Pergamon

*Tetrahedron: Asymmetry*, Vol. 8, No. 1, pp. 5–9, 1997

Printed in Great Britain
PII: S0957-4166(96)00496-X
0957-4166/97 $17.00 + 0.00

# A diastereoselective phenylselenium-induced lactamization of olefinic amides. A possible route to α-and β-amino acid derivatives

Sung-Kee Chung,* Tae-Heum Jeong and Dong-Ho Kang
Department of Chemistry, Pohang University of Science & Technology, Pohang 790-784, Korea

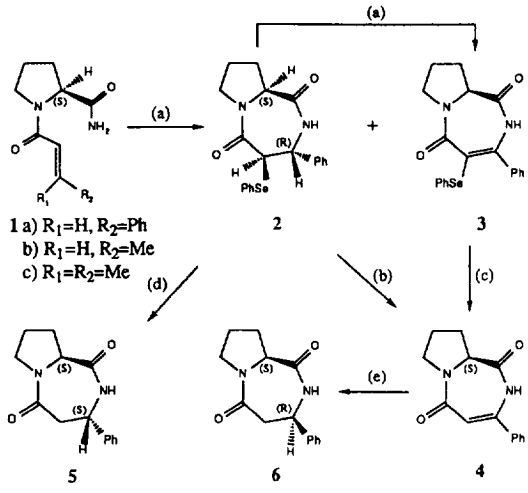
***Abstract:*** The organoselenium-induced cyclofunctionalization of (S)-N-(α,β-unsaturated-acyl)prolinamides was found to produce with a high degree of chirality transfer, 7- and 6-membered bislactam derivatives depending on the substitution pattern of the starting material. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Electrophilic heteroatom cyclizations of olefinic compounds leading to a variety of 5- and 6-membered ring heterocycles have been extensively investigated: for example, halolactonization of alkenes with the intramolecular carboxylate nucleophile and various cyclofunctionalizations of olefins with the hydroxyl, amino, sulfur and phosphorus functional groups.[1] The successful application of these methods to the synthesis of specific target molecules requires selection of appropriate combinations of substrate geometry,[2] nucleophilic functionality and the activating electrophile; the most frequently used electrophiles are halonium, Hg(II) and phenylselenium ions.[3]

In the cyclofunctionalization of olefinic amides promoted by a number of electrophiles, the predominant product is not the lactam, but the imino ether which subsequently hydrolyzes to the corresponding lactone, i.e. the oxygen atom instead of the nitrogen in the amide functionality preferrentially attacks the developing electrophilic center.[3c,4] The only reported exceptions include halocyclization of N-sulfonyl, N-butyl, N-isoxazolyl, N-thiazolyl olefinic amides.[5] In order to cyclofunctionalize olefinic amides to lactams, it is normally necessary to utilize the protected forms of amide functionality such as bis-silylated imidate, thioimidate, and O-acylhydroxamate.[6]

We have been exploring the asymmetric version of the organoselenium-induced cyclization of olefinic amides as an efficient route to chiral α- or β-amino acids, and wish to report a novel lactamization with a high degree of chirality transfer.[7] First, (S)-N-cinnamoyl-prolinamide **1a**, efficiently prepared from (S)-proline by successive reactions with i) cinnamoyl chloride and NaOH in aqueous acetone at 0°C, ii) methyl chloroformate and triethylamine, and iii) ammonium hydroxide at −10°C, was subjected to cyclization conditions. After considerable experimentation with a number of electrophiles under a variety of reaction conditions, phenylselenenyl bromide (PhSeBr), silver triflate (AgOTf),[8] and DMF in $CH_3CN$ was found to be most suitable for the desired cyclofunctionalization of **1a**. Thus, when compound **1a** was treated with PhSeBr (3 molar equiv), AgOTf (3 molar equiv) and DMF (20–30 molar equiv) in dry $CH_3CN$ at room temperature under Ar, a mixture of the cyclic products **2** and **3** was obtained in a varying ratio depending on the reaction time; after 12 hrs **2** was isolated in 31% yield together with **1a** (65%), whereas after 48 hrs products **2** (5%) and **3** (72%) were obtained along with a trace amount of **1a**. It could be shown that the pure product **2** was converted to product **3** in 70% yield under the identical reaction conditions, or in ca. 30% yield upon treatment with PhSeBr in DMF and $CH_3CN$. The conversion of compound **2** to **3** represents the overall *trans* dehydrogenation, and might be occurring through the initial N-phenylselenation followed by the elimination of a 'phenylselenol equivalent' to give an imine, which isomerizes to **3**. It was also found that the reaction of **1a** with PhSeBr (1.8 equiv), AgOTf (2 equiv) and DMF (20 equiv) in dry $CH_3CN$ at room temperature under Ar for 12 hrs gave almost exclusively product **2** (73% isolated

* Corresponding author. Email: skchung@chem.postech.ac.kr




(a) PhSeBr, AgOTf, DMF, $CH_3CN$. (b) $H_2O_2$ (30%), THF, 77%. (c) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF, MeOH, 88%. (d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF, MeOH, 87% ( 5:6 = 22.8:1 ). (e) Pd-C, $H_2$, MeOH, 89% ( 5:6 = 1:4.56 ).

**Scheme 1**. Cyclofunctionalization of **1a** and subsequent conversions to (L)- and (D)-β-AA derivatives.

yield) together with trace amounts of **1a** and **3** (Scheme 1). It is to be noted that without DMF the cyclization reaction did not proceed smoothly, although the role of DMF has not been clarified.

The structural elucidation and stereochemical assignments of products **2** and **3** were carried out by means of spectroscopic techniques including single crystal X-ray diffraction (Figs 1 and 2).[9] It is clear from the X-ray structure of **2** that the amide nitrogen attacks the β-position of the cinnamoylamide moiety thus generating a 7-membered ring system and that the electrophile promoted addition occurs in *anti* fashion resulting in the (R)-absolute configuration at the new stereogenic center of C*–NH. However, the reason for the exclusive formation of the lactam product as opposed to the usual lactone via imino ether species is not obvious at the moment. The crude product **2** was deselenenylated in 87% yield with nickel boride generated *in situ* from $NiCl_2{\bullet}6H_2O$ and $NaBH_4$ in THF–MeOH[10] to give compound **5**. The HPLC analysis of the crude product **5** (Alltech RP-18; 4.6 × 250 mm; 25% $CH_3CN$ in $H_2O$; 1.5 ml/min; detection at 208 nm) indicated that the diastereomeric ratio at this stage was ca. 22.8:1, equivalent to ca. 91.6%de. Similarly, compound **3** was deselenated to **4** in 88% yield by the nickel boride procedure. Alternatively, the oxidative elimination of compound **2** with $H_2O_2$ (30%) in THF[11] was carried out in 77% yield to provide **4**, which was hydrogenated over Pd/C in MeOH to give a diastereomeric mixture of **5** and **6** in the ratio of 1:4.56 (%de=64.0) on the basis of HPLC analysis.[12] It is noteworthy that in the catalytic hydrogenation of both compound **4** and the exocyclic double bond in the diketopiperazine derivatives,[13] derived from (S)-proline and α-keto acids, the catalyst-bound hydrogen approaches from the convex side of the molecules, i.e. the same side as the hydrogen on the stereogenic center of the (S)-proline auxiliary, although the 1,4-chirality transfer efficiency appears to be slightly higher in the 6-membered ring than in the 7-membered ring **4**.

Next, we examined the lactamization of (S)-N-crotonoylprolinamide **1b**, which was prepared from (S)-proline and crotonyl chloride. Under the identical reaction conditions described for **1a**, compound **1b** very slowly yielded four identifiable products: the 6-membered diketopiperazines **7** (13.2%) and **8** (4.2%), and the simple addition products **9** (46%) and **10** (19.4%). The product structures were elucidated by spectroscopy including X-ray diffractions for the diastereomeric 6-membered bislactams

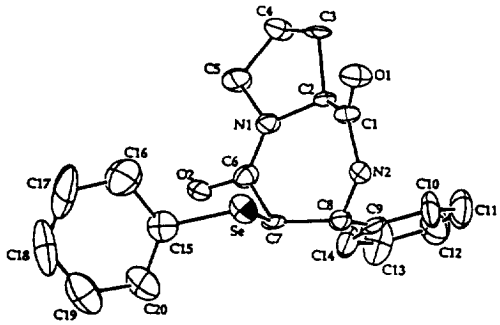



**Figure 1**. X-ray crystal structure of compound **2**.

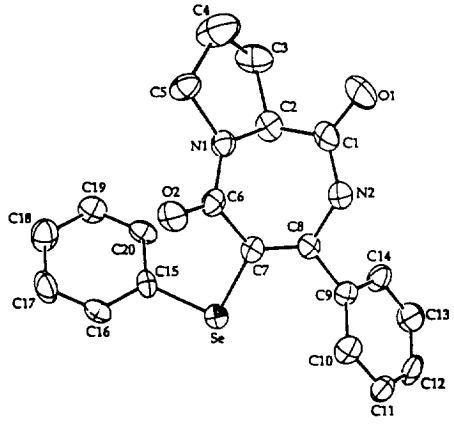
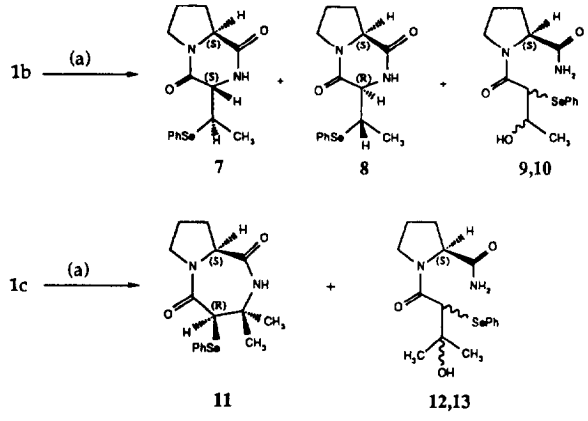



**Figure 2**. X-ray crystal structure of compound **3**.

(**7** and **8**).[14] The presence of the secondary hydroxyl groups in **9** and **10** was confirmed by acetylation. The characteristic chemical shift change for the carbinyl protons could be readily observed in the $^1$H-NMR of the acetylated products. However, the absolute stereochemistry of **9** and **10** has not been assigned. In the case of (S)-N-(β-methylcrotonoyl)prolinamide **1c**, the cyclofunctionalization provided the 7-membered lactam compound **11** (22.4%) together with two diastereomeric PhSe-added products **12** (49%) and **13** (13.3%).[15] The reductive deselenenylation ($NiCl_2 \bullet 6H_2O$ and $NaBH_4$ in THF–MeOH) of **11** gave the corresponding 7-membered ring compound, whose $^1$H-NMR exhibited two isolated methyl groups at δ 1.34 and 1.36, and two diastereotopic protons at δ 2.47 and 3.07 ppm with the geminal couplings (J=14.1Hz).




In summary, the observed efficiency of the cyclofunctionalization and the product structures clearly suggest that the electronic factor plays a predominant role in this phenylseleno-lactamization. It has been shown that the cyclofunctionalization can provide an efficient route to aromatic (S)- and (R)-β-amino acids,[16] since the diastereomeric cyclic dipeptides such as **5** and **6** can be easily purified and hydrolyzed to the corresponding chiral β-amino acids and the chiral auxiliary which can be recycled.[13c] In spite of the low chemical yield, the possibility that (S)- and (R)-α-amino acids can be synthesized by this approach has also been demonstrated in the cases where the substrate includes the electron-deficient olefin moiety.

## Acknowledgements

We wish to thank Korea Science & Engineering Foundation and POSCO for the financial support of this work. We also thank Mr. Dongmok Whang in Prof. Kimoon Kim's group for the X-ray works.

## References

1. (a) Harding, K. E.; Tiner, T. H. in *'Comprehensive Organic Synthesis'*, ed. Semmelhack, M. F., Pergamon Press, Oxford, **1991**, Vol. 4, p 363–421. (b) Kemp, J. E. G. in *'Comprehensive Organic Synthesis'*, ed. Ley, S. V., Pergamon Press, Oxford, **1991**, Vol. 7, p 469–513. (c) Swiss, K. A.; Liotta, D. C. *ibid.*, p 515–526.
2. Baldwin and J. E. *J. Chem. Soc. Chem. Commun.*, **1976**, 734–736.
3. (a) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. in *'Organic Selenium Chemistry'*, ed. Liotta, D., John Wiley & Sons, New York, **1987**. (b) Paulmier, C. *'Selenium Reagents and Intermediates in Organic Chemistry'*, Pergamon Press, Oxford, **1986**. (c) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc. Chem. Commun.* **1978**, 379–380. (d) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M., *ibid.*, **1993**, 1340–1342. (e) De Kimpe, N.; Boelens, M., *ibid.*, **1993**, 916–918. (f) Tiecco, M.; Testaferri, L.; Tingolo, M.; Bagnoli, L.; *ibid.*, **1995**, 235–236.
4. (a) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625–1626. (b) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079–1085. (c) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724–1729.
5. (a) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233–3235. (b) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018–2026. (c) Balko, T. W.; Brinkmeyer, R. S.; Terando, *Tetrahedron Lett.* **1989**, 2045–2048.
6. (a) Knapp, S.; Levorse, A. T. *ibid.*, **1988**, *53*, 4006–4014. (b) Takahata, H.; Takmatsu, T.; Yamazaki, T. *ibid.*, **1989**, *54*, 4812–4822. (c) Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, 4471–4477.
7. For a related asymmetric halolactonization, see Jew, S.-S.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2337.

8. Murata, S.; Suzuki, T. *Chemistry Lett.* **1987**, 849–852.
9. Compound **2**: mp 194–195°C; $[\alpha]_D$ +26.7 (c 1.02, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.79 (m, 2H), 2.03 (m, 1H), 2.59 (m, 1H), 3.60 (m, 2H), 4.19 (dd, J=7.5, 6.2Hz, 1H), 4.71 (d, J=8.7Hz), 4.82 (dd, J=8.7, 4.4Hz, 1H) 6.24 (d, J=4.4Hz, 1H), 7.07–7.32 (m, 10H). Compound **3**: mp 215–216°C; $[\alpha]_D$ +178.4 (c 1.05, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.86–2.12 (m, 3H), 2.71 (m, 1H), 3.26 (dt, J=11.8, 8.1Hz, 1H), 3.66 (m, 1H), 4.25 (dd, J=7.5, 2.6Hz, 1H), 7.11–7.42 (m, 10H).
10. Back and T. J. *J. Chem. Soc. Chem. Commun.*, **1984**, 1417–1418.
11. Toshimitsu, A.; Owada, H.; Uemura, S.; Okano, M. *ibid.*, **1981**, 546–547.
12. Compound **5**: mp 154–155°C; $[\alpha]_D$ −92.4 (c 0.61, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.80 (m, 2H), 2.18 (m, 1H), 2.76 (m, 2H), 3.20 (app.t, J=13.3Hz, 1H), 3.58 (t, J=6.8Hz, 2H), 4.59 (dd, J=8.1, 4.4Hz, 1H), 4.82 (dd, J=13.3, 1.5Hz, 1H) 5.83 (s, 1H), 7.26–7.41 (m, 5H); MS(EI) m/z 244($M^+$); High resolution MS(EI) calcd. for $C_{14}H_{16}O_2N_2$: 244.1212. found: m/z 244.1216. Compound **6**: mp 150–152°C; $[\alpha]_D$ −17.3 (c 0.75, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.88 (m, 2H), 2.15 (m, 1H), 2.70 (m, 1H), 2.95 (dd, J=16.5, 10.0Hz, 1H), 3.14 (dd, J=16.5, 3.7Hz, 1H) 3.61 (m, 2H), 4.62 (dd, J=7.5, 6.2Hz, 1H), 4.94 (dt, J=10.0, 3.7Hz, 1H), 6.09 (s, 1H), 7.26–7.43 (m, 5H); MS(EI) m/z 244($M^+$); High resolution MS(EI) calcd. for $C_{14}H_{16}O_2N_2$: 244.1212. found: m/z 244.1207.
13. (a) Bycroft, B. W.; Lee, G. R. *J. Chem. Soc. Chem. Commun.* **1975**, 988–989. (b) Izumiya, N.; Lee, S.; Kanmera, T.; Aoyagi, H. *J. Am. Chem. Soc.* **1977**, *99*, 8346–8348. (c) Kanmera, T.; Lee, S.; Aoyagi, H.; Izumiya, N. *Tetrahedron Lett.* **1979**, 4483–4486.
14. Compound **7**: mp 110–111°C; $[\alpha]_D$ −59.4 (c 0.65, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.60 (d, J=7.2Hz, 3H) 1.84 (m, 1H), 1.96–2.10 (m, 2H), 2.45 (m, 1H), 3.41 (ddd, J=11.8, 9.1, 2.6Hz, 1H), 3.59–3.70 (m, 2H), 4.33 (dd, J=9.7, 6.7Hz, 1H), 4.89 (d, J=5.9Hz, 1H), 7.27–7.64 (m, 5H). Compound **8**: mp 139–140°C; $[\alpha]_D$ −221.8 (c 0.82, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.52 (d, J=7.1Hz, 3H) 1.91 (m, 1H), 2.03 (m, 1H), 2.26 (m, 1H), 2.38 (m, 1H), 3.59 (m, 2H), 3.99 (dq, J=7.1, 2.4Hz), 4.20 (t, J=8.0Hz, 1H), 4.93 (d, J=2.4Hz, 1H), 7.26–7.62 (m, 5H); MS(FAB) 339 ($M^+$+1).
15. Compound **11**: mp 190–191.5°C; $[\alpha]_D$ −14.5 (c 1.00, $CHCl_3$); $^1H$ NMR($CDCl_3$) δ1.27 (s, 3H), 1.34 (s, 3H), 1.78 (m, 2H), 2.11 (m, 1H), 2.55 (m, 1H), 3.53 (m, 2H), 4.42 (dd, J=7.8, 4.9Hz, 1H), 4.46 (s, 1H), 7.19–7.59 (m, 5H); MS(EI) m/z 352($M^+$); HRMS(EI) calcd. for $C_{16}H_{20}N_2O_2Se$: 352.0690 found: m/z 352.0691.
16. (a) Griffith, O. W. *Ann. Rev. Biochem.* **1986**, *55*, 855–878. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582. (c) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3–11.

*(Received in Japan 24 September 1996; accepted 11 November 1996)*