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ASYMMETRIC SYNTHESIS OF L-AZETIDINE-2-CARBOXYLIC ACID AND 3-SUBSTITUTED CONGENERS – CONFORMATIONALLY CONSTRAINED ANALOGS OF PHENYLALANINE, NAPHTHYLALANINE, AND LEUCINE

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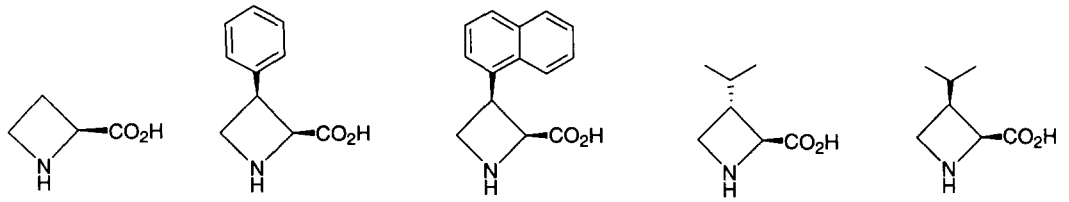
Abstract: Enantiopure L-azetidine-2-carboxylic acid, the (3*R*)-phenyl, (3*R*)-naphthyl and (3*S*)-isopropyl analogs were prepared based on a zinc-mediated asymmetric addition of allylic halides to the camphor sultam derivative of glyoxylic acid O-benzyl oxime.

L-Azetidine-2-carboxylic acid (L-Aze, **1**) (Figure 1) was first isolated by Fowden[1] from Convallaria majalis (lily-of-the-valley), and it represents the earliest known example of a naturally occurring azetidine. It is reported to inhibit the proliferation of E. coli,[2] and when fed to different plant species it exhibited marked inhibition of growth, becoming lethal at high concentration.

As the lower homologue of L-proline, L-Aze is believed to be an antagonist of the more ubiquitous natural amino acid.[3] It has also been useful in the study of the secondary structure of unnatural polypeptides such as poly-L-Aze.[4] Pharmacologically important compounds such as the thrombin inhibitor melagatran[5] and the analgesic ABT-594[6] incorporate L-Aze and the azetidine motif respectively in their structures. Natural products such as mugineic acid,[7] nicotianamine,[8] and the polyoxins,[9] contain L-Aze or a substituted analog as a constituent. Analogs of L-Azė with side-chains have been used as rigidified congeners of glutamic acid.[10]

Figure 1



1 **2** **3** **4** **5**

Applications in the area of asymmetric synthesis include the utilization of derivatives of L-Aze as chiral catalysts and auxiliaries in cyclopropanations,[11] Diels–Alder reactions,[12] in enantioselective reductions of ketones,[13] and in Michael additions.[14]

The first practical synthesis of racemic Aze was achieved from 2,4-dibromobutyric acid by Rodebaugh and Cromwell in 1969,[15] who subsequently developed a method of resolution. An enzymatic resolution method applicable to N-alkyl L-Aze was recently reported.[16] Miyoshi and cowokers[17] reported a synthesis of

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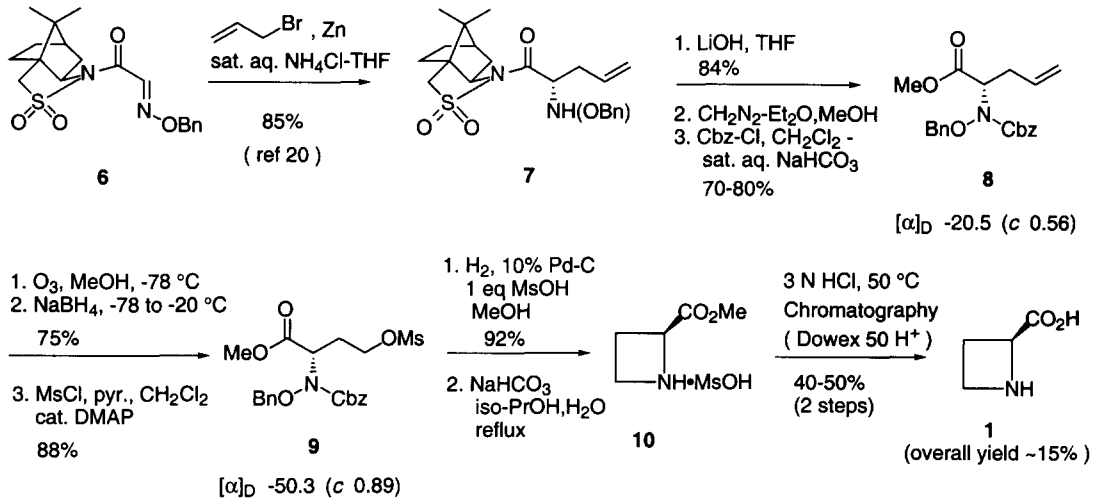
L-Aze starting with N-tosyl-L-homoserine lactone. Other syntheses of racemic L-aze[18] and of 3-substituted analogs have been disclosed.[19]

We wish to report an enantioselective synthesis of L-Aze adopting a method that is also applicable to the synthesis of selected 2,3-substituted derivatives such as **2–4**, their isomers, or their immediate precursors (Figure 1). Treatment of the Oppolzer sultam derivative of glyoxylic acid O-benzyl oxime **6** with allyl bromide and zinc dust in sat. aqueous ammonium chloride and THF led to an enantioenriched allyl glycine, derivative **7**[20] in excellent yield (Scheme 1). Hydrolysis of the chiral auxiliary afforded N-benzyloxy L-allyl glycine which was subsequently converted to the N-Cbz, N-benzyloxy methyl ester derivative **8** in excellent overall yield. Ozonolysis followed by reduction of the resulting aldehyde with sodium borohydride and mesylation, gave the mesylate derivative **9**. Hydrogenolysis gave the amine mesylate salt, which when refluxed in aq. 2-propanol in the presence of excess sodium bicarbonate gave L-Aze methyl ester **10** as the mesylate salt. Hydrolysis with 3 N HCl and purification on Dowex-50H$^+$ gave crystalline L-Aze **1** in ~15% overall yield, mp ~185 to >220 °C (dec); $[\alpha]_D$ -123.3 (c 3.6, H_2O); reported (Aldrich) mp 217 (dec); $[\alpha]_D$ –120 (c 3.6, H_2O); (Merck Index) mp discolors at 200 °C to >300 °C; $[\alpha]_D$ –108 (c 3.6, H_2O).

Scheme 1[a]

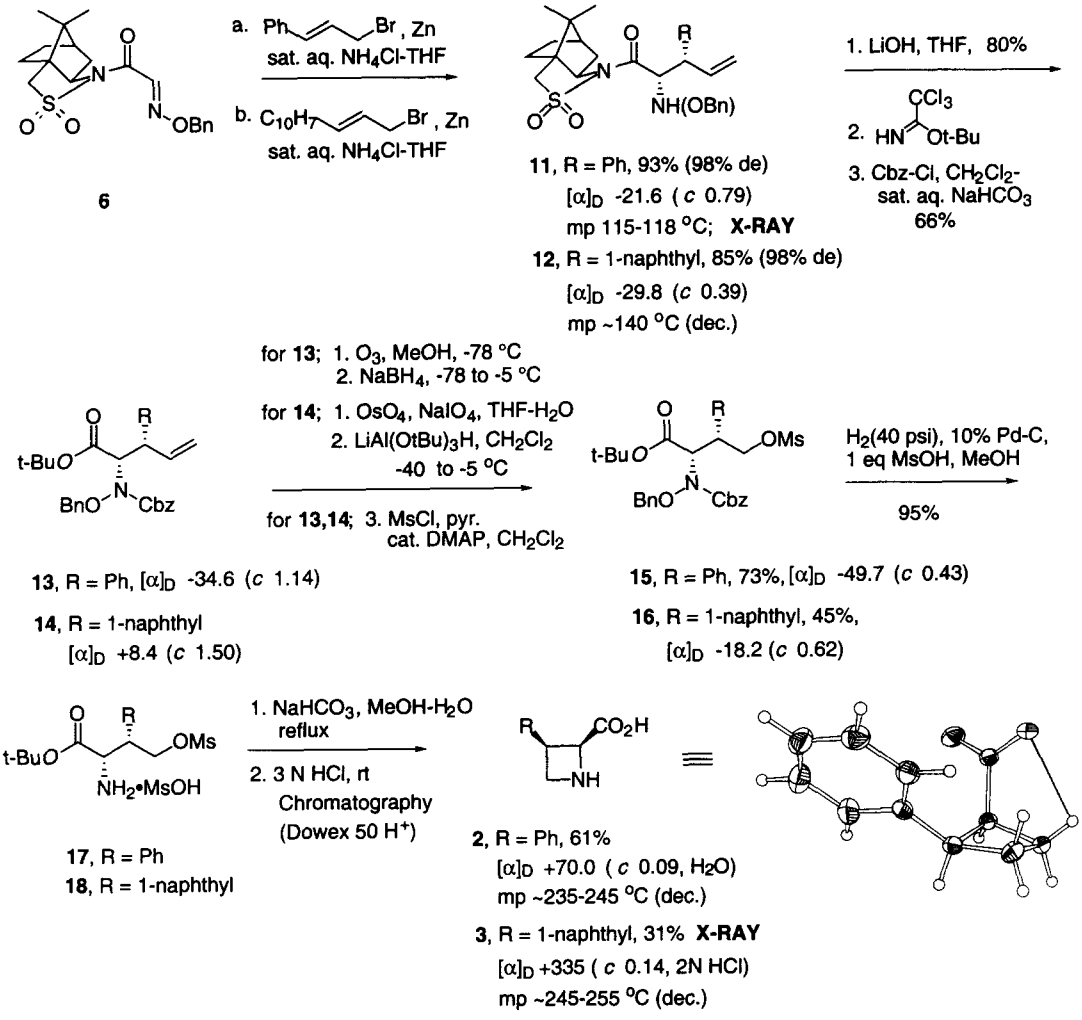


a. optical rotations recorded in CH_2Cl_2 at 25 °C

Application of the same protocol to cinnamyl bromide and 3-(1-naphthyl)allyl bromide proceeded uneventfully except for a minor modification in the nature of the ester (Scheme 2). Thus, treatment of the sultam **6** with the appropriate halide in the presence of zinc dust gave the *syn*-substituted analogs **11** and **12**, respectively, essentially as single diastereomers. In this series it was necessary to continue the syntheses with the *t*-butyl esters **13** and **14** as shown in Scheme 2 in order to avoid lactone formation. Oxidative cleavage, reduction and mesylation led to precursors **15** and **16**, respectively. Finally, hydrogenolysis and cyclization through the intermediacy of the amine mesylates **17** and **18** afforded (2*S*,3*R*)-3-phenyl azetidine-2-carboxylic acid **2** and the corresponding 1-naphthyl analog **3**, respectively, as enantiopure crystalline compounds. The absolute configuration of **2** was ascertained by single crystal X-ray analysis. It is of interest that racemic **2** and

its *trans*-isomer have been proposed as conformationally restricted analogs of phenylalanine,[21] and prepared as a 1:1 mixture of isomers via an intramolecular enolate alkylation reaction.

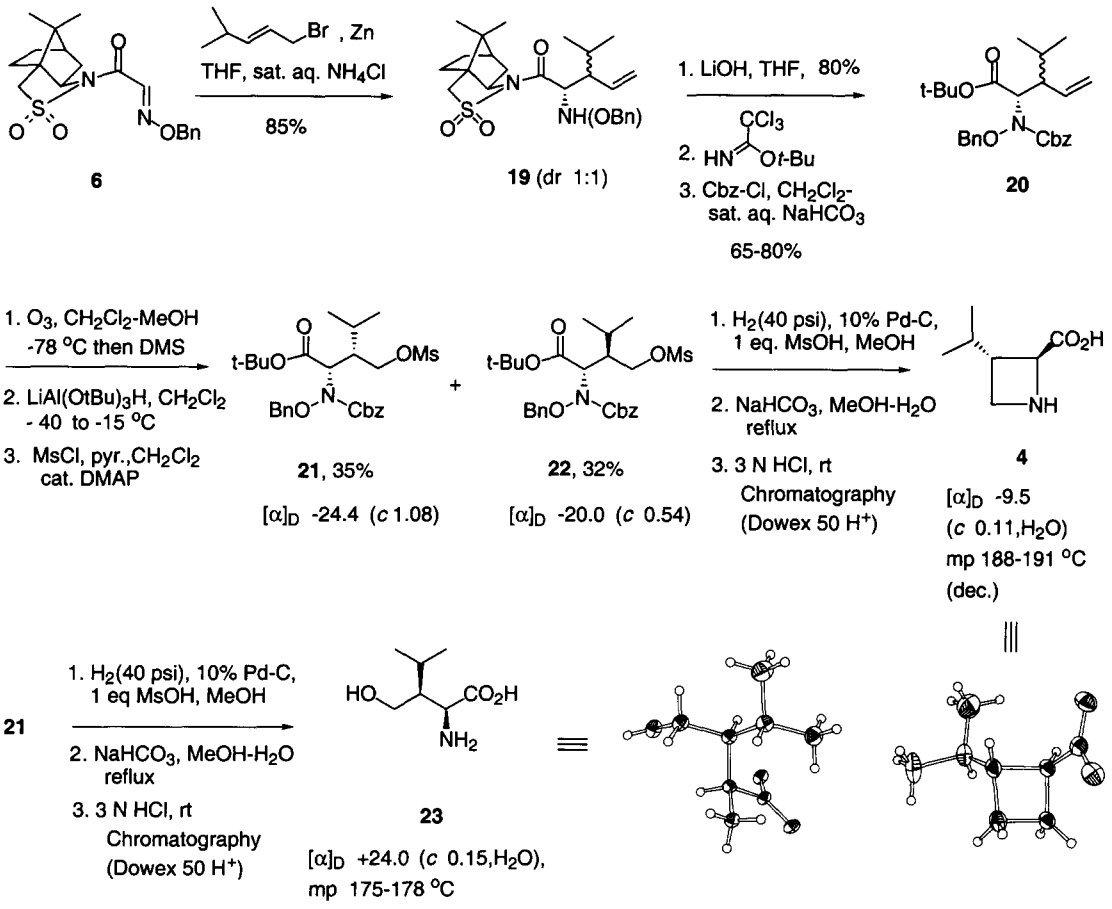
Scheme 2[a]



a. optical rotations recorded in CH_2Cl_2 at 25 °C

We also investigated the synthesis of the (2*S*,3*R*)-3-isopropyl-azetidine-2-carboxylic acid **5** (Figure 1) as another representative analog having a hydrophobic group at C-3. Surprisingly, the allylation reaction led to a 1:1 mixture of diastereoisomers **19** (Scheme 3) which was processed in the same manner as for the related isomers. Fortunately, the two diastereomers could be separated after oxidative cleavage, reduction and mesylation. Hydrogenolysis followed by cyclization and hydrolysis of the (2*S*,3*R*)-isomer **22** afforded the corresponding L-Aze derivative **4**. Unexpectedly however, application of the same protocol to the (2*S*,3*S*)-isomer **21**, resulted in the solvolysis of the mesylate, and the formation of **23** rather than cyclization to the desired azetidine **5** (Figure 1). The structure of **23** was ascertained from a single crystal X-ray analysis.

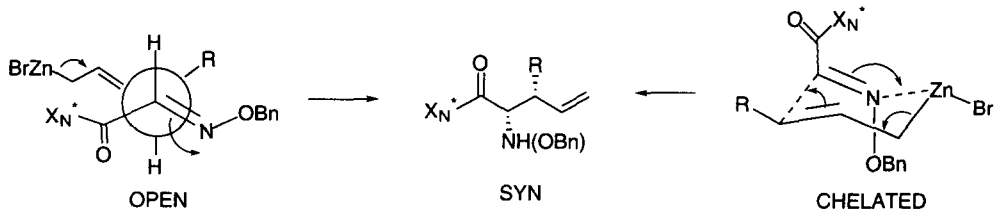
Scheme 3[a]



a. optical rotations recorded in CH_2Cl_2 at 25 °C

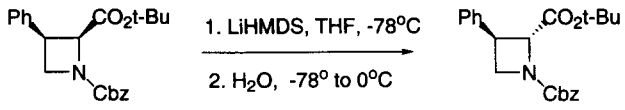
The quasi exclusive *syn*-orientation of substituents resulting from the allylation reactions shown in Scheme 2 can be rationalized based on a chelated[20,22] or an open transition state (Figure 2). The lack of selectivity in the 3-isopropyl series cannot be rationalized based on their transition state models, unless we consider equal contributions from other chelated structures.

Figure 2



In an effort to create stereochemical diversity, we were able to partially epimerize the *syn*-oriented ester **25** to the *anti*-isomer **26** in 54% isolated yield with recovery of unreacted ester (25-30%).

Scheme 4



25 54% **26**

$[\alpha]_D$ -14.5 (*c* 0.53, $CHCl_3$)

In conclusion, we have devised syntheses of enantiopure L-Aze and its (2*S*,3*R*)-phenyl and (2*S*,3*R*)-1-naphthyl analogs based on a zinc-mediated asymmetric allylation reaction in aqueous solution.[20,23] Access to the (2*S*,3*S*)-3-isopropyl analog is possible, although the overall yield is modest. Formation of an azetidine ring by intramolecular displacement of a mesylate in the presence of aq. $NaHCO_3$, rather than other bases in aprotic solvents (ex. NaH, THF)[24] is noteworthy.

These cyclic amino acid derivatives are of interest as novel scaffolds in peptidomimetic design,[25] as constrained analogs of natural amino acids,[26] and as catalysts in asymmetric processes.[27,28]

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28. Melting points are uncorrected. All new compounds were adequately characterized by spectroscopic and other analytical data.