AN ENANTIOSELECTIVE CONSTRUCTION OF PYRROLIDONES BEARING FUNCTIONALIZED APPENDAGES *VIA* AN ASYMMETRIC INTRAMOLECULAR MICHAEL REACTION

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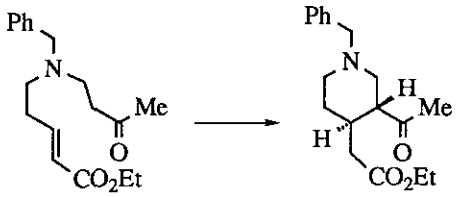
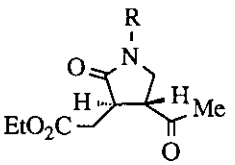
Abstract — The intramolecular Michael reaction of acyclic compounds **9** and **10** to form pyrrolidones is reported. Cyclization of **9** and **10** using (*R*)-(+)-1-phenylethylamine as a mediator gave the pyrrolidones (+)-**11** and (+)-**12** in 63% and 65% enantiomeric excess, respectively. When (*S*)-(-)-1-phenylethylamine was used, (-)-**11** and (-)-**12** were obtained in similar optical yields, respectively.

The intramolecular Michael reaction is among the most important procedures for the construction of cyclic systems,[1] and an asymmetric version of this procedure could provide us with a powerful tool for the chiral synthesis of various natural products and related compounds.[2] We have previously reported the design of the functionalized piperidine system **2** as an important key building block for the chiral synthesis of *Rauwolfia* alkaloids and accomplished its preparation from the acyclic compound **1** by employing an asymmetric intramolecular Michael reaction.[3] In the context with our ongoing program involving the application of an asymmetric intramolecular Michael reaction to the assembly of optically active ring systems, we became interested in the application to the construction of a heterocyclic five-membered ring system. Thus, we designed a 2-pyrrolidone (**3**) bearing the ring substituents of *trans* arrangement as a chiral building block for the synthesis of α-allo-kainic acid or *Strychnos* alkaloids. Now, we wish to describe the preparation of both enantiomers of **3** by employing an asymmetric intramolecular cyclization.

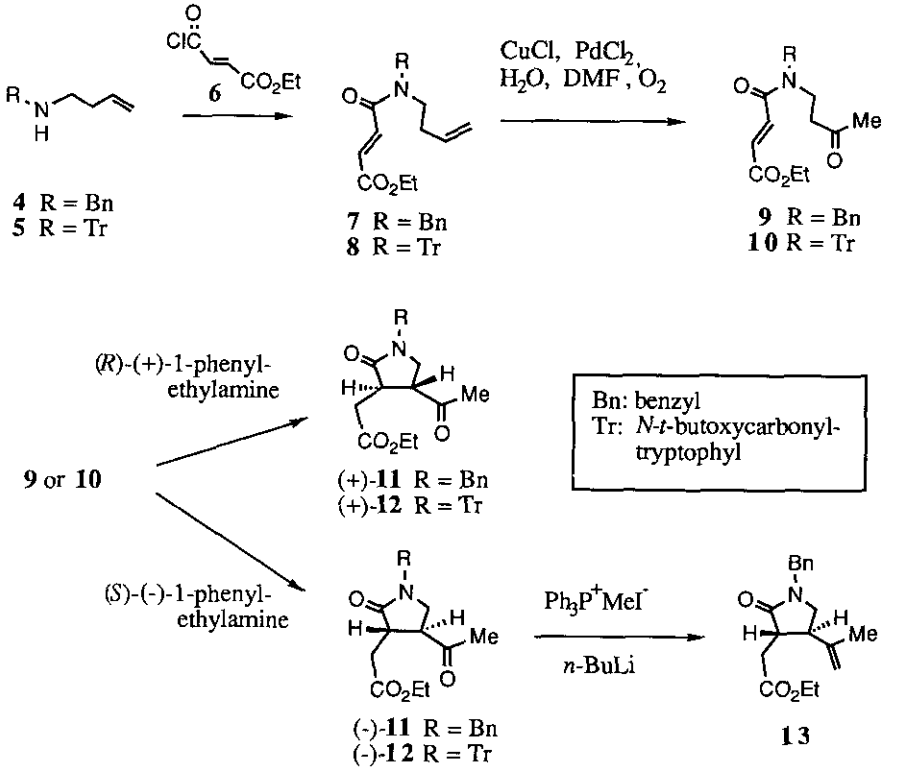


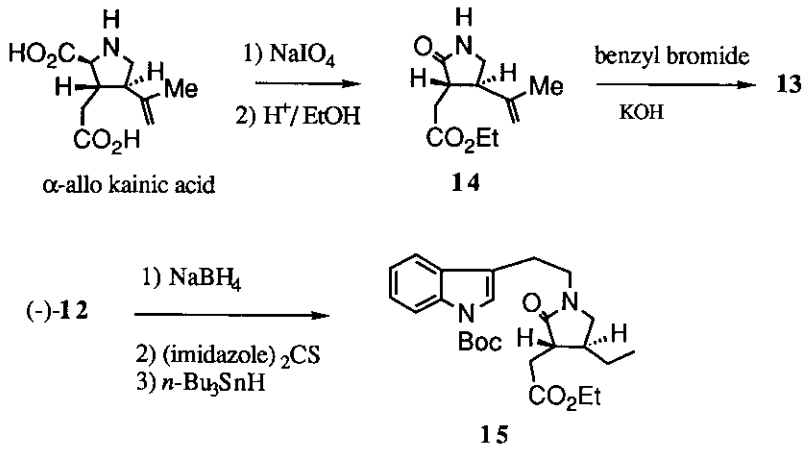
1 **2**



3 R = benzyl or tryptophyl

The substrates for cyclization were prepared according to the following sequence starting from the secondary amines **4**[4] and **5**.[5] Treatment of **4** and **5** with (*E*)-β-carbethoxyacrylyl chloride (**6**)[6] in ether in the presence of triethylamine gave the amides **7**[7] and **8**, which were subjected to the Wacker oxidation[8] to furnish the ketones **9** and **10** in 86% and 78% overall yield, respectively. Cyclization of **9** was carried out by the treatment with (*R*)-(+)-1-phenylethylamine[9] in THF in the presence of molecular sieve 5A at 5 °C to afford the pyrrolidone (+)-**11**,[10] $[\alpha]_D^{26}$ +24°($CHCl_3$), in 63% enantiomeric excess (ee)[11] (89% yield). When (*S*)-(-)-1-phenylethylamine[12] was used, (-)-**11**, $[\alpha]_D^{26}$ -22.6°($CHCl_3$), was obtained in 63% ee (84% yield). The optical yield (ee) of the cyclization was determined by hplc using a chiral column.[13] The absolute configuration of (+)-**11** and (-)-**11** was determined by the conversion of (-)-**11** into the olefin **13**. The Wittig reaction of (-)-**11** with methyltriphenylphosphonium iodide in the presence of *n*-butyllithium (*n*-BuLi) gave the olefin **13** in 54% yield. The synthetic pyrrolidone (**13**), $[\alpha]_D^{26}$ -24.2°(*c* 0.4, $CHCl_3$), was identical with an authentic sample, $[\alpha]_D^{26}$ -28.3°(*c* 0.4, $CHCl_3$) which was obtained from α-allo-kainic acid through the sequential oxidative decarboxylation,[14] esterification, and *N*-benzylation. Thus, the absolute configuration of (+)-**11** or (-)-**11** is (3*R*, 4*R*) or (3*S*, 4*S*).





Next, we examined the asymmetric Michael reaction of a substrate (**10**) having an indole moiety. Treatment of **10** with (*R*)-(+)-1-phenylethylamine under the same conditions as described above gave the pyrrolidone (+)-**12** in 65% ee[15] (95% yield). Its enantiomer [(-)-**12**] was obtained in a similar optical yield by using (*S*)-(-)-1-phenylethylamine as a chiral amine. The sodium borohydride reduction of (-)-**12** followed by the sequential treatment with 1,1'-thiocarbonyldiimidazole[16] and tributyltin hydride (*n*-Bu_3SnH) provided the *N*-tryptophylpyrrolidone **15** in 40 % yield from (-)-**12**.

The pyrrolidone [(-)-**11** or (-)-**12**] produced in this manner would be a useful key building block for α-allo-kainic acid or *Strychnos* alkaloids.[17] The synthesis of these natural products from (-)-**11** and (-)-**12** is under investigation.

ACKNOWLEDGEMENT

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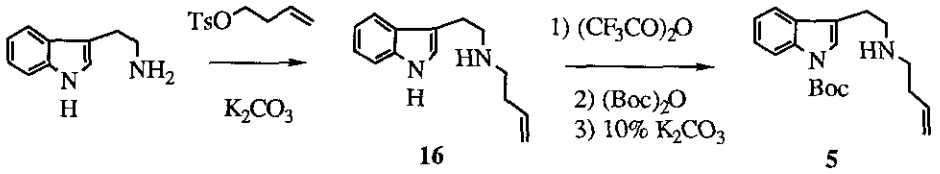
4. A. Padwa, H. Nimmesgern, and G. S. K. Wong, *J. Org. Chem.*, 1985, **50**, 5620.

5. The compound **5** was readily prepared from tryptamine *via* the amine **16** in 42% overall yield as follows:



16 **5**

6. U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, **1951**, 1501.
7. All new compounds gave satisfactory 270 Mz ^{1}H nmr, ir, and high resolution mass spectra and/or elemental analysis: for example, for (-)-**11**; ^{1}H nmr (270 MHz, $CDCl_3$) δ : 1.25 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.68 (3H, s, $COCH_3$), 2.68 (1H, dd, *J* = 7.1 and 16.9 Hz,$CH(H)CO_2$), 2.85 (1H, dd, *J* = 4.2 and 16.9 Hz, $CH(H)CO_2$), 3.09-3.16 (1H, m, $CHCH_2CO_2$), 3.21-3.33 (2H, m, CHCOMe and NCH(H)CH), 3.39-3.48 (1H, m, NCH(H)CH), 4.13 (2H, q, *J* = 7.1Hz, CO_2CH_2Me), 4.40 and 4.55 (2H, ABq, *J* = 14.7 Hz, $ArCH_2$) , 7.22-7.37 (5H, m, ArH); ir (film) ν_{max}: 1690, 1730 cm^{-1}; ms (m/z): 303 (M^+). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.11; H, 6.96; N, 4.32. For (-)-**12**; ^{1}H nmr ($CDCl_3$) δ: 1.23 (3H, *t*, *J* = 7.1 Hz, OCH_2CH_3), 1.65 (9H, s, O^{t}Bu), 2.14 (3H, s, $COCH_3$), 2.30-3.80 (10H, m), 4.12 (2H, q, *J* = 7.1 Hz, OCH_2Me), 7.10-7.70 (4H, m, ArH), 7. 93-8.16 (1H, m, ArH); ir (film) ν_{max}:1680, 1728 cm^{-1}. *Anal.* Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 65.44; H, 7.05; N, 5.84.
8. J. Tsuji, K. Masaoka, and T. Takahashi, *Tetrahedron Lett.*, **1977**, 2267.
9. Commercially available amine, $[\alpha]_D^{20}$ +39°(neat)(ee > 99%), was used.
10. An experimental procedure for the cyclization of **9** is as follows: (+)-Phenylethylamine (952 mg, 7.86 mmol) was added dropwise to a stirred solution of **9** (2.38 g, 7.86 mmol) in THF (25 mL) at 0°C. Molecular sieve 3A was added and the mixture was stirred at *ca.* 5°C. After disappearance of the starting material on inspection of its thin layer chromatography, the molecular sieve was filtered off through a Celite column. Usual work-up of the filtrate followed by column chromatography (silica gel 70g, elution with hexane : acetone = 5:1) gave (+)-**11** (2.1 g, 6.96 mmol) as a colorless oil.
11. The present moderate optical yield would be rationalized by assuming that the contribution of the free energy change in enantio-differentiation would be reduced for the transition state leading to the cyclization into a five-memberd ring as compared to that for six-membered one, becasuse the reaction period for the pyrrolidone was much shorter for completion than that for the piperidine[3] at 5°C (2 weeks for the pyrrolidone as against 3 weeks for the piperidine).
12. Commercially available amine, $[\alpha]_D^{20}$ -39°(neat)(ee > 99%), was used.
13. The chiral column OJ (Daicel Chemical Industries, Ltd.) was used.
14. The conversion of kainic acid into the pyrrolidine derivative *via* the oxidative decarboxylation process has been reported: R. D. Allan, *Tetrahedron Lett.*, **1978**, 2199.
15. Determined by hplc using the chiral column AS (Daicel Chemical Industries, Ltd.).
16. For the deoxygenation process, see: J. R. Rasmussen, C. J. Slinger, R. J. Kordish, and D. D. N.-Evans, *J. Org. Chem.*, 1981, **46**, 4843.
17. The synthesis of a framework of the *Strychnos* alkaloid from *N*-tryptophylpyrrolidone *via* the thio-Claisen rearrangement has been reported: S. Takano, M. Hirama, and K. Ogasawara, *Tetrahedron Lett.*, 1982, **23**, 881.

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