1). However, this approach raises several important difficulties which have to be examined. The presence of the oxygen functionality in the imine electrophile could modify the intrinsic stereoinduction previously observed from the *tert*-butanesulfinyl group in such reactions. Another issue to be considered is the influence of the new stereocenter α to the imine on the stereofacial selectivity compared to the sulfinyl chiral auxiliary. A Cram chelate versus a Felkin−Anh model could presumably be involved. Finally, the introduction of this oxygen functionnality α to the imine group could possibly modify the kinetic resolution efficiency of the starting allenylzinc (±)-**1**. Prompted by a recent report[11] on the addition of enolates on α,*β*-dialkoxy *t*BS-imines for the assembly of the polyhydroxylated amino acid constituents of microsclerodermins, we disclose hereafter our results concerning the reaction of allenylzinc reagent (±)-**1** with stereochemically pure chiral α-alkoxy *t*BS-imines.

The α-alkoxy *t*BS-imines necessary for our study were prepared by the reaction of the corresponding α-alkoxy aldehydes with enantiopure *tert*-butanesulfinamide[12] under standard conditions.[13,14]

Following our previously reported kinetic resolution conditions ((±)-**1**, 4 equiv, −80 °C),[4] the reaction of racemic allenylzinc (±)-**1** with enantiopure *t*BS-imines (*S,R*$_S$)-**3a** and (*S,R*$_S$)-**3b** proceeded in high yield and with high stereocontrol, as only one diastereomer **4a** (from **3a**) and **4b** (from **3b**) was obtained after hydrolysis.

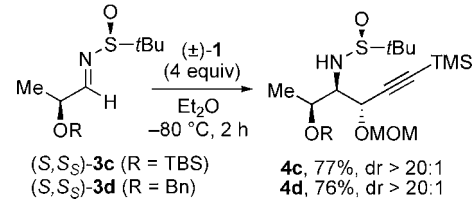
The relative and absolute configurations of the newly created stereocenters were determined unambiguously by various selective transformations into known compounds or oxazolidinones (see below). From all the correlation experiments we could determine that allenylzinc (±)-**1** reacts with imines (*S,R*$_S$)-**3a**,**b** from their *Re* face to give with a high stereoselectivity the corresponding protected acetylenic 2-amino-1,3-diols presenting an *anti*,*anti* relationship (Scheme 2).

Scheme 2. Reactions with Imines (*S,R*$_S$)-**3a**,**b**



The reactivities of the *t*BS-imines (*S,S*$_S$)-**3c**,**d** were then examined. A difference in the diastereoselectivity of the reaction could be expected, as these imines are diastereomeric to the imines **3a**,**b** previously used and a matched/mismatched effect might thus be expected. However, to our delight, here again, under kinetic resolution conditions, an excellent stereoselectivity in the reaction with (±)-**1** (4 equiv) was observed as only one diastereomer **4c** (respectively **4d**) was obtained from imine **3c** (respectively **3d**, Scheme 3),

Scheme 3. Reactions with Imines (*S,S*$_S$)-**3c**,**d**



both presenting a *syn*,*anti* relationship. Allenylzinc (±)-**1** reacts therefore with imines (*S,S*$_S$)-**3c**,**d** from their *Si* face to give with high stereoselectivity the corresponding protected acetylenic 2-amino-1,3-diols presenting a *syn*,*anti* relationship.

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(9) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358.
(10) Voituriez, A.; Ferreira, F.; Pérez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705.
(11) Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841.

The relative and absolute configurations of the stereocenters in **4a**−**d** were determined unambiguously after selective transformations[15] into the oxazolidinones **6a**−**c** (Figure 2) and ^{1}H NMR coupling constant measurements.[16]

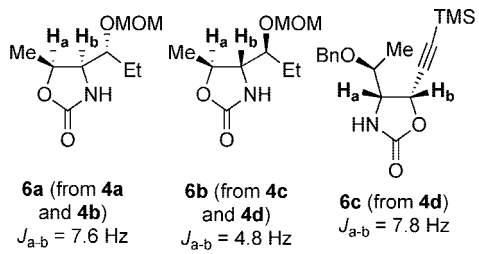
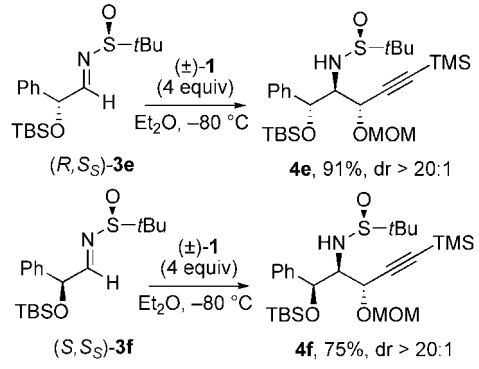


Figure 2. Oxazolidinones **6a**−**c** for stereochemical correlations.

The multistep transformation of compound **4a** into a known compound[17] was also performed.

The results reported above indicate that a high stereoinduction can be expected from the reaction of α-alkoxy *t*BS imines with allenylzinc (±)-**1**. To generalize this statement, we then tried the reaction of the two diastereomeric imines (*R*,*S*$_S$)-**3e** and (*S*,*S*$_S$)-**3f** derived from (+)- and (−)-mandelic acid, respectively. The reaction occurred smoothly under the same conditions as reported above, and here again, we obtained only one diastereomer **4e** or **4f**, respectively (Scheme 4).

Scheme 4. Reaction with Imines (*R*,*S*$_S$)-**3e** and (*S*,*S*$_S$)-**3f**



Structural determinations analoguous to those reported in the Figure 2 were conducted,[14] including the transformation of **4e** into a known compound.[16] The compound **4f** was also transformed after desilylation into the corresponding acetylenic alcohol **5f**, the configuration of which has been determined by X-ray crystallographic analysis. It could be unequivocally concluded that the reaction of (±)-**1** with imines (*R*,*S*$_S$)-**3e** and (*S*,*S*$_S$)-**3f** occurred from the *Si* face to give stereoselectively the corresponding *anti,anti* or *syn,anti* acetylenic stereotriad.

The addition of organometallic reagents onto *t*BS-imines has been largely studied,[18] and various models have been proposed to rationalize the stereoselectivity of such processes. More specifically, the influence of an oxygen or heteroatom functionality in the imine electrophile is a matter of interest since these groups can change the stereoinduction from the *tert*-butanesulfinyl group, as reported, for example, by Ellman, who observed a reversal of the stereofacial selectivity from simple *t*BS-imines[19] to α-alkoxy *t*BS-imines.[20] The origins for the inversion of the facial selectivity compared to simple alkyl *t*BS-imines remain under discussion, and models involving *E*/*Z* isomerization of imines as well as chelate versus open transition states have been proposed to account for the atypical stereochemical behavior. Moreover, it should be noted that this inversion in stereoselectivity does not seem general: it has been observed for *t*BS-imines derived from aldehydes bearing an α-alkoxy[10,18] or an α-chloro group,[21] independent of the organometallic species used (alkyl organometallics or enolates). By contrast, it has not been observed in the case of *t*BS-imines derived from aldehydes bearing an α-amino group[22] nor in the case of *t*BS-imines derived from ketones bearing an α-alkoxy group.[18b] The reduction of *t*BS-imines derived from ketones bearing an α-chloro group proceeds with face selectivities depending on the nature of the reducing agent.[23] In our case, no inversion of the stereochemical induction from the *t*BS group was noted, as the facial selectivity was the same in all cases we studied: imines (*S*,*R*$_S$)-**3a** and (*S*,*R*$_S$)-**3b** presenting a (*R*) configuration at the sulfur center reacted with (±)-**1** on their *Re* face, whereas products arising from the addition of imines (*S*,*S*$_S$)-**3c**, (*S*,*S*$_S$)-**3d**, (*R*,*S*$_S$)-**3e**, and (*S*,*S*$_S$)-**3f** presenting a (*S*) configuration at the sulfur center were obtained through reaction on the *Si* face.

Another point of interest concerns the relative influence on the stereofacial selectivity of the stereocenter α to the imine compared to the sulfinyl chiral auxiliary. A Cram chelate versus a Felkin−Anh model could presumably be involved, and the two possibilities have also been reported by Ellman.[12] Former reports dealing with organometallic species addition on α-alkoxy-[10,12] or α-amino-*t*BS-imines[20] bearing a stereocenter

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(15) See the Supporting Information.
(16) It is known that vicinal coupling constants in 4,5-disubstituted oxazolidinones are higher for the *cis* (6−8 Hz) than for the *trans* isomer (4−6 Hz); see: (a) Reference 3a and: (b) Foglia, T. A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680. (c) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308. (d) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci, A.; Varchi, G. *J. Org. Chem.* **1999**, *64*, 8008. (e) Poisson, J.-F.; Chemla, F.; Normant, J. F. *Synlett* **2001**, 305.
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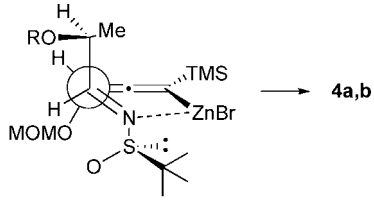
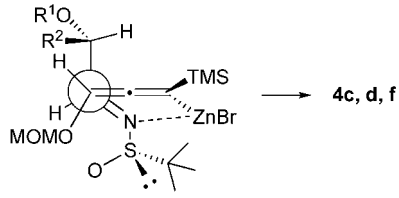
α to the imino group showed that generally the stereoselectivity is mainly defined by the sulfinyl moiety and not by the α stereocenter, although in some cases a drop in selectivity was observed.[12] In our case, the stereoselectivity is always excellent, and independent of the α stereocenter configuration, whatever the protecting group (TBS or Bn) on the oxygen atom. Though the stereoselectivity we obtained in the case of imines (S,R_S)-**3a**, (S,R_S)-**3b**, and (R,S_S)-**3e** is consistent with a Felkin-type control, in the case of imines (S,S_S)-**3c**, (S,S_S)-**3d**, and (S,S_S)-**3f**, anti-Felkin products are observed.

Finally, it should be noted that we have always used *racemic* allenylzinc (±)-**1**. The excellent selectivities we obtained in all cases can only be explained by a very efficient kinetic resolution: only one enantiomer of the racemic mixture in **1** is allowed to react with the enantiopure sulfinimines. We propose the Felkin-type transition state TS1 depicted in Scheme 5 to explain the stereoselectivities observed in the reactions with (S,R_S)-**3a** and (S,R_S)-**3b**. In this transition state, the *t*BS-imine is adopting its ground-state conformation where the S−O bond and the lone pair on the nitrogen atom are antiperiplanar.[5,24] The reaction of imine (R,S_S)-**3e** to afford **4e** presumably follows a transition state enantiomeric to TS1. On the other hand, the anti-Felkin-type transition state TS2 is proposed for the reactions of imines (S,S_S)-**3c**, (S,S_S)-**3d**, and (S,S_S)-**3f**. In each case, only the matched reacting enantiomer of (±)-**1** is represented.

Scheme 5. Plausible Transition States TS1 and TS2



TS1 (Felkin) : R = TBS, Bn



TS2 (anti-Felkin) : R^1 = TBS, Bn; R^2 = Me, Ph

In conclusion, we have disclosed a high-yielding and highly efficient stereoselective synthesis of enantiopure *anti,anti* and *syn,anti* acetylenic 2-amino-1,3-diol stereotriads from α-alkoxy-*t*BS-imines bearing a stereocenter α to the imino group. The stereoselectivity was found to be controlled only by the configuration of the *tert*-butanesulfinyl group and an excellent kinetic resolution of racemic allenylzinc (±)-**1** was observed, no matter what the configuration or the protecting group of the α-alkoxy substituent. These acetylenic stereotriads should be highly versatile stereodefined building blocks for the total synthesis of indolizidine or quinolizidine alkaloids. Further studies in this area from our laboratory will be reported in due course.

Acknowledgment. Thanks are due to Patrick Herson for single-crystal X-ray analysis and to the CNRS for a post-doctoral fellowship grant (to A.V.).

Supporting Information Available: Preparation and characterization data for imines **3e** and **3f** and acetylenic aminoethers **4a**−**f** and chemical correlations into known compounds **5a**−**c** and 2-oxazolidin-3-ones **6a**−**e**, including ^{1}H and ^{13}C data. This material is available free of charge via the Internet at http://pubs.acs.org.

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