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Synthetic studies on polyoxypeptins: stereoselective synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline using SmI_2-mediated cyclization

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Abstract—Stereoselective synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**), a component of polyoxypeptins, has been achieved by use of SmI_2-mediated diastereoselective cyclization reaction as a key step. © 2002 Elsevier Science Ltd. All rights reserved.

Polyoxypeptin A (**1**),[1] a novel 19-membered cyclic hexadepsipeptide antibiotic, was isolated from the culture broth of a *Streptomyces* strain together with polyoxypeptin B by Umezawa and co-workers in 1998 (Fig. 1). Polyoxypeptin A is known to induce apoptotic cell death against apoptosis-resistant human pancreatic adenocarcinoma AsPC-1 cells. The relative and absolute stereostructure of polyoxypeptin A was determined by X-ray crystallographic analysis and degradation studies. The cyclic hexadepsipeptide structure of polyoxypeptin A contains a novel (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**) and other non-proteogenic α-amino acids. The challenging structure in addition to the novel biological activity of polyoxypeptin A prompted us and others[2] to undertake a program directed toward its total synthesis. Herein we report the stereoselective synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline based on a SmI_2-mediated intramolecular reaction.[3] Recently, Kobayashi[2b] and Yao[2c] have independently reported the synthesis of **3** using palladium-catalyzed intramolecular *N*-allylation of alkenyloxirane, and Sharpless asymmetric dihydroxylation followed by regioselective opening of cyclic sulfate by sodium azide.

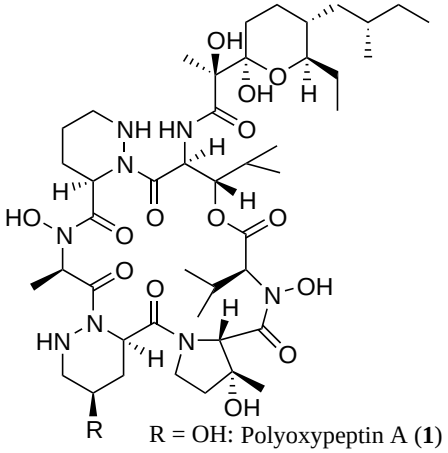

Figure 1. Structure of polyoxypeptins.

Our synthetic strategy for (2*S*,3*R*)-3-hydroxy-3-methylproline is outlined retrosynthetically in Scheme 1. The asymmetric quaternary center at C3 might be constructed by diastereoselective cyclization using SmI_2 between the carbonyl carbon and alkyl iodide functions in **4**, which could be readily derived from (2*S*,3*R*) threonine (**5**). Our synthesis was commenced with preparation of tosylamide **6** through a sequence of the usual manipulations in overall 81% and four steps: (1) *N*-tosylation, (2) esterification with iodomethane and potassium bicarbonate in dimethyl formamide, (3) reduction of the ester function with lithium borohydride in tetrahydrofuran and (4) protection of the resulting diol function with dimethoxypropane and toluenesulfonic acid. We first attempted direct introduction of a 2-iodoethyl group at the nitrogen atom of the sulfonamide. The reaction with diiodoethane in the presence of a base completely failed to produce **9** and resulted in recovery of the starting sulfonamide. Thus, we turned our attention to an indirect route through 5 steps. *N*-Allylation of **6** afforded the alkene **7** in 96% yield. Oxidative cleavage of olefin in **7** with OsO_4–

Keywords: (2*S*,3*R*)-3-hydroxy-3-methylproline; samarium iodide; Barbier-type reaction.

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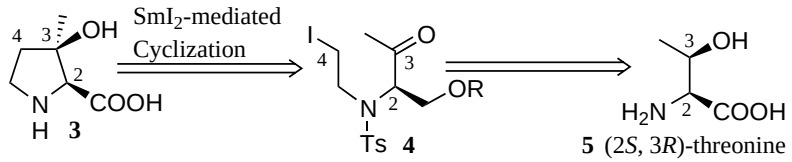
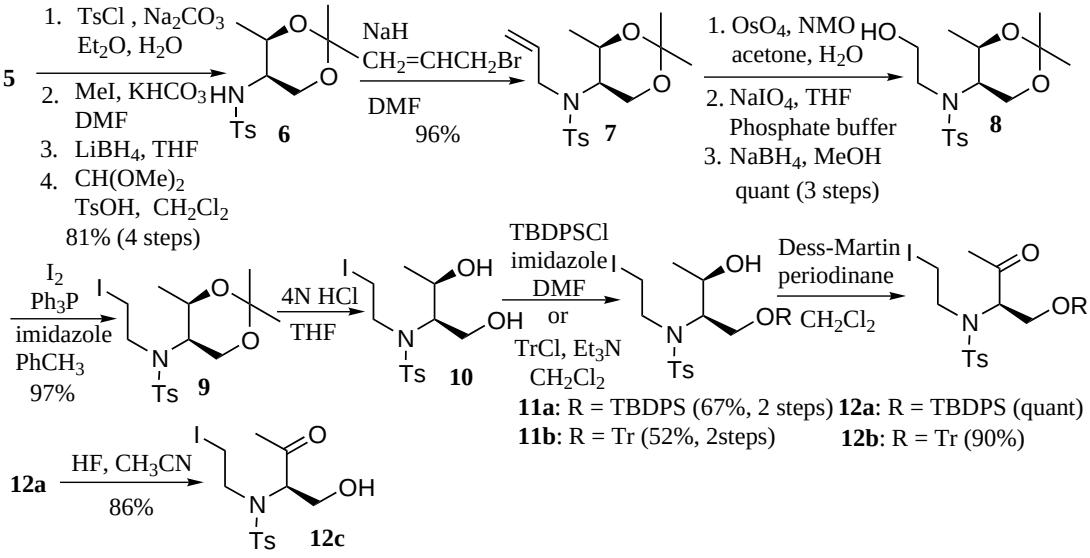


Scheme 1. Retrosynthetic analysis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**).

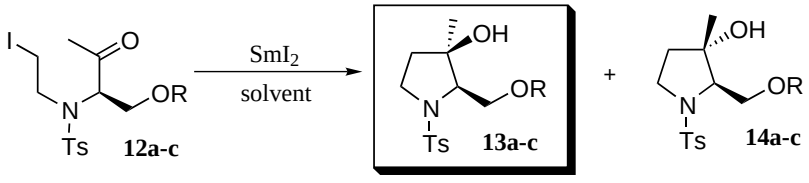
NMO followed by treatment of $NaIO_4$ and subsequent reduction of the aldehyde functionality with $NaBH_4$ gave the alcohol **8** in quantitative yield. Halogenation of the hydroxyl group of **8** with iodine and triphenylphosphine in the presence of imidazole provided the iodoalkane **9** in 97% yield. After acid-catalyzed deprotection of isopropylidene acetal of **9**, the selective protection of the primary alcohol of **10** as a *tert*-butyldiphenylsilyl (TBDPS) or trityl (Tr) ether (TBDPS ether **11a**: 67%, Tr ether **11b**: 52%) and subsequent oxidation of the secondary alcohol using Dess–Martin periodinane[4] furnished the iodoketone **12a** and **12b** in quantitative and 90% yield, respectively. Non-protected iodoketone **12c** was prepared by deprotection of TBDPS ether with aqueous hydrofluoric acid in 86% yield (Scheme 2).

With the three iodoketones in hand, we next examined cyclization reaction using SmI_2 as a key step in this synthesis. The results of this cyclization are summarized in Table 1. The ring closure of the TBDPS-protected iodoketone **12a** using SmI_2 in THF at −78°C gave no product, and the starting material was decomposed under conditions of increasing temperature (entry 1). In the presence of HMPA as a co-solvent (THF/HMPA = 10/1), the cyclization reaction proceeded smoothly at −78°C for 20 min to afford the undesired diastereomer as a major product (**13a**:**14a** = 13:87) in 76% yield (entry



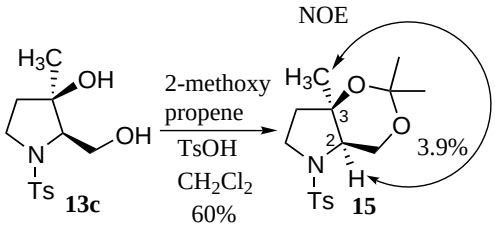
Scheme 2. Synthesis of the iodoketones **12**.

Table 1. Diastereoselective Barbier-type cyclization using SmI_2

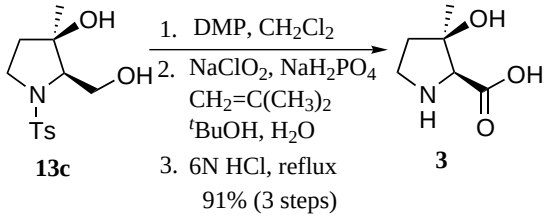


Entry	R	Solvent	Conditions	Yield	**13**:**14**
1	TBDPS	THF	−78°C to rt, 20 h	Complex mixture	
2	TBDPS	THF/HMPA (10:1)	−78°C, 20 min	76%	13:87[a]
3	Tr	THF/HMPA (10:1)	−78°C, 20 min	45%	31:69[a]
4	H	THF/HMPA (10:1)	−78 to −55°C, 1.5 h	75%	97:3[a,b]

[a] Determined by ^1H NMR analysis.
[b] Determined by HPLC analysis using Daicel Chiralcel OD-H.



Scheme 3. Determination of the stereochemistry at C3.



Scheme 4. Synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**).

2). An attempt using the iodoketone **12b** protected by the Tr group showed low diastereoselectivity (**13b**:**14b** = 31:69) in moderate yield. Finally, we continued our investigation in the hope that non-protected iodoketone **12c** could cyclize through a hydroxy-directed intermediate[3b,7] to give the desired diastereomer. Thus, **12c** was treated with SmI_2 in THF–HMPA (10:1) at −78 to −55°C for 1.5 h to exclusively afford the cyclized product **13c** with a ratio of 97:3 in 75% yield.[5] In addition, the mixture could be easily separated by silica gel chromatography to provide the diastereomerically pure product **13c**.[6] The stereochemistry of **13c** was verified by the ^{1}H-NOE difference studies of **15** after protection of the diol as an isopropylidene acetal (Scheme 3). As indicated by Matsuda and Shirahama,[3b,7] the observed diastereoselectivity can be rationalized by invoking a six-membered cyclic transition state, wherein Sm chelation between the primary hydroxyl function and the ketyl radical forms a six-membered chair, which directs the methyl group to the equatorial position, thus allowing the iodoalkyl function to be attacked exclusively at the axial side (Fig. 2).

The synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**) was completed by selective oxidation of primary alcohol to carboxylic acid by use of a stepwise procedure (1. Dess–Martin periodinane, CH_2Cl_2. 2. $NaClO_2$, NaH_2PO_4, ^{t}BuOH–H_2O) and subsequent deprotection of the tosyl group by treatment of 6N HCl under refluxing conditions in 91% yield without epimerization (Scheme 4). The synthetic material[8] was spectroscopically (^{1}H and ^{13}C NMR, HRMS) identical to the natural product, and also had a specific rotation, $[\alpha]_D^{27}$ −42.0 (*c* 1.30, H_2O), in good agreement with literature value ($[\alpha]_D^{18}$ −41 (*c* 0.4, H_2O),[1b] $[\alpha]_D^{26}$ −40.2 (*c* 0.42, H_2O),[2b] $[\alpha]_D^{25}$ −38.6 (*c* 0.40, H_2O)[2c]).

In conclusion, we have achieved the stereoselective synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**) using a highly diastereoselective intramolecular cyclization reaction using SmI_2 as a pivotal step. Further investigation directed towards the total synthesis of polyoxypeptin is under way in this laboratory.

Acknowledgements

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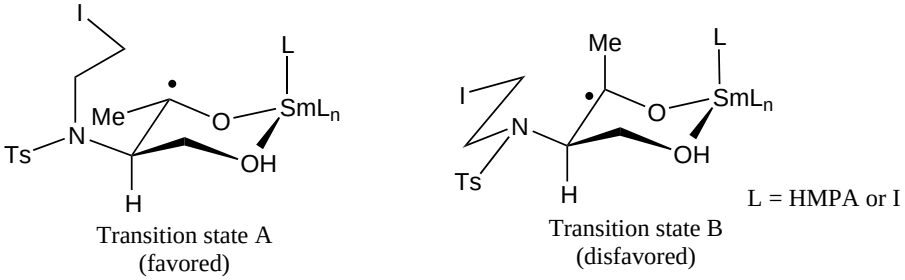

Figure 2. The plausible transition states in the intramolecular Barbier-type reaction promoted by samarium iodide(II) in the presence of HMPA.

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5. The ratio of diastereomers was determined by HPLC analysis using a Daicel Chiralcel OD-H and ^{n}hexane–^{i}PrOH (75:25, 0.6 mL/min) as an eluent (retention times **13c**: 9.9 min, 1**4c**: 8.0 min).
6. Data for **13c**: mp 100–101°C (AcOEt–^{n}hexane); $[\alpha]_D^{24}$ −83.8 (*c* 1.09, MeOH); IR (KBr) 3398, 2974, 1339, 1157, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.49 (dt, J=12.3, 6.5 Hz, 1H), 1.94 (dt, J=12.5, 7.4 Hz, 1H), 2.44 (s, 3H), 3.14 (t, J=4.0 Hz, 1H), 3.17 (dt, J=10.3, 7.3 Hz, 1H), 3.52 (brs, 1H), 3.59 (dt, J=10.3, 6.7 Hz, 1H), 3.94 (dd, J=12.1, 3.1 Hz, 1H), 4.07 (dd, J=12.1, 4.7 Hz, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.72 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.5, 39.1, 46.9, 62.6, 67.6, 78.9, 127.6, 129.8, 133.7, 144.0; HRMS (FAB) calcd for $C_{13}H_{20}NO_4S$: 286.1113 (M^++1). Found: 286.1112.
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8. Data for **3**; mp 198–201°C (H_2O–EtOH); $[\alpha]_D^{23}$ −42.0 (*c* 1.30, H_2O); IR (KBr) 3398, 3115, 2983, 1618, 1406 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 1.59 (s, 3H), 2.12–2.16 (m, 2H), 3.45 (ddd, J=11.0, 7.0, 4.6 Hz, 1H), 3.51–3.58 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 24.4, 39.9, 43.8, 70.1, 78.8, 171.1; HRMS (FAB) calcd for $C_6H_{12}NO_3$: 146.0817 (M^++1). Found: 146.0830 (M^++1).