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A Novel Synthetic Route to Chiral γ-Lactams from α-Amino Acids via Rh-Catalyzed Intramolecular C−H Insertion

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Abstract: Highly functionalized γ-lactams are key intermediates for the synthesis of numerous biologically significant natural products. We herein described the synthesis of various chiral γ-lactams via intramolecular C−H insertion of α-diazo-α-(phenylsulfonyl)acetamides derived from α-amino acids, which possess various functional groups. The cyclizations were highly regio- and stereoselective to afford chiral γ-lactam motifs in high yields.

The pyrrolidinone (γ-lactam) functionality is a prevalent theme in various natural product syntheses, and serves as a crucial intermediate for numerous natural products. For example, lactacystin (**1**)[1] and pramanicin (**2**)[2] possess highly functionalized γ-lactam cores (Figure 1). Although a vast number of synthetic methods have been reported to date, syntheses of chiral γ-lactams seem to be limited and inefficient, resulting in lengthy and costly synthetic sequences.[3,4]

Recently, we developed intramolecular C−H insertion of α-diazo-α-(phenylsulfonyl)acetamides to afford γ-lactams with high regio- and stereoselectivities.[5] Regarding chiral pyrrolidinones, we considered α-amino acids versatile chiral starting materials, which possess a variety of functional groups and are commercially available, usually in both enantiomeric forms. To our surprise, an extensive literature search revealed that various α-diazo amides derived from α-amino acids were poor substrates for ring closures through C−H insertions, due to competing side reactions and poor regio- and stereoselectivities.[6]

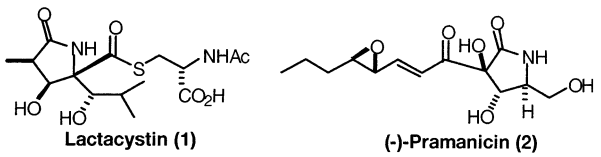
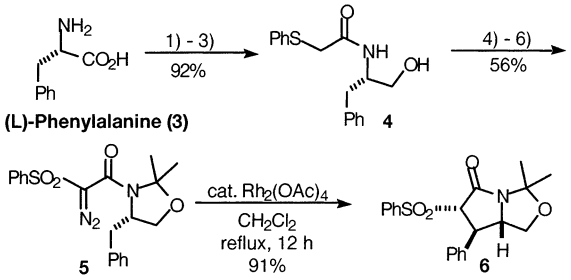


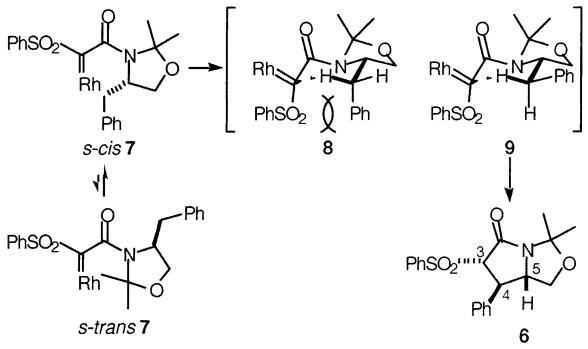
FIGURE 1. The structures of lactacystin and (−)-pramanicin.

SCHEME 1



[a] Key: (1) HCl (g), MeOH; (2) $PhSCH_2CO_2H$, DIC, imidazole, DMF, rt; (3) $NaBH_4$, LiCl, THF-MeOH (1:1); (4) $Me_2C(OMe)_2$, cat. *p*-TsOH, benzene, reflux; (5) *m*-CPBA, CH_2Cl_2; (6) *p*-ABSA, DBU, CH_3CN.

SCHEME 2



We herein describe an efficient synthesis of chiral γ-lactams with α-diazo-α-(phenylsulfonyl)acetamides derived from α-amino acids using our developed methodology.

As shown in Scheme 1, cyclization precursor **5** was prepared from (L)-phenylalanine (**3**) in 6 steps, and then subjected to Rh(II)-catalyzed C−H insertion cyclization.[7] Remarkably, the diazo compound **5** was smoothly converted to the desired trans γ-lactam **6** as a single isomer in 91% yield without the formation of β-lactam or aromatic cycloaddition products.[8]

The observed stereochemical outcomes are rationalized in Scheme 2. During the insertion reaction, the conformationally restricted metallocarbenoid **7** adopts the *s-cis* conformer due to the severe nonbonded interaction between the *gem*-dimethyl group and the carbonyl sub-

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(2) Barrett, A. G.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005 and references therein.

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(5) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539.

(6) (a) Zaragoza, F.; Zahn, G. *J. Prakt. Chem.* **1995**, 292. (b) Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371.

(7) General procedure for C−H insertion reactions: $Rh_2(OAc)_4$ (11 mg, 2.5 mol %) was added to a solution of an α-diazo-α-(phenylsulfonyl)-acetamide (1 mmol) in dry CH_2Cl_2 (20 mL, C = 0.05 M). The mixture was refluxed for 12 h under N_2, cooled to rt, and concentrated. The residue was chromatographed to give a γ-lactam.

(8) Padwa, A. P.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.

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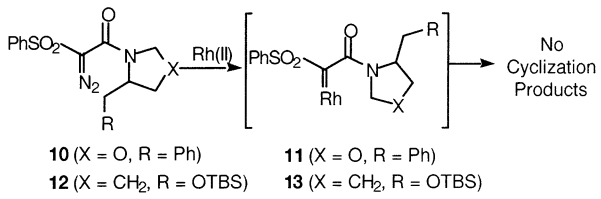
SCHEME 3



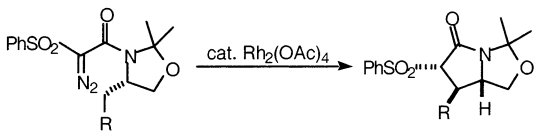
stituents present in the *s-trans* conformer.[9] Only the *s-cis* conformer **7** is suitable for cyclization. This explanation is based on the following observation. In the absence of the *gem*-dimethyl moiety, no cyclization products were obtained from diazo compounds **10** and **12**, which were derived from phenylalanine and proline, respectively (Scheme 3). As predicted, favorable conformers **11** and **13** would not effect the desired cyclization, thus failing to form desired γ-lactams. Therefore, the *gem*-dimethyl group is requisite to the formation of the favorable conformer during cyclization for the synthesis of desired γ-lactams.

There are two possible transition states, **8** and **9**, where the phenyl group can be located in either the pseudoaxial or the pseudoequatorial positions, respectively.[10] The former case experiences a severe 1,3-diaxial nonbonded interaction, whereas the latter adopts a stable chairlike transition state with large groups occupying equatorial positions, which leads to relative stereochemistries at C-3, C-4, and C-5 of compound **6**. The newly generated stereochemical senses at C-3 and C-4 were induced by the chirality of α-amino acid during the insertion reaction. The stereochemical assignment for **6** was confirmed by X-ray crystallographic analysis.[11]

Having established the methodology, various α-amino acids were also subjected to the same procedure[12] to give α-diazo-α-(phenylsulfonyl)acetamides, which underwent the intramolecular C−H insertion to afford chiral γ-lactams exclusively or predominantly in high yields regardless of the substituent R (Table 1). Although each diazoamide has the possibility of forming δ-lactams through insertion into the reaction site on the substituent R, γ-lactam was selectively obtained as a single stereoisomer except **18**. Insertion of **18** afforded γ-lactam **19** along with a small amount of δ-lactam (6%), resulting from insertion into the reactive methine carbon on the substituent R (entry 3).[13] Insertion of **22** yielded γ-lactam **23** in a moderate yield as a result of the deactivating influence of the carbomethoxy group (entry 5). In the case of **24**, the yield was not better than that of the reaction with **5** despite the electron-donating *p*-methoxy group on the phenyl ring (entry 6).

However, the insertion reaction of substrates **26** and **28**, which possess an electron-donating TBS ether, yielded

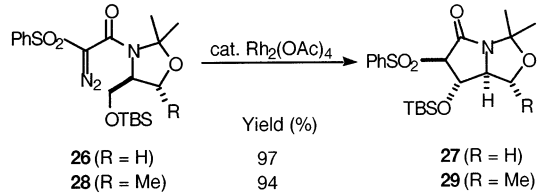
TABLE 1. C−H Insertion of α-Diazo Compounds Derived from Various α-Amino Acids



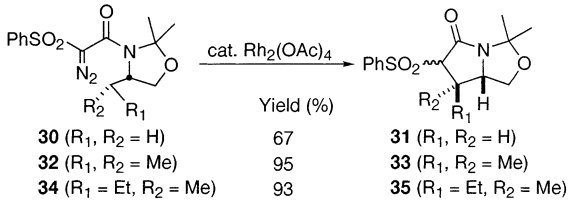
entry	R	reactant	yield (%)	product
1	Me	**14**[a]	87	**15**
2	Et	**16**[a]	92	**17**
3	*i*-Pr	**18**[b]	87[c]	**19**
4	Bn	**20**[a]	87	**21**
5	CH_2CO_2Me	**22**	64	**23**
6	4-(MeO)Ph	**24**[d]	86	**25**

[a] Starting with the corresponding racemic α-amino acid. [b] $Rh_2(pfb)_4$ was used. [c] δ-Lactam was also obtained (6%). [d] Starting with 4-methoxytyrosine.

SCHEME 4



SCHEME 5



trans γ-lactams **27** and **29** in very high yields, respectively (Scheme 4). Interestingly, γ-lactam **27** has very similar structure to the lactam cores embedded in lactacystin (**1**) and pramanicin (**2**) (Figure 1). Therefore, **27** is believed to be a promising intermediate for the synthesis of **1** and **2**.

Since the C−H insertions occurred at methylene centers in the aforementioned examples, methyl and methine centers were also examined (Scheme 5). The methyl C−H insertion (**30**) took place smoothly to provide the desired product in a moderate yield. As expected, C−H insertions at methine carbons (**32**, **34**) were facile to furnish the γ-lactams in high yields. However, inseparable diastereomeric mixtures were obtained due to the small or no difference in the relative stability of the two possible transition states during cyclization. Desulfonylation of γ-lactam **35** with Na(Hg)[14] afforded a single isomer, which suggested that C−H insertion proceeded with retention of the configuration of the methine reaction site.[15]

In conclusion, intramolecular C−H insertion of α-diazo-α-(phenylsulfonyl)acetamides prepared from α-amino

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(11) See the Supporting Information.

(12) For the preparation of compounds **22**, **24**, and **26**, see the Supporting Information.

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(15) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.

acids led to the formation of various chiral γ-lactams, which were functionalized at every center on the ring. By varying substituents and structure, this developed methodology will be utilized in the synthesis of biologically significant natural products possessing γ-lactam moieties.

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Supporting Information Available: Representative experimental procedures with spectral data, X-ray crystallography data for compound **6**, and further schemes for the preparation of compounds **22**, **26**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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