Zirconium-Mediated, Highly Diastereoselective Ring Contraction of Vinylmorpholine Derivatives from α-Amino Acids: An Application to the Synthesis of (-)-Macronecine

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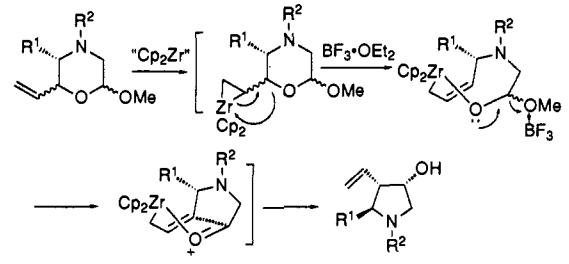
Received February 4, 1994

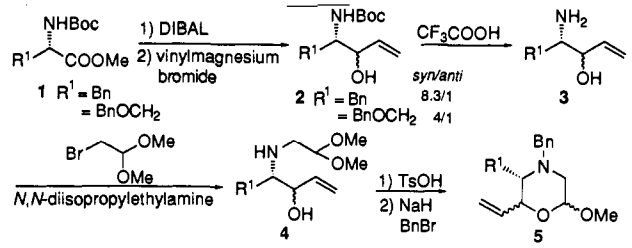
Rich chemistry has been developed by using catalytic or stoichiometric amounts of the zirconocene complex in organic synthesis.[1] Recently our progress in zirconocene equivalent ("Cp_2Zr") promoted chemistry threw light on the clear transformation of allylic or propargylic ethers to allylic[2] or allenic zirconium species[3] and highly diastereoselective ring contraction of vinyl pyranoside or furanosides to optically pure polyfunctionalized carbocycles.[4] The "Cp_2Zr"-mediated ring contraction procedure was applied to the preparation of a key intermediate of carbocyclic oxetanocin analog,[5] which is expected to be used as an anti-HIV agent. We report herein highly effective construction of optically pure pyrrolidines and the enantioselective synthesis of the pyrrolizidine alkaloid "(-)-macronecine" through "Cp_2Zr"-mediated ring contraction of vinylmorpholines (Scheme 1).[6] Optically pure polyfunctionalized pyrrolidine is not only an important structural component of alkaloids, antibiotics, and glycosidase-inhibitory aza sugars[7] but also an important chiral source, chiral auxiliary, and chiral ligand for asymmetric synthesis.[8]

Vinylmorpholines **5** were prepared from α-amino acids as follows (Scheme 2). DIBAL (1.3 equiv) reduction of *N*-Boc-amino acid methyl ester (**1**) at –78 °C followed by the addition of vinylmagnesium bromide afforded *syn*-Boc-amino alcohol

Scheme 1



Scheme 2



derivative **2** as the major product (35–60%).[9] Deprotection of amino alcohol **2** to **3** with trifluoroacetic acid followed by *N*-alkylation with α-bromoacetaldehyde dimethyl acetal in the presence of *N*,*N*-diisopropylethylamine gave **4** (40–70% in two steps). The acid-mediated intramolecular acetalization of **4** (TsOH, benzene reflux) followed by *N*-benzylation provided vinylmorpholine derivative **5** as a mixture of four diastereomers (43–92% in two steps).

The results of "Cp_2Zr"-mediated ring contraction of vinylmorpholines **5** are summarized in Table 1. The reaction of vinylmorpholine **5a** (a mixture of diastereomers) in THF with "Cp_2Zr" prepared *in situ* from Cp_2ZrCl_2 with 2 equiv of *n*-butyllithium (at –78 °C to room temperature)[10] followed by addition of $BF_3{\cdot}OEt_2$ readily gave pyrrolidine derivative **6a** as a single isomer in good yield.[11] The reaction conditions were optimized with **5b** prepared from L-phenylalanine. In the absence of $BF_3{\cdot}OEt_2$, ring contraction in THF gave **6b** as a diastereomer mixture (91:9) in 66% yield (entry 2). The addition of $BF_3{\cdot}OEt_2$ before quenching of the reaction mixture with aqueous 5% NaOH increased the diastereoselectivity (95:5) and chemical yield (86%) of **6b** (entry 3). The use of toluene as a solvent gave less satisfactory results (entries 4 and 5). To confirm the effects of the stereochemical relationship of starting morpholines on the diastereoselectivity of the ring contraction reaction, the reaction of **5c**, a diastereomeric isomer of **5b**, was carried out. Although diastereoselectivity was slightly decreased, a product identical to **6b** was obtained (entry 6). Compound **5d** derived from D-phenylglycine was also converted to **6d** with excellent selectivity (entry 7). In all products, the *cis* relationship between newly formed vinyl and hydroxyl groups and the *trans* relationship between the vinyl group and substituent from the original chiral

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(2) (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295–1298. (b) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 7873–7876. (c) Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774–775.

(3) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769–3772.

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(6) A reactive intermediate of the present reaction could not be identified spectroscopically. However, the reaction mechanism shown in Scheme 1, which is similar to that in ref 4, may be assumed because of the same stereochemical outcome of the product as that in ref 4.

(7) (a) Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed: Academic Press: New York, 1986; Chapter 3, p 27. (b) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768. (c) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182–190. (d) Fellows, L. E.; Fleet, G. W. J. In *Natural Product Isolation*; Wagman, G. H., Cooper, R., Eds.; Elsevier: Amsterdam, 1988; Chapter 13, pp 540–560. (e) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555–4558 and referrences cited therein.

(8) (a) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165–246. (b) Tomioka, K. *Synthesis* **1990**, 541–549. (c) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935–952. (d) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York, 1985; Vol. 5. (e) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; John Wiley & Sons: New York, 1987.

(9) (a) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399–5401. (b) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947–5955. (c) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4307–4382.

(10) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.

(11) Typical experimental procedure: To a solution of $Cp_2Zr(nBu)_2$, prepared *in situ* by reaction of zirconocene dichloride (235 mg, 0.805 mmol) in THF (4 mL) with 2 equiv of *n*-butyllithium in hexane at –78 °C for 1 h, was added a solution of vinylmorpholine **5** (0.62 mmol) in THF (3 mL) at –78 °C, and the temperature was raised to ambient temperature. After stirring for 4 h, a solution of $BF_3{\cdot}OEt_2$ (1.24 mmol) in THF (2 mL) was added to the reaction mixture at 0 °C and stirring was continued for 1 h at the same temperature and for 1 h at ambient temperature. After addition of aqueous 5% NaOH, the mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

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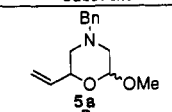
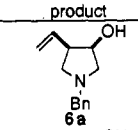
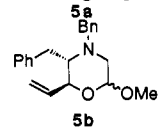
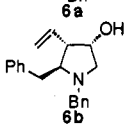
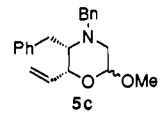
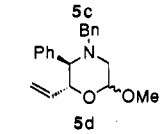
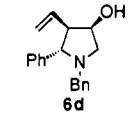
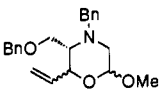
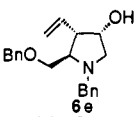
Table 1. "Cp_2Zr"-Mediated Ring Contraction Reaction of Vinylmorpholines

entry	substrate	product	diastereomer ratio[a]	yield (%)[b]
1	 **5a**	 **6a**	>98 : 2[c]	82[d]
2	 **5b**	 **6b**	91 : 9	66[e]
3	**5b**	**6b**	95 : 5	86[d]
4	**5b**	**6b**	94 : 6	70[f]
5	**5b**	**6b**	80 : 20	41[g]
6	 **5c**	**6b**	92 : 8	83[d]
7	 **5d**	 **6d**	>98 : 2[c]	82[d]
8	 **5e**	 **6e**	>98 : 2[c]	72[d]

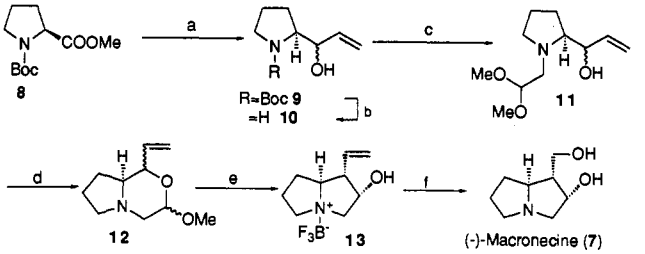
[a] The ratio was determined by 300-MHz ^{1}H NMR. [b] Isolated yield. [c] The minor isomer could not be detected with 300-MHz ^{1}H NMR. [d] Solvent: THF in the presence of BF_3·OEt_2. [e] Solvent: THF. [f] Solvent: toluene in the presence of BF_3·OEt_2. [g] Solvent: toluene.

center were observed (*vide infra*). It is evident from these results that the stereochemistry depends on the absolute configuration of the starting amino acid. It should thus be emphasized that *the stereochemistry of product 6, due to the present ring contraction, is not affected by diastereomers generated at any step to produce morpholines 5.* Reaction of a mixture of four diastereomers **5e** thus gave only **6e** (entry 8).[12]

The stereochemisty of products was determined by phase sensitive 2D-NOESY.[13] For confirmation of the stereochemical assignments, the structure of pyrrolidine derivative **6b** was finally defined by X-ray diffraction analysis.[13] The stereochemical relationship of the pyrrolidine obtained by the present reaction is the same as that of a ring contraction product of a vinyl carbohydrate derivative.[4]

The present method was used for the total synthesis of a pyrrolizidine alkaloid, (–)-macronecine (**7**),[14] an enantiomer of

Scheme 3



[a] (a) DIBAL (1.1 equiv, -78 °C/THF), then vinylmagnesium bromide, 83%; (b) TFA, 91%; (c) α-bromoacetaldehyde dimethyl acetal, *N,N*-diisopropylethylamine, CH_3CN reflux, 68%; (d) TsOH, benzene reflux, 58%; (e) "Cp2Zr"/THF, then BF3·OEt2, 57%; (f) (i) O3, -78 °C, then $NaBH_4$, (ii) 10% NaOH, 60%.

naturally occurring (+)-macronecine[15] (Scheme 3). DIBAL reduction of *N*-Boc-L-proline methyl ester (**8**) and subsequent addition of vinylmagnesium bromide gave amino alcohol **9** in 65% yield (diastereomer ratio, 5:1).[16] A mixture of diastereomers **9** was converted to morpholine derivative **12** (mixture of four diastereomers) as described above. Reaction of **12** with "Cp_2Zr" in the presence of BF_3·OEt_2 readily gave pyrrolizidine–BF_3 complex derivative **13** as a single isomer (57% yield). Treatment of **13** with O_3 in CH_2Cl_2 at –78 °C and reduction of $NaBH_4$ at ambient temperature followed by decomplexation of BF_3 complex by heating at 80 °C in aqueous 10% NaOH gave (–)-macronecine (**7**, 60%) as a crystalline compound: mp 124–127 °C, $[\alpha]_D$ –49.4° (*c* 0.96, EtOH). Spectroscopic and physical data except for the sign of the optical rotation were identical to those of natural[15] and resolved synthetic material.[14]

In conclusion, a method for the zirconium-mediated highly diastereoselective formation of enantiomerically pure pyrrolidine derivatives from easily available α-amino acids was developed. The stereochemistry of the polyfunctionalized optically pure pyrrolidine was shown to depend only on the absolute configuration of the starting amino acid. The enantioselective synthesis of (–)-macronecine through our methodology was carried out efficiently.

Supplementary Material Available: ^{1}H and ^{13}C NMR, specific rotation, IR, and elemental analysis of products [**6a,b,d,e**, **13**, (–)-macronecine (**7**)], NOE data of **6a,d,e**, and X-ray crystallographic data for **6b** (34 pages); listing of observed and calculated structure factors for **6b** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) In place of *N*-benzylmorpholine, *N*-methylmorpholine, *N*-Boc-morpholine, and *N*-H morpholine derivatives were examined. Although reaction of the *N*-methyl derivative with "Cp_2Zr" gave a ring contraction product in fair yield, a significant amount of undesired product possibly produced through elimination of the *N*-alkyl group from intermediary allylic zirconium species was formed. Reactions of the *N*-Boc and *N*-H derivatives gave a complex mixture.

(13) Details are described in supplementary material.

(14) Aasen, A. J.; Culvenor, C. C. J. *J. Org. Chem.* **1969**, *34*, 4143–4147.

(15) Danilova, A.; Utkin, L.; Massagetov, P. S. *J. Gen. Chem. USSR* **1955**, *25*, 797–799.

(16) Although separation of the diastereomers at this stage is unnecessary, the optical purity of each separated product **9** was determined by the MTPA method. The ^{1}H NMR spectrum of the MTPA ester of **9** showed no racemization at this stage.