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Sterically Biased 3,3-Sigmatropic Rearrangement of Azides: Efficient Preparation of Nonracemic α-Amino Acids and Heterocycles

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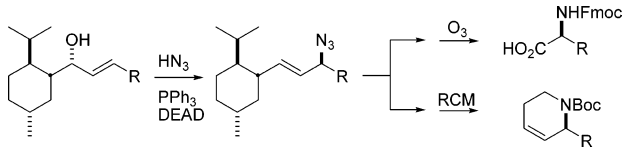
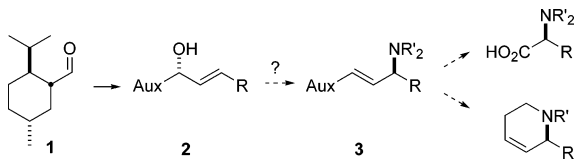
ABSTRACT



Homochiral α-amino acids, heterocycles, and carbocycles are efficiently constructed via a short sequence of reactions starting from the chiral auxiliary *p*-menthane-3-carboxaldehyde. The key feature of the sequence is a highly selective tandem Mitsunobu/3,3-sigmatropic rearrangement of hydrazoic acid that procures enantiomerically enriched allylic azides. The sequence is either terminated by oxidative cleavage to provide amino acids or by ring-closing metathesis to provide heterocycles or carbocycles bearing nitrogen.

p-Menthane-3-carboxaldehyde **1** is a useful chiral auxiliary used for the construction of chiral α-alkylated carbonyl compounds,[1] including quaternary carbons.[2] Effecting stereoselective C−N bond formation from allylic alcohol **2** with complete transposition of the double bond would usefully expand our methodology to make nitrogen-containing products (Scheme 1).[3]

Scheme 1. Intended C−N bond formation from **1**



Cleavage of the auxiliary on this system is usually done by ozonolysis such that alcohol, aldehyde, or acid products are obtained. We surmised that the transposed double bond in **3** should be amenable to a ring-closing metathesis (RCM) reaction such that carbo- or heterocycles could be formed concomitantly (Scheme 1).

With regard to the C−N bond formation, allylic azides are known to rearrange at temperatures ranging from below 0 to 100 °C.[4] However, Trost and Pulley pointed out that

(1) For a review on chiral enolate alkylation equivalents, see: Spino, C. *Org. Proc. Prepr. Int.* **2003**, *35*, 1−133.

(2) (a) Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1930−1932. (b) Spino, C.; Godbout, C.; Beaulieu, C.; Harter, M.; Mwene-Mbeja, T. M.; Boisvert, L. *J. Am. Chem. Soc.* **2004**, *126*, 13312−13319. (c) Spino, C.; Godbout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106−12107.

(3) For selected examples of C−N bond formation from allylic alcohols, including those with double bond transposition, see: (a) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. Imidate rearrangement: (b) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (c) Jiang, Y.; Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 1449−1450. (d) Kang, J.; Yew, K. H.; Kim, T. H.; Choi, D. H. *Tetrahedron Lett.* **2002**, *43*, 9509−9512. (e) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291−3303. (f) Metz, P.; Mues, C.; Schoop, A. *Tetrahedron* **1992**, *48*, 1071−1080. (g) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218−224. (h) Eguchi, T.; Koudate, T.; Kakinuma, K. *Tetrahedron* **1993**, *49*, 4527−4540. (i) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225−12231. Phosphorimidate rearrangement: (j) Chen, B.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 6712−6718. (k) Lee, E. E.; Batey, R. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1865−1868. Pd-catalyzed nucleophilic displacement: (l) Godleski, S. A. In Comprehensive Organic Synthesis, 1st ed.; Semmelhack, M. F., Ed.; Pergamon Press: New York, 1991; Vol. 4, p 585. (m) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173−1192. (n) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

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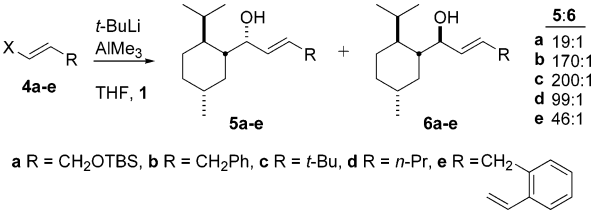
the reaction has not been used very often because its synthetic utility depends on the ability to control the thermodynamic ratio of the two regioisomeric azides.[5] This is infrequently observed as it is normally substrate-dependent. Herein, we report the successful execution of this transposition via a Mitsunobu reaction of **2** with hydrazoic acid followed by a sterically biased 3,3-sigmatropic rearrangement of the resulting allylic azide with extraordinarily good thermodynamic selectivity. Amino acids[6,7] or *N*-heterocycles[8] are obtained depending on the method of cleavage of the chiral auxiliary.

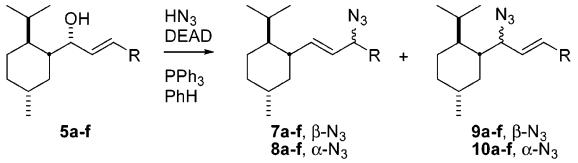
Metal−halogen exchange reaction of vinyl iodides **4a**−**d** or vinyl bromide **4e** furnished the corresponding vinyllithiums. Each was added separately and stereoselectively to **1** in the presence of $AlMe_3$[9] to give **5a**−**e** in 54−67% yields and excellent isomeric ratios (Scheme 2). In all cases, the diastereomeric alcohols were separable by silica gel column chromatography.

Scheme 2. $AlMe_3$-Promoted Vinyllithium Addition to **1**



Mitsunobu[10] reaction of allylic alcohols **5a**−**e** with hydrazoic acid gave exclusively azides **7a**−**e** and no detectable amount of S_N2 product **9a**−**e** (Table 1). The stereoselectivity (**7**/**8**) of the reaction varied from very good (92:8) to excellent (98:2).

Table 1. Selectivities in the Mitsunobu/Azide Rearrangement of **5**



entry	R	prod	yield (%)[a]	**7** : **8**[b]	(**7**+**8**) : (**9**+**10**)[c]
1	CH_2OTBS	**a**	76	>98 : 2	>98 : 2
2	CH_2Ph	**b**	80	97 : 3	>98 : 2
3	*t*-Bu	**c**	78	94 : 6	>98 : 2
4	*n*-Pr	**d**	80	92 : 8	>98 : 2
5		**e**	81	97 : 3	>98 : 2
6	Ph	**f**	78	---	6 : 94

[a] Isolated yield. [b] Measured by HPLC against authentic mixtures of **7** and **8**. [c] Measured by ^1H NMR.

It is unusual for the Mitsunobu reaction of allylic alcohols to give S_N2'-displacement products. There are known cases of S_N2' regioselectivity in that reaction, but in most of these cases the alkene is electronically biased.[11] Mulzer and coworkers have performed Mitsunobu reactions of several chiral allylic alcohols with phthalimide and reported that regioselectivities depended on the substitution pattern of the alkene (electronic and steric biases).[12]

Azides **7** are thus more likely formed via a normal S_N2-selective Mitsunobu reaction followed by a 3,3-sigmatropic rearrangement of the resulting allylic azides. The rearrangement, we believe, is under thermodynamic control, and the steric bulk of the menthyl moiety destabilizes regioisomers **9** (or **10**). Also, the stereochemical integrity of the initially formed azides **9** is preserved during the concerted rearrangement.[13] We believe that the minor isomer **10** arises from some S_N2' displacement by the azide. Preliminary evidence for this mechanistic rational comes from the Mitsunobu reactions of **5f** (R = Ph, entry 6), which gave predominantly **9f**, presumably because of its increased stability due to conjugation of the double bond with the phenyl ring.[14] In this case, the reaction was much less selective giving a 3:1 ratio of **9f**/**10f**. More importantly, when the diastereomeric alcohol **6f** was submitted to the Mitsunobu conditions, the ratio of **9f**/**10f** was now reversed (1:3). The rearrangement being concerted, this lower diastereoselectivity cannot be explained by an S_N2 displacement followed by rearrangement. The identical but reversed ratios observed from **5f** and **6f** rules out an S_N1 mechanism to explain the lower

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(12) Mulzer, J.; Funk, G. *Synthesis* **1995**, 101−112.

(13) Evidence for a concerted mechanism for azide rearrangement was provided by Padwa and co-workers. See: Padwa, A.; Sà, M. M. *Tetrahedron Lett.* **1997**, *38*, 5087−5090.

(14) Further discussion on the mechanism will be presented in the full account of this work.

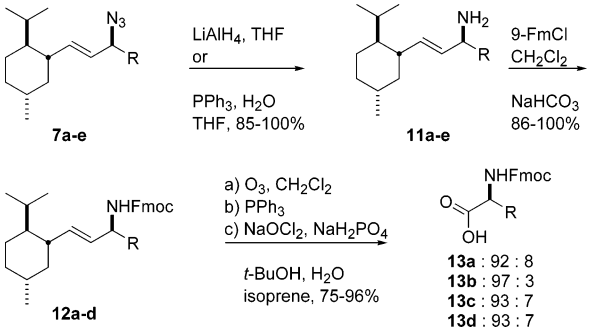
diastereoselectivity. Moreover, according to the work of Mulzer, a Mitsunobu reaction on **5f** without the possibility of rearrangement should have given predominantly the S_N2' displacement product **7f** because of the aromatic ring.[12] Therefore, we propose that an increased amount of S_N2' displacement occurs in the case of **5f** and **6f** because of the phenyl ring. The S_N2' is less selective and gives a lower ratio of **7f** and **8f**, which then rearrange to **9f** and **10f**, respectively, with preservation of their stereochemical integrity. This explains why **5f** leads to a 3:1 ratio of **9f**/**10f** while **6f** affords a 1:3 ratio of those same compounds.

The azides **7a**−**e** were then reduced to the corresponding amines **11a**−**e** with lithium aluminum hydride or using Staudinger's reaction (Scheme 3). Protection as a 9-fluorenylmethyl (9-Fm) carbamate proceeded in excellent yield to give **12a**−**d**. Oxidative cleavage of the auxiliary in **12a**,**b**,**d** afforded the amino acids **13a**,**b**,**d** in good to excellent yields. In the case of N-protected *tert*-leucine **13c**, we isolated the sensitive α-amino aldehyde and then oxidized it with Jones' reagent without racemization. This is significant because α-amino aldehydes are difficult to obtain in the nonracemic form. They are used as starting material for the synthesis of complex amino alcohols.[15] Enantiomeric ratios (HPLC) were consistent with the % dr obtained for azides **7b**−**d, 13a** having suffered a slight loss of enantiomeric purity. The sign of optical rotation of amino acids **13a**−**d** confirmed their absolute stereochemistries and thus our stereochemical assignments of **7a**−**d**.

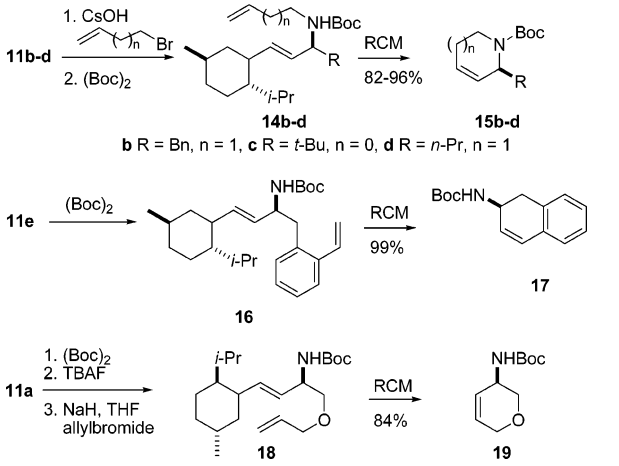
Alternatively, amines **11b**−**d** were monoalkylated with 4-bromo-1-butene or allyl bromide (Scheme 4).[16] Ring-closing metathesis (RCM) cleavage of the chiral auxiliary was performed using the Grubbs or the Grubbs−Nolan catalyst in refluxing dichloromethane (dichloroethane for **18**).[17] Gratifyingly, these RCM were highly efficient and gave pyrrolidine (**15c**), piperidines (**15a**, **15d**), or carbo- and heterocycles bearing an exocyclic nitrogen (**17**, and **19**). Compound **15d** was hydrogenated to give (+)-*N*-Boc-coniine.[18]

In summary, we have developed a short and highly selective synthesis of α-amino acids and heterocycles. The excellent regioselectivity of the azide rearrangement and the efficient cleavage of the chiral auxiliary by RCM is of note. We are currently applying the methodology to the synthesis of more complex alkaloid natural products.

Scheme 3. Synthesis of α-Amino Acids **13a**−**d**



Scheme 4. Synthesis of Heterocycles and Carbocycles



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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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