

Practical synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline, a constituent of papuamides, using a diastereoselective tandem Michael-aldol reaction

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Received 22 August 2005; revised 14 September 2005; accepted 20 September 2005

Available online 6 October 2005

Abstract—(2*S*,3*R*)-3-Hydroxy-3-methylproline, a constituent of cyclodepsipeptides polyoxypeptins A and B, was efficiently synthesized by lithium chloride-induced diastereoselective tandem Michael-aldol reaction using methyl vinyl ketone and *N*-1-naphthylsulfonylglycine (*R*)-binaphthyl ester and subsequent hydrolysis of the product in 39% overall yield and five steps.

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The naturally occurring (2*S*,3*R*)-3-hydroxy-3-methylproline (HOMePro) is found as a unique constituent of apoptosis-inducing cyclodepsipeptide polyoxypeptins A and B, novel 19-membered cyclic hexadepsipeptides, isolated from the culture broth of *Streptomyces* species by Umezawa and co-workers in 1998 (Fig. 1).¹ In connec-

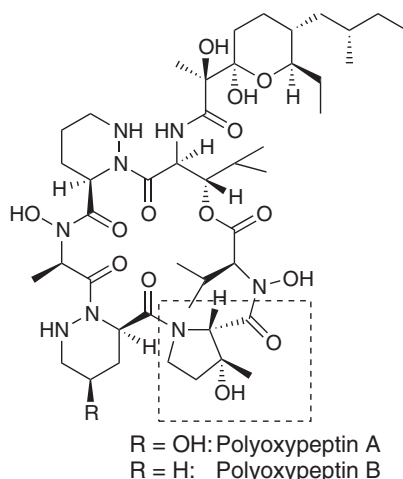
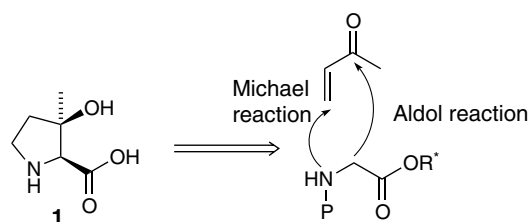


Figure 1. Structure of polyoxypeptins.

Keywords: (2*S*,3*R*)-3-Hydroxy-3-methylproline; Tandem Michael-aldol reaction; Polyoxypeptin A; Methyl vinyl ketone; Glycine (*R*)-binaphthyl ester.

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tion with our efforts to synthesize these cyclodepsipeptides and relatives,² we needed large quantities of the (2*S*,3*R*)-3-hydroxy-3-methylproline. Synthesis of the 3-hydroxy-3-methylproline has been already reported by several groups including us.^{2e,h,3} However, these methods require multi-steps and the overall yields are unsatisfactory in most cases. Thus, expedient synthesis of this unique component is still required. Recently, we have demonstrated that the racemic 3-hydroxy-3-methylproline is synthesized by the tandem Michael-aldol reaction^{2h,4,5} using methyl vinyl ketone and *N*-tosylglycine methyl ester in the presence of a base as shown in Scheme 1 and the resulting *N*-Ts-3-hydroxy-3-methylproline is resolved by use of (–)-cinchonidine. Incidentally, the tandem reaction to a diastereomeric mixture of HOMePro derivatives was originally investigated by two groups⁶ for pyrrole synthesis without stereochemical assignment. We describe here chiral auxiliary-mediated asymmetric synthesis of (2*S*,3*R*)-3-hydroxy-3-methyl proline by lithium chloride-induced diastereo-



Scheme 1.

selective tandem Michael-aldol reaction using chiral glycine esters as a key step.

Our synthetic plan is illustrated in Scheme 1, in which we envisaged that asymmetric synthesis using the chiral auxiliary in the ester function might be a practical solution for a large-scale synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline. Thus, we chose binaphthol as a chiral auxiliary.⁷ Binaphthyl monoester **2a** of *N*-tosylglycine was prepared by careful treatment of *N*-tosylglycyl chloride with (*S*)-binaphthol in the presence of pyridine at 0 °C.⁸ The diastereoselective tandem Michael-aldol reaction of **2a** was extensively investigated and is summarized in Table 1. The reaction in the presence of diazabicyclo[5.4.0]undecane (DBU) as a base in tetrahydrofuran stereorandomly proceeded to give four diastereomers (entry 1). So we examined additive effects. Addition of 1 equiv of lithium chloride (LiCl), however, impressively improved the diastereomeric ratio to 77:20:3:0 (entry 2).⁹ The stereostructure of the major isomer **3a** was unambiguously determined to be unnatural 2*R*,3*S* after conversion to the prolinol derivative **5**¹⁰ with lithium aluminum hydride by comparison with the authentic sample.^{2c} With this encouraging result in hand, we surveyed further additive effects of several metal salts. Most of the examined salts resulted in no reaction or had no positive effect for the diastereoselectivity. Calcium chloride was found to also affect the diastereoselectivity but to have no effect on the chemical yield (entry 5). From the view point of chemical yield we chose lithium chloride as the additive and next examined effects of the *N*-protecting group in the glycine derivative as shown in Table 2. The reaction was conducted in the presence of DBU (0.2 equiv) and lithium chloride (1 equiv) at –15 °C for 65 h. The *N*-1-naphthylsulfonylglycine (*S*)-binaphthyl ester (**2d**) was the most efficient in terms of diastereoselectivity and chemical yield to afford

the desired isomer in a ratio of 91:8:1:0 and in 71% yield (entry 4). The *N*-aromatic group in the *N*-sulfonamide proved to serve face-selectively in the intramolecular aldol condensation. Using the optimized conditions, we carried out synthesis of natural (2*S*,3*R*)-3-hydroxy-3-methylproline in a laboratory scale (20 mmol) as shown in Scheme 2. Thus, *N*-1-naphthylsulfonylglycine (**6**) was esterified with (*R*)-binaphthol by the acid chloride method in two steps and the thus-obtained chiral ester was subjected to the tandem Michael-aldol reaction under the conditions described above to afford (2*S*,3*R*,a*R*)-3-hydroxy-3-methylproline ester **3d** as a major product in 77% yield and the same diastereomeric ratio. The product (2*S*,3*R*,a*R*)-**3d** without purification was hydrolyzed with a mixture of concentrated hydrochloric acid–acetic acid–water (1.2:2.8:1) at 95 °C for 24 h. Purification of the crude product using ion-exchange resin furnished the (2*S*,3*R*)-3-hydroxy-3-methylproline with concomitant diastereomers. Pure **1** was obtained after conversion to the toluenesulfonic acid salt by crystallization from 2-propanol in 68% yield.¹¹ The overall yield of (2*S*,3*R*)-3-hydroxy-3-methylproline (**1**) as the toluenesulfonic acid salts from **6** was 39%.

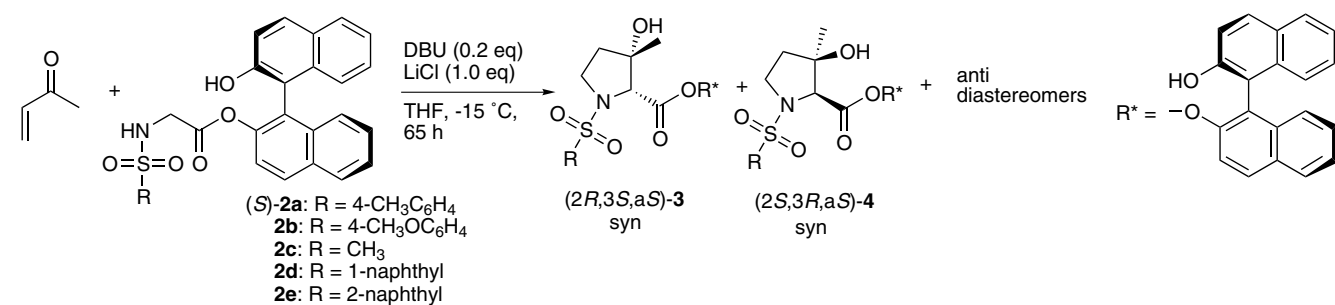
For elucidation of the reaction mechanism, we first examined whether the reaction proceeds under kinetic or thermodynamic control. Thus, a 98:2 mixture of (2*R*,3*S*,a*S*)-**3a** and (2*S*,3*R*,a*S*)-**4a** was treated with DBU (0.2 equiv) and lithium chloride (1 equiv) at –15 °C for 65 h and the recovered material showed no change in the diastereomeric ratio. Therefore, the reaction proved to be kinetic. From the experiments described above it is apparent that the diastereoselectivity is attributed to the presence of lithium chloride and the *N*-protecting group. Although the origin of this interesting lithium chloride-induced diastereoselectivity is not clear at present, lithium chloride seems to play an

Table 1.^a

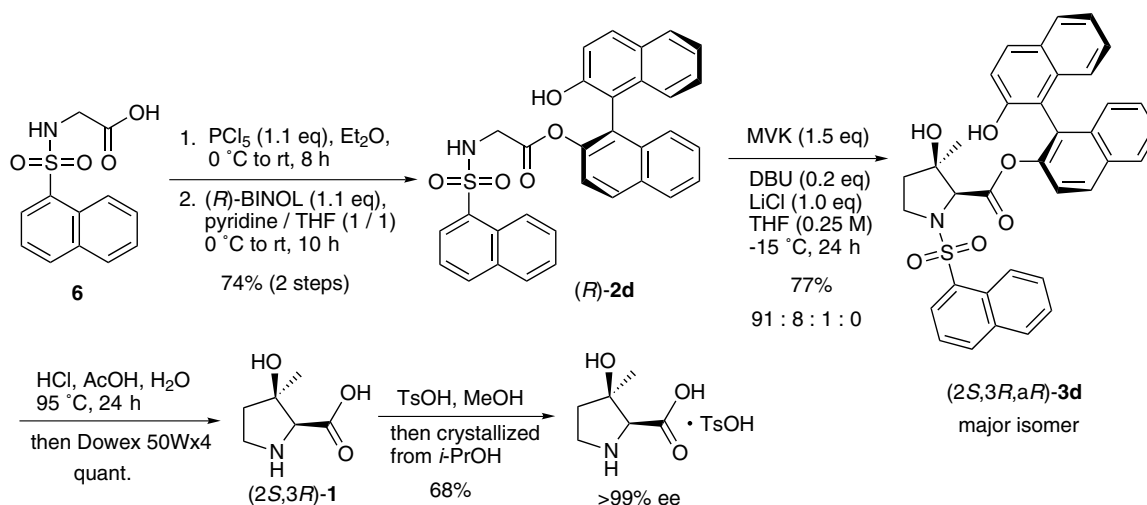
Entry	Additive	Temperature (°C)	Time (d)	Yield (%)	3a:4a	
					syn	anti
1	—	–71 to rt	1	18	23:30	30:17
2	LiCl	–71 to rt	1	44	77:20	3:0
3	NaCl	–15	>2	4	29:42	21:8
4	KCl	–15	>2	6	27:44	22:7
5	CaCl ₂	–15	>2	6	89:9	2:0

^a Addition of other metal salts such as MgCl₂, ZnCl₂, FeCl₃, LaCl₃·7H₂O, TiCl₄, and Ti(O-*i*Pr)₄ gave no Michael-aldol adduct.

Table 2.



Entry	R	Yield (%)	Ratio of diastereomers 3:4	
			<i>syn</i>	<i>anti</i>
1	4-CH ₃ C ₆ H ₄	56	84:16	0:0
2	4-CH ₃ OC ₆ H ₄	45	87:13	0:0
3	CH ₃	19	58:42	0:0
4	1-Naphthyl	71	91:8	1:0
5	2-Naphthyl	61	83:15	2:0

Scheme 2. Diastereoselective synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline.

important role in *Z*-selective formation of the glycine enolate with the *N*-sulfonamide function and *syn*-selective aldol reaction.

In conclusion, we have succeeded in efficient and practical asymmetric synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline in five steps and 39% overall yield using the lithium chloride-induced diastereoselective tandem Michael-aldol reaction. In this reaction, lithium chloride proved to play an important role in the diastereoselective aldol reaction. Further investigation directed toward total synthesis of polyoxypeptins is underway in this laboratory.

Acknowledgements

This work was supported by Grant-in-Aid for Scientific Research on Priority Areas 17035015 from The Ministry

of Education, Culture, Sports, Science and Technology (MEXT).

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9. The authentic mixture (53:44:3:0) was prepared by condensation of racemic *N*-Ts-3-hydroxy-3-methylproline (*syn:anti* = 95:5) with (*S*)-BINOL using *N,N'*-dicyclohexylcarbodiimide and *N,N*-dimethylaminopyridine in methylene chloride in 51% yield. Respective identification of the major two isomers as **3a** and **4a** by the ¹H NMR spectrum of the mixture determined both *syn*-stereochemistry.
10. (2*S*,3*S*)-Isomer: $[\alpha]_{\text{D}}^{23} +88$ (*c* 1.10, MeOH). The known (2*R*,3*R*)-*N*-Ts-3-hydroxy-3-methylprolinol derived from L-threonine: $[\alpha]_{\text{D}}^{23} -88.5$ (*c* 1.09, MeOH).^{2c}
11. (2*S*,3*R*)-3-Hydroxy-3-methylproline toluenesulfonic acid salts (>99% ee): mp 198–199 °C (2-propanol); $[\alpha]_{\text{D}}^{23} -9.7$ (*c* 0.53, H₂O). Anal. Calcd for C₁₃H₁₉NO₆S: C, 49.26; H, 6.03; N, 4.41. Found: C, 49.21; H, 5.98; N, 4.43.