Arch Pharm Res Vol 27, No 10, 985-989, 2004

Archives of Pharmacal Research
http://apr.psk.or.kr

Functional Divergency Oriented Synthesis of Azoninones as the Key Intermediates for Bioactive Indolizidine Alkaloids Analogs

Jae-Kyung Jung[1], Nam-Song Choi, and Young-Ger Suh

College of Pharmacy, Seoul National University, Seoul 151-742 and [1]College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

(Received July 2, 2004)

A functional divergency oriented synthetic approach to the azoninone (9-membered lactams), key intermediate for the indolizidine alkaloids library, using amide enolate induced aza-Claisen rearrangement has been achieved.

Key words: Azoninone, Ring-expansion, Indolizidine, aza-Claisen rearrangement, Alkaloid

INTRODUCTION

The importance of medium-sized rings as well as their structural divergency in medicinal chemistry is exemplified by their being the structural core of a number of biologically important natural product and their serving as target molecules (Yet, 2000). Conventional cyclization strategies to medium-sized rings are often limited due to entropic factors, transannular interaction, and lack of the functional diversity of the reaction products.

Among these medium-sized rings, nitrogen containing heterocycles (e.g. lactam) as well as their structural diversity have generated considerable interest (Nubbemyer, 2001; Evans *et al.*, 1991), because these compounds have displayed as intermediates in the synthesis of natural products and as scaffolds for the functionalized indolizidine (e.g. polyhydroxylated indolizidine) synthesis by transannular ring contractions (Michael, 2001). For example, slaframine (**4**) can be medicinally useful for the treatment of diseases arising from cholinergic dysfunctions (Guengerich *et al.*, 1979). (+)-7-Deoxy-6-epicastanospermine (**5**) isolated from *Castanospermum australe* is known to be an inhibitor of amyloglucosidase and yeast a-glucosidase (Molyneux *et al.*, 1990). Although there are some elegant examples of stereocontrolled construction of 9-membered lactams *via* ring expansion, this is still an underdeveloped area in organic synthesis (Nubbemyer, 2001; Diederich *et al.*, 1995; Sudau *et al.*, 1998; Edstrom, 1991; Vedejs *et al.*, 1994). For example, starting from *N*-benzyl-2-vinyl pyrrolidine, the ketene Claisen rearrangement using an in situ generated dichloroketene led to the corresponding azoninone. However, rearrangements suffered from a complete loss of chiral information because of the use of terminally substituted olefins (Edstrom, 1991).

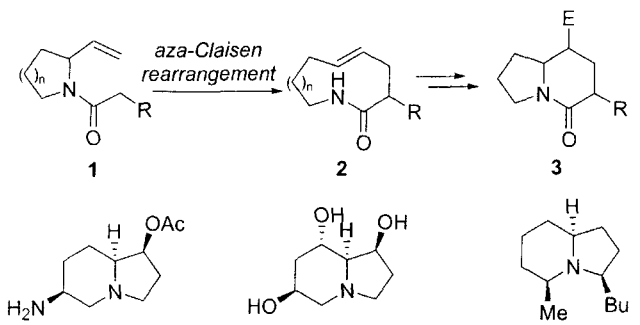


Fig. 1. Strategy for the synthesis of 9-membered lactam and representative Indolizidines

Recently, we have reported a novel ring expansion reaction of 1-acyl-2-vinyl piperidine, leading to the 10-membered lactam (azecinone), as well as its application to the synthesis of fluvirucin antibiotics (Suh *et al.*, 1996 and 1999). As a part of our ongoing studies toward the synthesis of the medium-sized lactams for the indolizidine alkaloid library, we have been interested in adopting our ring expansion strategy for the synthesis of the 9-membered lactam (**2**, azoninone). Introduction of various substituents at α-position of an amide as well as further modification of the internal olefin was viewed as a key to a

Correspondence to: Young-Ger Suh, College of Pharmacy, Seoul National University, Seoul 151-742, Korea
Tel: 82-2-880-7875, Fax: 82-2-888-0649
E-mail: ygsuh@snu.ac.kr

diversity-oriented synthetic strategy (Burke *et al.*, 2004). Herein is described the preparation of *N*-acylvinylpyrrolidines **1** and their amide enolate-induced ring expansions into the functionally divergent 9-membered unsaturated lactams **2**, which could be key building blocks for the indolizidone alkaloids **3** libraries. Furthermore, mechanistic scope and limitations have also been investigated.

MATERIALS AND METHODS

General procedure

Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used *without further purification. Air and moisture sensitive* reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel F_{254} plates (Merck).

(2*S*)-1-(*tert*-Butoxycarbonyl)tetrahydro-1*H*-pyrrole-2-carboxylic acid (8)

To a stirred solution of D-proline (**7**) (1.00 g, 8.68 mmol) in 10 mL of CH_3OH:H_2O:dioxane (3:2:1), BOC-ON (2.35 g, 9.55 mmol) and triethylamine (1.80 mL, 13.0 mmol) was added. After stirring for 1 h, the reaction mixture was diluted with H_2O (10 mL) and Et_2O (20 mL). The aqueous portion was extracted again, and acidified with cold 2.5 N aqueous HCl (pH = 2). The mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined extracts was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by recrystallization (hexanes) provided the *compound* **8** (1.81 g, 97%) as a white crystal; IR (KBr) cm^{-1} 3444, 1680, 1415; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.34-4.24 (m, 1H), 3.42-3.33 (m, 2H), 2.37-2.24 (m, 1H), 1.97-1.84 (m, 3H), 1.46 (s, 9H); MS (EI) 170(M^+-CO_2H).

tert-Butyl (2*S*)-2-[methoxy(methyl)amino]carbonyltetrahydro-1*H*-pyrrole-1-carboxylate (9)

To a solution of acid **8** (1.31 g, 6.09 mmol), *N,O*-dimethylhydroxylamine (728 mg, 7.31 mmol) and DMAP (cat. amount) in CH_2Cl_2 (30 mL) was added triethylamine (1.02 mL, 7.31 mmol). To this solution was added 1,3-dicyclohexylcarbodiimide (1.51 g, 7.31 mmol) at 0 °C. The resulting solution was stirred for 3 h. After evaporation of solvent, the residue was diluted with EtOAc (30 mL). The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4:1 hexane:EtOAc) to afford the Weinreb amide **9** (1.40 g, 91%) as a colorless oil; IR (KBr) cm^{-1} 2974, 1694; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 4.67 and 4.57 (m, 1H), 3.75 and 3.69 (s, 3H), 3.60-3.33 (m, 2H), 3.16 (s, 3H), 2.94-1.75 (m, 4H), 1.43 and 1.38 (s, 9H); MS (EI) 258(M^+).

tert-Butyl (2*S*)-2-formyltetrahydro-1*H*-pyrrole-1-carboxylate (10)

To a solution the amide **9** (1.51 g, 5.85 mmol) in THF (25 mL) was added DIBAL (1.0 M solution in toluene, 7.02 mL, 7.02 mmol) dropwise at -78 °C. After 2 h, the reaction mixture was quenched with 15% aqueous sodium potassium tartrate (10 mL), and diluted with EtOAc (30 mL). The resultant mixture was warmed to room temperature and stirred vigorously until two layers were completely separated. The mixture was extracted with EtOAc and combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:EtOAc) to afford the aldehyde **10** (1.06 g, 91%) as a colorless oil; IR (KBr) cm^{-1} 2975, 1735, 1694; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 9.53 and 9.43 (d, 1H, J = 2.7 Hz), 4.17 and 4.02 (m, 1H), 3.57-3.41 (m, 2H), 2.16-1.81 (m, 4H), 1.45 and 1.40 (s, 9H); MS (EI) 170(M^+-CHO)

tert-Butyl (2*S*)-2-vinyltetrahydro-1*H*-pyrrole-1-carboxylate (11)

To a suspension of trimethyltriphenylphosphonium bromide (4.44 g, 10.9 mmol) in THF (30 mL) was added dropwise at 0 °C *n*-butyllithium in hexane (1.6 M, 5.95 mL, 9.53 mmol), and stirring was continued for additional 1 h. The resulting yellow ylide solution was cooled to -78 °C and treated with the aldehyde **10** (1.78 g, 8.93 mmol) in THF (30 mL). The resulting slurry was warmed to room temperature and stirred additional 3 h and diluted with ether (50 mL) and water (30 mL). The aqueous layer was back-extracted with ether (50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in a minimum amount of EtOAc and purified by flash column chromatography (15:1 hexane:EtOAc) to afford the carbamate **11** (951 mg, 55%) as a colorless oil; IR (KBr) cm^{-1} 1695,1393; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.70 (ddd, 1H, J = 16.8, 10.5, 2.4 Hz), 5.02 (m, 2H), 4.23 (m, 1H), 3.36 (s, 2H), 2.04-1.89 (m, 1H), 1.87-1.75 (m, 2H), 1.75-1.63 (m, 1H), 1.41 (s, 9H).

1-[(2*S*)-2-Vinyltetrahydro-1*H*-pyrrol-1-yl]-1-propanone (1a)

To a solution of the carbamate **11** (81 mg, 0.359 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.08 mL, 1.07 mmol) at 0 °C and the ice bath was removed. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to afford amine salt. To a solution of crude amine salt and DMAP (cat. amount) in CH_2Cl_2 (10 mL) was added triethylamine (0.15 mL, 1.07

mmol) and propionic anhydride (0.14 mL, 1.07 mmol). The resulting solution was stirred for 24 h. After evaporation of solvent, the residue was diluted with EtOAc (30 mL). The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2:1 hexane:EtOAc) to afford **1a** (54 mg, 77%) as a colorless oil; IR (KBr) cm^{-1} 1633, 1428; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 5.80-5.69 (ddd, 1H, J = 16.8, 10.2, 5.4 Hz), 5.13-4.98 (m, 2H), 4.68-4.60 and 4.33-4.29 (m, 1H), 3.52-3.48 (m, 2H), 2.32-2.19 (m, 2H), 2.02-1.72 (m, 4H), 1.10 (t, 3H, J = 7.6 Hz); MS (EI) 153(M^+).

2-Methoxy-1-[(2*S*)-2-vinyltetrahydro-1*H*-pyrrol-1-yl]-1-ethanone (1b)

To a solution of the carbamate **11** (70 mg, 0.355 mmol) in CH_2Cl_2 (6 mL) was added TFA (0.08 mL, 1.06 mmol) at 0 °C and the ice bath was removed. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to afford amine salt. To a solution of crude amine salt and DMAP (cat. amount) in CH_2Cl_2 (6 mL) was added triethylamine (0.20 mL, 1.42 mmol) and methoxyacetyl chloride (0.081 mL, 0.888 mmol). The resulting solution was stirred for 4 h. After evaporation of solvent, the residue was diluted with EtOAc (30 mL). The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4:1 hexane:EtOAc) to afford **1b** (49 mg, 75%) as a colorless oil; IR (KBr) cm^{-1} 1644, 1454, 1125; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 5.75 (ddd, 1H, J = 16.8, 10.2, 5.4 Hz), 5.08 (dd, 2H, J = 16.8, 10.2 Hz), 4.68 and 4.35 (m, 1H), 4.05 (d, 1H, J = 14.4 Hz), 3.92 (d, 1H, J = 14.1 Hz), 3.57-3.39 (s, 3H), 2.14-1.74 (m, 4H); MS (EI) 169(M^+).

tert-Butyl *N*-2-oxo-2-[(2*S*)-2-vinyltetrahydro-1*H*-pyrrol-1-yl]ethylcarbamate (1c)

To a solution of the carbamate **11** (98 mg, 0.497 mmol) in CH_2Cl_2 (8 mL) was added TFA (0.112 mL, 1.48 mmol) at 0 °C and the ice bath was removed. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to afford amine salt. To a solution of crude amine salt and *t*-butoxycarbonylglycine (104 mg, 0.596 mmol) in DMF (8 mL) was added triethylamine (0.28 mL, 1.98 mmol) and DEPC (0.09 mL, 0.596 mmol) at 0 °C. The resulting solution was stirred for 4 h. After evaporation of solvent, the residue was diluted with EtOAc (30 mL). The organic phase was washed with 5% HCl, water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (3:1 hexane:EtOAc) to afford the Boc-protected amine **1c** (105 mg, 83%) as a colorless oil; IR (KBr) cm^{-1} 3420, 1713, 1648, 1434; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 5.71 (ddd, 1H, J = 16.8, 10.2, 6.1 Hz), 5.47 (brs, 1H), 5.17-5.00 (m, 2H), 4.64 and 4.28 (m, 1H), 3.89-3.78 (m, 2H), 3.56-3.36 (m, 2H), 2.11-1.76 (m, 4H), 1.41 (s, 9H); MS (EI) 254(M^+).

2-Amino-1-[(2*S*)-2-vinyltetrahydro-1*H*-pyrrol-1-yl]-1-ethanone (1d)

To a solution of the Boc-protected amine **1c** (134 mg, 0.525 mmol) in CH_2Cl_2 (8 mL) was added TFA (0.11 mL, 1.50 mmol) at 0 °C and the ice bath was removed. The mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (5 mL) and basified with saturated $NaHCO_3$. The mixture was separated and aqueous phase was extracted with CH_2Cl_2 (20 mL). The resulting organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 hexane:EtOAc) to afford the amine **1d** (66 mg, 81%) as a colorless oil; IR (KBr) cm^{-1} 3442, 1633, 1455; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 5.67 (ddd, 1H, J = 16.8, 10.2, 5.8 Hz), 5.01 (dd, 2H, J = 17.0, 10.2 Hz), 4.61 and 4.44 (m, 1H), 3.50-3.28 (m, 2H), 2.03-1.50 (m, 8H); MS (EI) 155(M^+ + 1).

3-Methoxy-1,3,4,7,8,9-hexahydro-2*H*-azonin-2-one (2b)

To a solution of the amide **1b** (22 mg, 0.13 mmol) in toluene (2 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.26 mL, 0.26 mmol) at 130 °C and the resulting solution was refluxed for 20 min. After addition of water (0.1 mL), the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (EtOAc only) to afford the lactam **2b** (16.5 mg, 75%, E : Z = 1 : 1.2) as a white solid; IR (KBr) cm^{-1} 3442, 1633, 1455; for the (*Z*)-isomer: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.06 (brs, 1H), 5.75-5.65 (m, 1H), 5.38 (dd, 1H, J = 10.9, 8.0 Hz), 4.19 (q, 1H, J = 12.4 Hz), 3.81 (d, 1H, J = 5.6 Hz), 3.30 (s, 3H), 3.03 (dd, 1H, J = 13.4, 6.5 Hz), 2.59-2.49 (m, 2H), 1.95-1.88 (m, 3H), 1.69-1.56 (m, 1H); for the (*E*)-isomer: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.74 (brs, 1H), 5.47-5.42 (m, 1H), 5.29 (dt, 1H, J = 15.6, 7.6 Hz), 3.80 (d, 1H, J = 7.5 Hz), 3.71-3.59 (q, 1H, J = 11.6, 7.8 Hz), 3.34 (s, 3H), 3.30 (dt, 1H, J = 13.6, 3.0 Hz), 2.54-2.42 (m, 1H), 2.43-2.37 (m, 1H), 2.11-1.91 (m, 2H), 1.82-1.49 (m, 2H); MS (EI) 169(M^+).

3-Amino-1,3,4,7,8,9-hexahydro-2*H*-azonin-2-one (2d)

To a solution of the amide **1d** (25 mg, 0.16 mmol) in toluene (2 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.32 mL, 0.32 mmol) at 130 °C and

the resulting solution was refluxed for 20 min. After addition of water (0.1 mL), the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (EtOAc only) to afford the lactam **2d** (20.5 mg, 82%, *E* : *Z* = 2 : 1); IR (KBr) cm^{-1} 3442, 1650, 1455; for the (*E*)-isomer: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.70 (brs, 1H), 5.65 (dt, 1H, *J* = 16.5, 8.0 Hz), 5.44 (dd, 1H, *J* = 19.4, 8.5 Hz), 4.17 (m, 1H), 3.70 (d, 1H, *J* = 5.8 Hz), 3.05 (dd, 1H, *J* = 13.7, 6.6 Hz), 2.43 (m, 1H), 2.31 (m, 1H), 2.12-1.59 (m, 4H); for the (*Z*)-isomer: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.68 (dd, 2H, *J* = 10.5, 5.4 Hz), 5.09 (m, 1H), 4.17 (m, 1H), 2.93 (d, 1H, *J* = 8.8 Hz), 2.60 (m, 1H), 2.16 (m, 1H), 1.99-1.59 (m, 5H); MS (EI) 154(M^+).

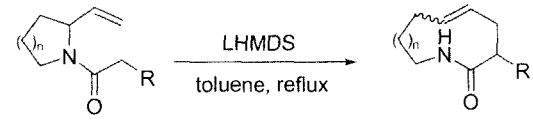
RESULTS AND DISCUSSION

Our initial studies began with the preparation of the requisite rearrangement precursors **1**. We envisioned that *D*-proline (**7**) could be the optimal starting compounds. Thus, after Boc protection of **7**, the resulting Boc-protected lactam **8** was converted into the corresponding Weinreb amide **9** in 90% yield (2 steps). DIBAL reduction of **9** afforded the desired aldehyde **10**, which was subjected to the Wittig olefination condition ($MeP^+Ph_3I^-$, *n*-BuLi, THF, -78 °C) to give **11** in 50% overall yield. Finally, Boc-deprotection of **11** and consecutive acylation of the resulting amine salt **12** with the various acid derivatives afforded the *N*-acyl-2-vinylpyrrolidines **1**, requisite precursors of the objective aza-Claisen rearrangement.

With the desired *N*-acyl-2-vinylpyrrolidines **1** in hand, we next attempted the projected aza-Claisen rearrangement using the established conditions (LHMDS, toluene, reflux) and the result was summarized in Table I (Suh *et al.*, 1996).

When α-heteroatom bearing substrates **1b** and **1d** were treated with LHMDS (lithium bis(trimethylsilyl)amide) in refluxing toluene, ring-expanded lactams **2b** and **2d** were formed in 75% and 82% yields, respectively (entry 2 and 3). It is well known that in α-heteroatom bearing amide, chelation between α-heteroatom and amide enolate oxygen promotes the facile aza-Claisen rearrangement (Tsunoda *et al.*, 1993; Coates *et al*, 1987), resulting in short reaction time and good yield; however, substrate **1a** bearing the propionyl group (R = Me) failed to afford the corresponding product. At present, the reason of these results is not clear and under investigation.

Table I. Aza-Claisen rearrangement of *N*-acyl-2-vinylpyrrolidines (**1**)



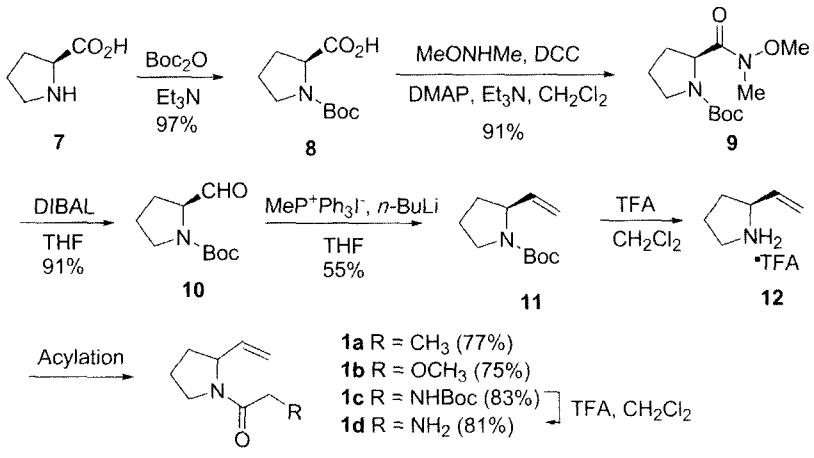
1a R = CH_3
1b R = OCH_3
1d R = NH_2

2

entry	2-vinyl pyrrolidine	R	yields (%)
1	**1a**	Me	–[b]
2	**1b**	OMe	75 (1 : 1)[c]
3	**1d**	NH_2	82 (2 : 1)[c]

[a] isolated yields after column chromatography
[b] decomposed product was formed
[c] ratio of *trans* : *cis*

The synthetic potential of the Claisen and related [3,3]-sigmatropic rearrangements arise from the high degree of control over the stereochemical outcome. Thus, we explored the stereochemistry of the olefin-geometry in ring-expanded lactams. Extensive NMR studies revealed that the α-methoxy lactam **2b** and α-amino lactam **2d** were obtained with 1 : 1 and 2 : 1 mixtures of the corresponding (*E*) and (*Z*) isomers, respectively. While the (*E*) isomer of **2b** showed coupling constant of 15.6 Hz



Scheme 1. Preparation of precursors **1** for aza-Claisen rearrangement

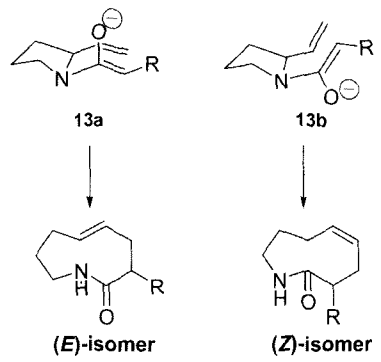


Fig. 2. Proposed boat-like transition state

between two olefinic protons, that of the corresponding (*Z*) isomer was 10.9 Hz. Rearrangement in benzene having the lower boiling point gave similar results. All of the results from the rearrangements of *N*-acyl-2-vinylpyrrolidines (**1**) can be rationalized by assuming that the aza-Claisen reaction proceeds through the 6-membered boat-like transition state such as **13a** and **13b** rather that the typical chair-like transition state (Castro, 2004).

To our knowledge, the formation of the azoninone bearing (*Z*)-olefin through aza-Claisen rearrangement was not yet reported, although boat-like transition state have been invoked previously to explain the outcome in Claisen type rearrangements of certain cyclic substrate (Pereira *et al.*, 1993). The olefinic mixture was easily separable through simple flash column chromatography and thus could be used for the diversity-oriented indolizidine syntheses (Burke *et al.*, 2004; Michael, 2001).

In closing, we have shown that *N*-acyl-2-vinylpyrrolidines are good substrate in the amide-enolate-induced aza-Claisen rearrangement to afford the substituent divergent 9-membered lactams, which could be potential templates for the synthesis of the medicinally important indolizidine alkaloids library. In addition, aza-Claisen rearrangement proceeded through a boat-like transition state to furnish the mixture of (*E*) and (*Z*) isomer of azoninones by single reaction. The studies on application of this methodology for indolizidine alkaloids library is in progress and the results will be forthcoming.

ACKNOWLEDGEMENT

This work was supported in part by Chungbuk National University Grant in 2004.

REFERENCES

Burke, M. D. and Schreiber, S. L., A planning strategy for diversity-oriented synthesis. *Angew. Chem., Int. Ed. Engl.*, 43, 46-58 (2004).

Castro, A. M. M., Claisen rearrangement over the past nine decades. *Chem. Rev.*, 104, 2939-3002 (2004).

Coates, R. M., Rogers, B. D., Hobbs, S. J., Curran, D. P., and Peck, D. R., Synthesis and Claisen rearrangement of alkoxyallyl enol ethers. Evidence for a dipolar transition state. *J. Am. Chem. Soc.*, 109, 1160-1170 (1987).

Diederich, M. and Nubbemeyer, U., Synthesis of optically-active 9-membered ring lactams by a zwitterionic, aza-Claisen reaction. *Angew. Chem., Int. Ed. Engl.*, 34, 1026-1028 (1995).

Edstrom, E. D., New methodology for the synthesis of functionalized indolizidine and quinolizidine ring systems. *J. Am. Chem. Soc.*, 113, 6690-6692 (1991).

Evans, P. A. and Holmes, A. B., Medium ring nitrogen heterocyles. *Tetrahedron*, 47, 9131-9166 (1991).

Guengerich, F. P. and Bronquist, H. P., In *Bioorganic Chemistry*, Ed. Van Tameleon, E. E. Academic, New York, Vol 2, 97-109 (1979).

Michael, J. P., Indolizidine and quinolizidine alkaloids. *Nat. prod. Rep.*, 18, 520-542 (2001).

Molyneux, R. J., Tropea, J. E., and Elbein, A. D., 7-Deoxy-6-epi-castanospermine, a trihydroxyindolizidine alkaloid glycosidase inhibitor from Castanospermum australe. *J. Nat. Prod.*, 53, 609-614 (1990).

Nubbemeyer, U., Synthesis of medium-sized ring lactams. *Top. Curr. Chem.*, 216, 125-196 (2001).

Pereira, S. and Srebnik, M., The Ireland-Claisen rearrangement. *Aldrichimica Acta*, 26, 17-29 (1993)

Sudau, A. and Nubbemeyer, U., Unusual diastereoselection in the synthesis of 9-membered ring lactams and conformation-controlled transannular reactions to generate optically active indolizidinones. *Angew. Chem. Int. Ed. Engl.*, 37, 1140-1143 (1998).

Suh, Y.-G., Kim, S.-A., Jung, J.-K., Shin, D.-Y., Min, K.-H., Koo, B.-A., and Kim, H.-S., Asymmetric Total Synthesis of Fluvirucinine A_1. *Angew. Chem. Int. Ed. Engl.*, 38, 3545-3547 (1999).

Suh, Y.-G., Lee, J.-Y., Kim, S.-A., and Jung, J.-K., A new ring expansion reaction of 1-acyl-2-vinylpiperidine and 1-acyl-2-vinylpiperazine *via* aza-Claicen rearrangement of amide enolate. *Synth. Commun.*, 26, 1675-1680 (1996).

Tsunoda, T., Tatsuki, S., Shiraishi, Y., Akasaka, M., and Ito, S., Asymmetric aza-Claisen rearrangement of glycolamide and glycinamide enolates. Synthesis of optically active a-hydroxy and a-amino acids. *Tetrahedron Lett.*, 34, 3297-3300 (1993).

Vedejs, E. and Gingras, M., Aza-Claisen rearrangements initiated by acid-catalyzed Michael addition. *J. Am. Chem. Soc.*, 116, 579-588 (1994).

Yet, L., Metal-mediated synthesis of medium-sized rings. *Chem. Rev.*, 100, 2963-3007 (2000).