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Stereocontrolled Route to Vicinal Diamines by [3.3] Sigmatropic Rearrangement of Allyl Cyanate: Asymmetric Synthesis of *anti*-(2*R*,3*R*)- and *syn*-(2*R*,3*S*)-2,3-Diaminobutanoic Acids

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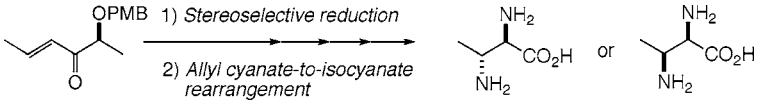
ABSTRACT



A stereocontrolled route via allyl 1,2-diols to vicinal diamines based on the [3.3] sigmatropic rearrangement of allyl cyanate has been developed. Our approach consists of two consecutive steps: stereoselective construction of allyl *anti*- and *syn*-1,2-diols followed by [1,3]-chirality transfer by sigmatropic rearrangement, which allow an access to *anti*-(2*R*,3*R*)- and *syn*-(2*R*,3*S*)-2,3-diaminobutanoic acids.

Over the course of the past decades, chiral 1,2-diamines have become an increasing targeted functional motif in organic synthesis owing to their ubiquity in natural products and medicinal agents.[1] For example, it is found in biotin, penicillins, α,β-diamino acids, and antiinfluenza neuraminidase inhibitor Tamiflu. Moreover, chiral vicinal diamines and their metal complexes have been employed in stereoselective organic synthesis, in particular, as chiral auxiliaries and ligands in catalytic asymmetric synthesis. Although a number of strategies for the synthesis of vicinal diamines have been developed, there are few synthetic methods that allow one to obtain 1,2-diamino building blocks with all possible absolute and relative stereochemical arrangements.

Among many reports for the synthesis of vicinal diamines, there are two representative approaches based upon the sigmatropic rearrangement. Weinreb reported stereocontrolled synthesis of unsaturated vicinal diamines from Diels−Alder adducts of sulfur dioxide diimides and 1,3-dienes.[2] In this case, [2.3] sigmatropic rearrangement of allyl sulfinimines to allyl sulfenamides followed by desulfurization with trimethylphosphite afforded the *syn*- and *anti*-diamine derivatives. Ernst and Bellus reported a strategy based on the [3.3] sigmatropic rearrangement of allyl trichloroacetimidate derived from α-amino acids, which underwent palladium-catalyzed aza-Claisen rearrangement to afford *anti* vicinal diamines with good diastereoselectivity.[3]

Recent reports from our group have presented a stereoselective synthesis of allyl amines based upon allyl cyanate-

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(1) For a review on the synthesis of vicinal diamines, see: (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1988**, *37*, 2580−2627. For recent examples on the synthesis of vicinal diamines, see: (b) Ooi, T.; Kameda, M.; Fuji, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397−2399. (c) Rondot, C.; Zhu, J. *Org. Lett.* **2005**, *7*, 1641−1644.

(2) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7867−7872.

(3) Gonda, J.; Helland, A.-C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729−733.

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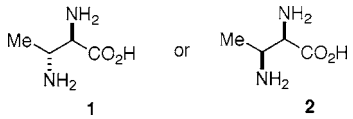
to-isocyanate rearrangement.[4] We envisioned that an extension of this sigmatropic reaction to the synthesis of allyl vicinal diamines would control two stereogenic centers attached to nitrogens. To realize this plan, we set up the synthesis of α,β-diaminobutanoic acids (α,β-Dabs) **1** and **2**.

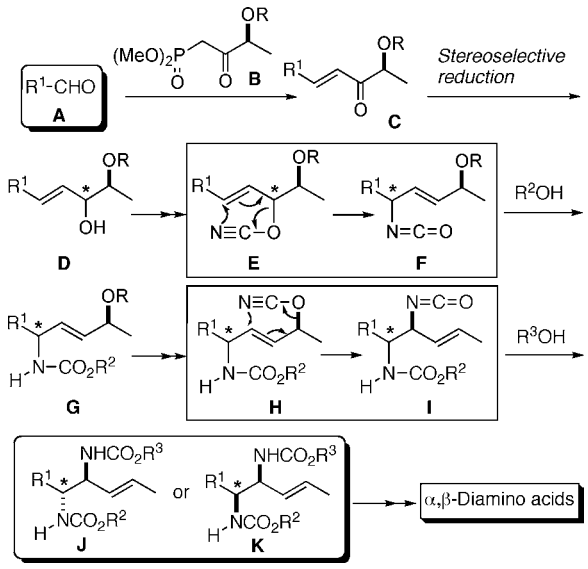


1 **2**

The α,β-diamino acid family constitutes a key structural element found in a variety of antibiotics, antifungal peptides, and other biologically active compounds.[5] In particular, α,β-Dabs have attracted numerous synthetic efforts because they are the simplest member of the α,β-diamino acid family yet form key elements in both peptide antibiotics and toxins.[6] In this communication, we show our approach to the synthesis of allyl vicinal amines based upon allyl cyanate-to-isocyanate rearrangement, which allowed the stereoselective synthesis of these α,β-Dabs.

Our strategy starts with aldehyde **A**, as outlined in Scheme 1. Horner−Emmons reaction of chiral phosphonate **B** with

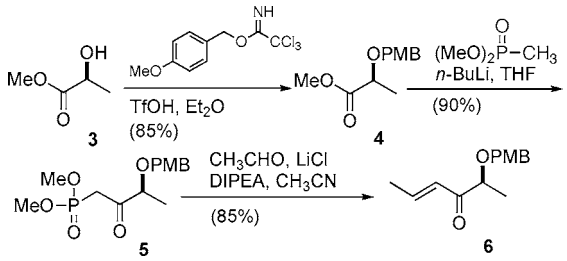
Scheme 1. Strategy for the Synthesis of Allyl Vicinal Amines



A would afford enone **C**, a common intermediate, which would give access to both allyl *anti* and *syn* vicinal diamines. Allyl *anti*- and *syn*-1,2-diols **D** were envisioned to derive from stereoselective reduction of enone **C**. [3.3] Sigmatropic rearrangement of allyl cyanates **E** and **H** would furnish the allyl *anti* and *syn* vicinal diamine derivatives **J** and **K**. In these transformations (**E**→**F** and **H**→**I**), we would take advantage of the concerted nature of sigmatropic rearrangement to achieve a high level of [1,3]-chirality transfer of two stereogenic centers attached to oxygens during the C−O to C−N bond reorganization.[7] Finally, oxidative cleavage of alkene moieties in **J** and **K** would furnish the α,β-diamino acids. One merit of this strategy is that a variety of α,β-diamino acids could be synthesized by simply choosing an appropriate aldehdyde **A**.

A common intermediate for the synthesis of α,β-Dabs was an α,β-unsaturated ketone **6**, which was readily obtained by the condensation of chiral phosphonate **5** with acetaldehyde (Scheme 2). Protection of the hydroxy group in L-lactic acid

Scheme 2. Synthesis of a Common Intermediate **6**



methyl ester (**3**) with *p*-methoxybenzyl (PMB) trichloroacetimidate in the presence of trifluoromethanesulfonic acid gave the PMB ether **4** in 85% yield.[8] Condensation of **4** with lithium methyldimethyl phosphonate in THF furnished the chiral phosphonate **5**, which was then subjected with acetaldehyde under Masamune−Roush conditions (LiCl, *i*-Pr_2NEt, CH_3CN)[9] to furnish the α,β-unsaturated ketone **6** predominantly in 77% yield over two steps.

Stereocontrolled reduction of α-oxygenated enone **6** for the preparation of allyl *anti*- and *syn*-1,2-diols (**7** and **8**) was examined employing several reducing reagents (Table 1). In the case of lithium aluminum hydride (entry A), the modest level of diastereoselection was observed (83:17) to deliver an inseparable mixture of **7** and **8** in a combined yield of 98%.[10] Although L-selectride reduction in toluene (entry B) showed good selectivity (99:1),[11] appreciable amounts (29%) of the competitive conjugate reduction product were formed, resulting in a reduced yield (59%). Chelation-

(4) (a) Ichikawa, Y.; Ito, T.; Nishiyama, T.; Isobe, M. *Synlett* **2003**, 1034−1036. (b) Ichikawa, Y.; Ito, T.; Isobe, M. *Chem.−Eur. J.* **2005**, *11*, 1949−1957.

(5) For a comprehensive summary of literature related to the synthesis of α,β-diamino acids, see: (a) Luo, Y.; Blaskovich, M. A.: Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106−6111. (b) Viso, A.; Fernandez, P.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167−3196. For a recent report on the asymmetric synthesis of α,β-diamino acids, see: (c) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789−2792.

(6) (a) Atherton, E.; Meienhofer, J. *J. Antibiot.* **1972**, *25*, 539−540. (b) Atherton, E.; Meienhofer, J. *Hoppe-Seyler's Z. Physiol. Chem.* **1973**, *354*, 689−696. (c) Schmidt, U.; Mundinger, K.; Riedl, B.; Hass, G.; Lau, R. *Synthesis* **1992**, 1201−1202. (d) Burke, A. J.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1996**, 621−622. (e) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045−2048.

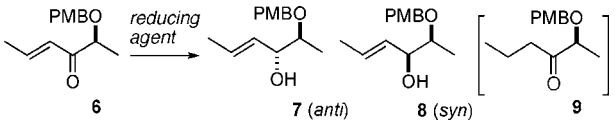
(7) Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791−2796.

(8) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139−4142.

(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(10) 1,2-Asymmetric induction of a similar α-oxygenated enone using LAH was reported by Overman: (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355−2358. See also: (b) Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353−5362.

Table 1. Stereocontrolled Reduction of α-Oxygenated Enone **6**



entry	reducing agent	**7/8**[a]	% yield
A	$LiAlH_4$, Et_2O, −10 °C	83:17	98
B	L-selectride, toluene, −78 °C	99:1	59 (29)[b]
C	$Zn(BH_4)_2$, Et_2O, −10 °C	91:9	99
D	L-selectride, THF, −78 °C	12:88	77 (23)[b]
E	DIBAL, CH_2Cl_2, −78 °C	30:70	60 (35)[b]
F	$NaBH_4$, $CeCl_3$, MeOH, 0 °C	10:90	82

[a] Ratio based on ^1H NMR analysis. [b] Number in parentheses is the yield of **9**.

controlled zinc borohydride reduction (entry C) proved to be our choice for the preparation of allyl *anti*-1,2-diol **7** with a 99% yield and 91:9 selection.[12]

Felkin−Ahn selective reduction of **6** with L-selectride in THF (entry D) resulted in a 77% yield and 12:88 selectivity, accompanied by unwanted conjugate reduction product **9** (23%).[13] DIBAL reduction (entry E) also resulted in undesirable results: modest selectivity (30:70) and more conjugate addition product **9** (35%). To suppress this conjugate reduction problem, Luche reduction was examined (entry F) and proved to be effective, furnishing products with an 82% yield and 10:90 selection.[14]

We initially assigned the stereochemistry of the products **7** and **8** on the basis of chelation-control and Felkin−Ahn models, which was firmly secured by the Mosher−Kusumi MTPA ester analysis as illustrated in Figure 1.[15] Thus,

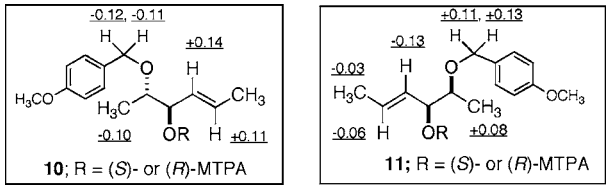
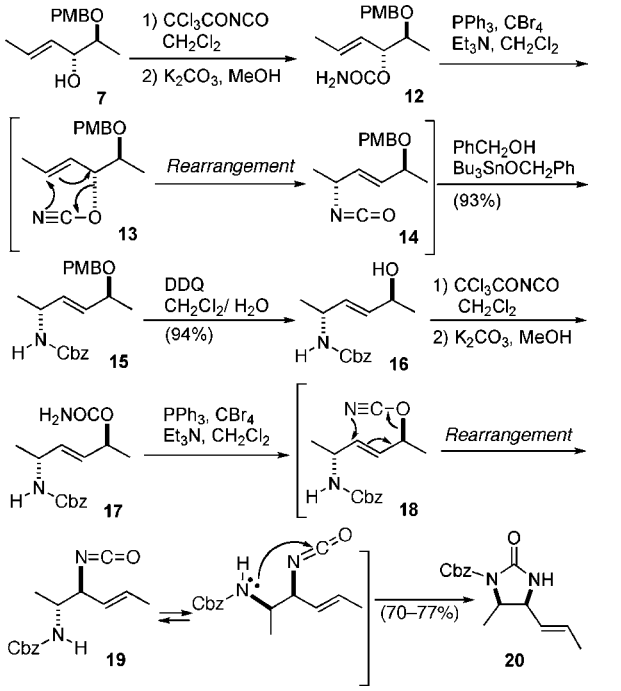


Figure 1. Mosher−Kusumi MTPA ester analysis: $\Delta\delta$ values for the Mosher ester derivatives **10** and **11**.

secondary alcohols **7** and **8** were transformed into the corresponding (*S*)- and (*R*)-MTPA esters **10** and **11**. Stereochemical assignment according to the Mosher−Kusumi analysis was carried out by calculation of the chemical shift differences ($\Delta\delta$ values: $\Delta\delta = \delta_S - \delta_R$), which proved to be identical to those predicted on the basis of the chelation-control and Felkin−Ahn models.

With the preparation of both allyl *anti*- and *syn*-1,2-diols established, we undertook the synthesis of vicinal diamines via sigmatropic rearrangement (Scheme 3). Treatment of **7**

Scheme 3. Construction of Allyl *anti*-1,2-Diamine



with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol provided allyl carbamate **12**. Dehydration of allyl carbamate **12** using modified Appel's conditions (PPh_3, CBr_4, Et_3N)[16] provided allyl cyanate **13**, which underwent facile [3.3] sigmatropic rearrangement to afford allyl isocyanate **14**. To avoid the hydrolysis of **14** during aqueous workup, benzyl alcohol and a substoichiometric amount of tributyltin benzylalkoxide (30 mol %) were added to the reaction mixture. After stirring at room temperature overnight followed by workup and chromatography, the Cbz-carbamate **15** was obtained in 93% overall yield from **12**. It should be noted that the yields of **15** decreased to ca. 60−70% in the absence of tributyltin benzylalkoxide.[17] The next construction of the stereogenic center attached to nitrogen began with oxidative deprotection of the PMB ether in **15** with DDQ in 94% yield.[18] The allyl alcohol **16** was transformed into the carbamate **17**, which

(11) Faucher, A-M.; Brochu, C.; Landry, S. R.; Duchesne, I.; Hantos, S.; Roy, A.; Myles, A.; Legault, C. *Tetrahedron Lett.* **1998**, *39*, 8425−8428.

(12) (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653−2656. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344.

(13) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1976**, 61−70. See also refs 10b and 11.

(14) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

(15) Ohtani, I.; Kusumi, K.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

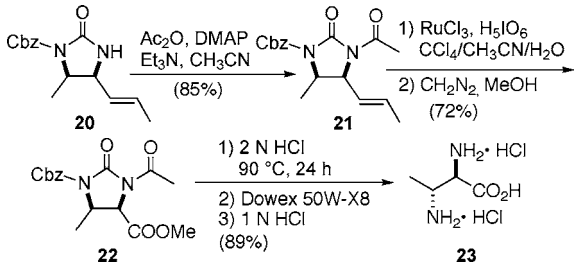
(16) (a) Ichikawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2135−2139. (b) O'Neil, I. A. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A.; Meth-Cohn, O.; Ress, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 3, pp 696.

(17) Addition of tributyltin alkoxide enhanced the efficiency of this in situ trapping isocyanate. See: Ichikawa, Y.; Osada, M.; Ohtani, I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449−1455.

was then dehydrated as before, to afford the rearranged product **19**. To our delight, the resultant isocyanate **19** was efficiently trapped in situ by intramolecular attack of nitrogen in the Cbz group providing imidazolidinone **20** in 70−77% yields.[19] Furthermore, **20** was isolated as crystals, and the minor isomer arising from the reduction step (**6**→**7**) was removed at this stage by recrystallization.

The next task for the synthesis of α,β-Dab is the functional group transformation of the alkene moiety in **20** into the corresponding carboxylic function (Scheme 4). This oxidative

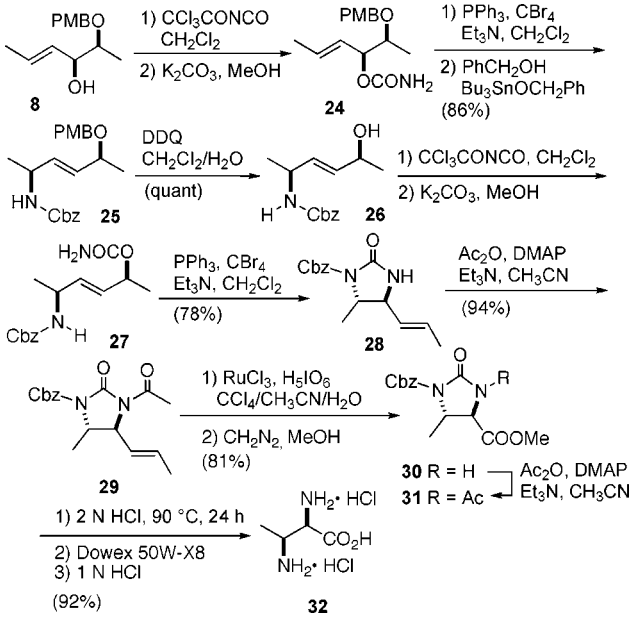
Scheme 4. Synthesis of *anti*-(2*R*,3*R*)-Dab Hydrochloride



cleavage was found to be more difficult than initially expected: attempts using several oxidizing reagents (OsO_4/$NaIO_4$, O_3, $RuCl_3$/$NaIO_4$) proved futile. We finally found that protection of the NH in imidazolidinone **20** had a dramatic effect on this oxidative transformation. Thus, acetylation of **20** (Ac_2O, DMAP, CH_3CN) followed by ruthenium-catalyzed oxidation of **21** under Sharpless conditions ($RuCl_3$, H_5IO_6, $CCl_4/H_2O/CH_3CN$)[20] resulted in the smooth cleavage of the double bond. Esterification of the resultant carboxylic acid by treatment with diazomethane then led to the methyl ester **22** in 72% isolated yield over two steps. Removal of the Cbz and acetyl groups and hydrolytic cleavage of the imidazolidinone ring in **22** were carried out by acid-catalyzed hydrolysis (2 N HCl, 90 °C, 24 h) to afford the (2*R*,3*R*)-Dab hydrochloride **23**.

The synthesis of (2*R*,3*S*)-Dab **2** starting from allyl *syn*-1,2-diol **8** was then explored (Scheme 5). The [1,3]-chirality transfer of two stereogenic centers attached to oxygen in **8** was accomplished (**8**→**25** and **26**→**28**) using reaction condi-

Scheme 5. Synthesis of *syn*-(2*R*,3*S*)-Dab Hydrochloride



tions similar to those employed in Scheme 3, and the imidazolidinone **28** was obtained with comparable efficiency (67% overall yield from **8** to **28**). After acetylation of NH in **28**, the resultant **29** was subjected to the ruthenium-catalyzed oxidative transformation into the corresponding carboxylic acid. Although esterification with diazomethane generated **31** along with **30**, separation of **30** followed by acetylation (Ac_2O, DMAP, Et_3N, CH_3CN) then furnished **31**; a total yield of 81% for the methyl ester **31** was obtained. As before, hydrolysis of **31** with 2 N HCl followed by ion-exchange chromatography then completed the synthesis of (2*R*,3*S*)-Dab hydrochloride **32**.

We have proposed a new route for the stereocontrolled construction of allyl 1,2-diamines, which was realized in the synthesis of *anti*-(2*R*,3*R*)- and *syn*-(2*R*,3*S*)-Dabs, **1** and **2**, starting from L-lactic acid methyl ester (**3**). Because enantiomeric D-lactic acid derivatives are commercially available, the present method described here also constitutes a formal synthesis of the enantiomers of both **1** and **2**. Further progress toward the synthesis of other α,β-diamino acids by choosing appropriate aldehydes is now underway in our laboratory.

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Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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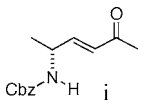
(18) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888. It should be noted that because the prolonged reaction time of this oxidative deprotection resulted in the formation of enone **i**, it was necessary to perform a workup immediately after checking the consumption of starting material by TLC analysis.



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(19) (a) Dunn, P. J.; Haner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017−5025. (b) Englund, E. A.; Gopi, H. N.; Appella, D. H. *Org. Lett.* **2004**, *6*, 213−215.

(20) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560−1563. (c) Nuñez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928−1932.