ORGANIC
LETTERS

2007
Vol. 9, No. 13
2457−2460

Organocatalytic Synthesis of (2*S*,3*R*)-3-Hydroxy-3-methyl-proline (OHMePro), a Component of Polyoxypeptins, and Relatives Using OHMePro Itself as a Catalyst

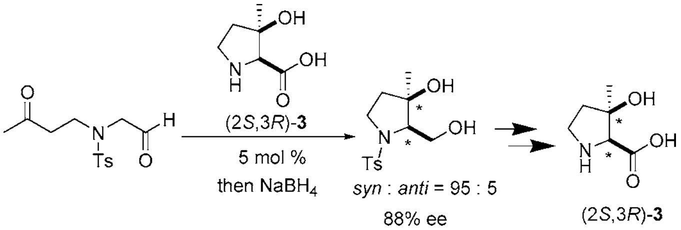
Yayoi Yoshitomi, Kazuishi Makino, and Yasumasa Hamada*

*Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku,
Chiba 263-8522, Japan*

hamada@p.chiba-u.ac.jp

Received March 12, 2007

ABSTRACT



"Organocatalytic Intramolecular Asymmetric Aldol Reactions"

An efficient synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (OHMePro), a component of polyoxypeptins, and relatives was achieved, in which an intramolecular asymmetric aldol reaction of the ketoaldehyde using OHMePro itself as an organocatalyst constitutes a key step.

Organocatalysis has become a rapidly expanding area in modern organic synthesis during the past few years, and many stereoselective reactions, asymmetric aldol reactions, asymmetric Mannich reactions, asymmetric aminations, and asymmetric oxidations, catalyzed by proline or its analogues have been reported to date.[1] In particular, organocatalytic asymmetric aldol reactions have attracted attention in view of the facile and highly stereoselective formation of the carbon−carbon bond and the efficient construction of the cyclic framework.[2] In the course of synthetic studies on polyoxypeptins as shown in Figure 1,[3−5] we have discovered that (2*S*,3*R*)-3-hydroxy-3-methylproline (OHMePro, **3**), one of the required components, serves as an efficient catalyst for intramolecular asymmetric aldol reaction leading to the

---

[1] (a) For recent reviews on asymmetric organocatalytic reactions, see: List, B. *Synlett* **2001**, 1675−1686. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748. (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495. (d) List, B. *Tetrahedron* **2002**, *58*, 5573−5590. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (f) Houk, K. N.; List, B., Eds. *Acc. Chem. Res.* **2004**, *37*, 487−631. (g) List, B.; Bolm, C., Eds. *Adv. Synth. Catal.* **2004**, *346*, 1007−1249. (h) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Bio-mimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (i) Kocovsky, P.; Malkov, A. V., Eds. *Tetrahedron* **2006**, *62*, 243−502.

[2] For examples of organocatalytic asymmetric intramolecular aldol reactions: (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (c) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213. (d) Agami, C.; Platzer, N.; Puchot, C.; Sevestre, H. *Tetrahedron* **1987**, *43*, 1091−1098. (e) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785−2788. (f) Clemente, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 11294−11302.

10.1021/ol0706004 CCC: $37.00

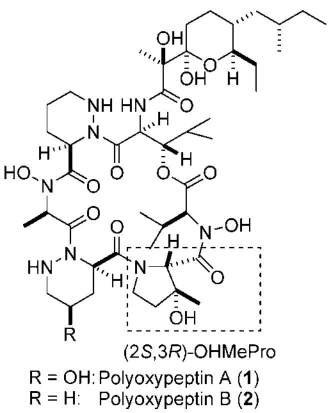
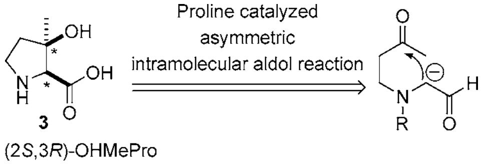


Figure 1. Structure of polyoxypeptins.

OHMePro precursor. We would like to report here an efficient synthesis of (2*S*,3*R*)-OHMePro and its relatives using OHMePro-catalyzed intramolecular asymmetric aldol reaction. We have already developed several methods for the synthesis of (2*S*,3*R*)-OHMePro,[5,6] including diastereoselective SmI_2-mediated cyclization,[5a] optical resolution of racemic *N*-tosyl-OHMePro-OH using (−)-cinchonidine,[5b] and tandem Michael−aldol reaction between the glycine (*R*)-binaphthyl ester derivative and methyl vinyl ketone.[5c] These methods, however, are based on diastereoselective synthesis or resolution and have the drawback of requiring more than 1 equiv of a chiral auxiliary. Thus, a catalytic asymmetric synthesis using a small amount of a chiral source would become an ideal method for preparation of (2*S*,3*R*)-OHMePro.

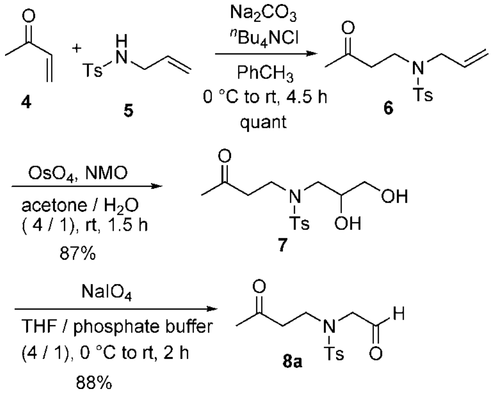
Our strategy is illustrated in Scheme 1, in which we envisaged that a proline-catalyzed intramolecular asymmetric aldol reaction of the ketoaldehyde should directly produce the (2*S*,3*R*)-OHMePro backbone with two continuous asymmetric carbons containing a quaternary stereogenic center. Several proline-catalyzed intramolecular asymmetric aldol reactions of dicarbonyl compounds have been reported.[2,7] To our knowledge, however, there is no report for cyclization leading to the pyrrolidine ring using intramolecular proline-catalyzed aldol reaction.[8]

Scheme 1. Synthetic Strategy



Ketoaldehyde **8a** was easily prepared with excellent purity by a three-step sequence of the usual manipulations in 77% overall yield (Scheme 2): (1) conjugate addition of *N*-tosylallylamide **5** to methyl vinyl ketone (**4**) in the presence of the quaternary ammonium salt, (2) dihydroxylation of the allylic function with osmium tetroxide-*N*-methylmorpholine *N*-oxide, and (3) oxidative cleavage of the resulting 1,2-diol with sodium periodate in THF−phosphate buffer (pH 7). The thus-obtained ketoaldehyde **8a** was prone to cyclize under the conditions of silica gel chromatographic purification but could be directly used in the next aldol reaction without any further purification. The yields and stereoselectivities were determined after in situ reduction of the crude aldol products with $NaBH_4$ (Table 1). Initially, the intramolecular aldol reaction of **8a** using (*S*)-proline (30 mol %) was investigated. The reaction in methylene chloride or acetonitrile proceeded smoothly to give a diastereomeric mixture of the products in good yield but with no enantioselectivity (entries 1 and 2). The syn and anti stereochemistry of the products has been determined according to our previous report.[5c] On the other hand, the use of THF as the solvent was found to enhance the enantioselectivity (49% ee, entry 3). From our interest in the potential of (2*S*,3*R*)-OHMePro (**3**) , our final product, as the chiral organocatalyst, we applied (2*S*,3*R*)-**3** to this intramolecular aldol reaction. To our delight, the reaction

Scheme 2. Synthesis of Substrate **8a**



---

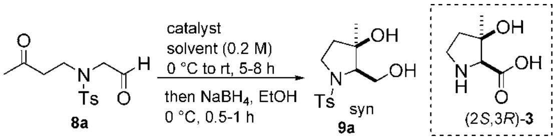
(3) Isolation and structure determination of polyoxypeptins: (a) Umezawa, K.; Nakazawa, K.; Uemura, T.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Kinoshita, N.; Hashizume, H.; Hamada, M.; Takeuchi, T.; Ohba, S. *Tetrahedron Lett.* **1998**, *39*, 1389−1392. (b) Umezawa, K.; Nakazawa, K.; Ikeda, Y.; Naganawa, H.; Kondo, S. *J. Org. Chem.* **1999**, *64*, 3034−3038.

(4) (a) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757−1762. (b) Makino, K.; Suzuki, T.; Awane, S.; Hara, O.; Hamada, Y. *Tetrahedron Lett.* **2002**, *43*, 9391−9395. (c) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882−884. (d) Henmi, Y.; Makino, K.; Yoshitomi, Y.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3477−3481. (e) Makino, K.; Henmi, Y.; Terasawa, M.; Hara, O.; Hamada, Y. *Tetrahedron Lett.* **2005**, *46*, 555−558. (f) Makino, K.; Jiang, H.; Suzuki, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1644−1649.

(5) Synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline by us: (a) Makino, K.; Kondoh, A.; Hamada, Y. *Tetrahedron Lett.* **2002**, *43*, 4695−4698. (b) Makino, K.; Suzuki, T.; Hamada, Y. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1649−1653. (c) Makino, K.; Nagata, E.; Hamada, Y. *Tetrahedron Lett.* **2005**, *46*, 8159−8162.

(6) Synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline by other groups: (a) Noguchi, Y.; Uchihiro, H.; Yamada, T.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 5253−5256. (b) Qin, D.-G.; Zha, H.-Y.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 1038−1040. (c) Shen, J.-W.; Qin, D.-G.; Zhang, H.-W.; Yao, Z.-J. *J. Org. Chem.* **2003**, *68*, 7479−7484. (d) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776−782. (e) Davis, F. A.; Ramachandar, T.; Liu, H. *Org. Lett.* **2004**, *6*, 3393−3395. (f) Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2243−2247. (g) Chen, Z.; Ye, T. *Synlett* **2005**, 2781−2785.

Table 1. Optimization of the Catalytic Asymmetric Intramolecular Aldol Reaction



8a **9a** (2*S*,3*R*)-**3**

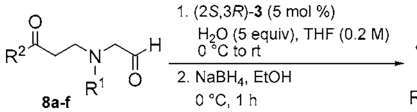
entry	catalyst (mol %)	solvent	H_2O	yield (%)^a	syn/anti^b	% ee^c
1	(*S*)-proline (30)	CH_2Cl_2	–	79	64:36	1
2	(*S*)-proline (30)	CH_3CN	–	59	67:33	4
3	(*S*)-proline (30)	THF	–	58	78:22	49
4	(2*S*,3*R*)-**3** (30)	THF	–	64	95:5	62
5	(2*S*,3*R*)-**3** (30)	THF	5 equiv	69	96:4	85
6	(2*S*,3*R*)-**3** (30)	THF	10 vol %	79	92:8	81
7	(2*S*,3*R*)-**3** (10)	THF	5 equiv	73	95:5	89
8	(2*S*,3*R*)-**3** (5)	THF	5 equiv	73	95:5	88

^{a} Isolated yield. ^{b} Determined by ^{1}H NMR. ^{c}Determined by HPLC analysis.

gave (2*R*,3*R*)-**9a** as a major stereoisomer in excellent yield, syn selectivity, and moderate enantioselectivity (64% yield, syn/anti = 95:5, 62% ee, entry 4). Interestingly, the thus-obtained (2*R*,3*R*)-**9a** had the same stereochemistry with the catalyst, which means that the reaction amplifies the final product, (2*S*,3*R*)-OHMePro, by the catalysis of (2*S*,3*R*)-HOMePro itself. Although the stereoselectivity of the reaction was still moderate, further enhancement of the stereoinduction was achieved when 5 equiv of water was added to the reaction mixture. The enantioselectivity was improved from 62% to 85% ee (entry 5). Further addition of water (10 vol %) had a slightly negative effect on the diastereo- and enantioselectivities (entry 6). The catalyst amount can be reduced from 30 to 5 mol % without any loss of the stereoselectivity or chemical yield, and even in the use of 5 mol % of (2*S*,3*R*)-OHMePro, high enantioselectivity was observed (entries 7 and 8).

Encouraged by these results, we further explored the scope of this aldol reaction under the same reaction conditions (Table 2). The *N*-tosyl (R^1 = Ts) group was the most suitable as the N-protective group in terms of diastereo- and enantioselectivity compared with the benzyloxycarbonyl (Cbz) and benzylsulfonyl ($BnSO_2$) groups (entries 1−3). The intramolecular aldol reaction of other alkyl ketones **8d** (R^2 = Et) and **8e** (R^2 = $(CH_2)_2CH(CH_3)_2$) also proceeded with good yields and stereoselectivities (entries 4 and 5). The introduction of an aryl group (**8f**: R^2 = Ph) instead of an alkyl group, however, decreased the yield and enantioselectivity (entry 6).

Table 2. Asymmetric Intramolecular Aldol Reaction Catalyzed by (2*S*,3*R*)-3-Hydroxy-3-methylproline (**3**)



8a-f **9a-f**

entry	8	R^1	R^2	time (h)	yield (%)^a	syn/anti^b	% ee^c
1	**8a**	Ts	$-CH_3$	5.5	73	95:5	88 (9)^d
2	**8b**	Cbz	$-CH_3$	48	49	89:11	80
3	**8c**	SO_2Bn	$-CH_3$	24	90	91:9	73
4	**8d**	Ts	$-CH_2CH_3$	24	74	90:10	80
5	**8e**	Ts	$-(CH_2)_2CH(CH_3)_2$	24	67	>99:1	76
6	**8f**	Ts	Ph	24	30	nd	30

^{a} Isolated yield. ^{b}Determined by ^{1}H NMR. ^{c}Determined by chiral HPLC. ^{d}% ee of the anti isomer.

A rational explanation for the syn selectivity of this unique reaction catalyzed by proline and OHMePro is difficult at the present. However, we believe that the reaction proceeds through the ordinary cyclic chairlike transition state as shown in Figure 2. The reason for the excellent selectivity of OHMePro might derive from the 3-hydroxy-assisted rigid bicyclic conformation, which might serve to enhance the stereoselectivities.

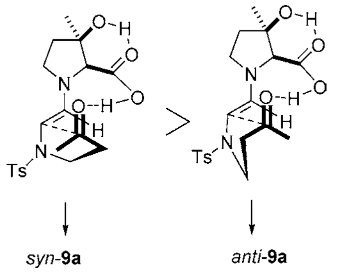


Figure 2. Plausible mechanism.

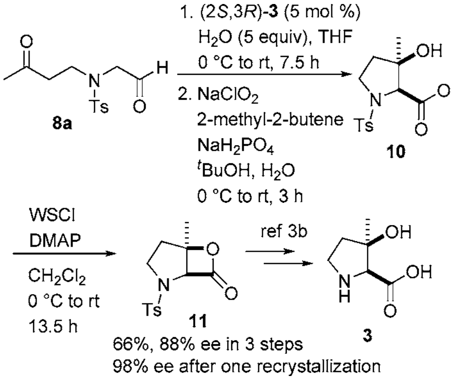
---

(7) For examples of organocatalytic asymmetric intermolecular aldol reactions: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. (d) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220−3221. (e) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (f) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F. *Tetrahedron Lett.* **2002**, *43*, 9591−9595. (g) Cordova, A.; Notz, W.; Barbas, C. F. *Chem. Commun*. **2002**, 3024−3025. (h) Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, Y. *Synlett* **2003**, *11*, 1655−1658. (i) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891−1896. (j) Cordova, A. *Tetrahedron Lett.* **2004**, *45*, 3949−3952. (k) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, M. *Tetrahedron Lett*. **2004**, *45*, 4353−4356. (l) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347−8350. (m) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. Ó. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983−1986. (n) Wang, G.-W.; Zhang, Z.; Dong, Y.-W. *Org. Process Res. Dev*. **2004**, *8*, 18−21. (o) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181−1184. (p) Wu, Y.-S.; Chen, Y.; Deng, D.-S.; Cai, J. *Synlett* **2005**, 1627−1629. (q) Sun, B.; Peng, L.; Chen, X.; Li, Y.; Li, Y.; Yamasaki, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1305−1307. (r) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210−1212. (s) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343−1345. (t) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734−735. (u) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron* **2006**, *62*, 311−316. (v) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317−328. (w) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329−337.

(8) For other examples of construction of a five-membered ring using proline-catalyzed reactions, see: (a) ref 2e. (b) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450−451. (c) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958−3960.

We next investigated the conversion to (2*S*,3*R*)-3-hydroxy-3-methylproline from the aldol product (Scheme 3). After the asymmetric intramolecular aldol reaction of **8a** using 5 mol % of (2*S*,3*R*)-**3** in THF (0.2 M) in the presence of water (5 equiv), the obtained crude product was oxidized to carboxylic acid **10** with sodium chlorite. The resulting acid **10** was converted to *β*-lactone **11** for the optical purification in 66% yield with 88% ee in three steps, which was recrystallized from ethyl acetate and *n*-hexane to provide optically enriched **11** with 98% ee. The final transformation of **11** to (2*S*,3*R*)-OHMePro (**3**) was achieved according to our previous report.[5b]

Scheme 3. Synthesis of (2*S*,3*R*)-OHMePro from **8a**



In conclusion, we have found that (2*S*,3*R*)-3-hydroxy-3-methylproline is an efficient organocatalyst for intramolecular asymmetric aldol reaction and have succeeded in an efficient synthesis of (2*S*,3*R*)-OHMePro with two continuous asymmetric carbons containing a quaternary stereogenic center using this reaction. This approach enables us to obtain large quantities of (2*S*,3*R*)-OHMePro required for synthesis of polyoxypeptins and elucidation of OHMePro-catalyzed organocatalysis and will also be useful for preparing a variety of enantiomerically enriched 3-substituted proline derivatives.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (17035015) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0706004