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Synthetic study of polyoxypeptin: stereoselective synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline

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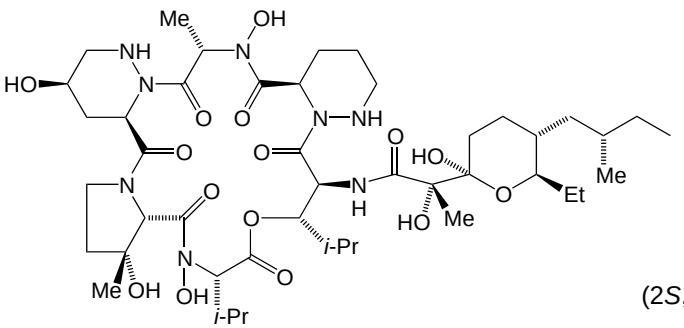
Abstract—The first synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline, which is a novel amino acid of polyoxypeptin, a potent inducer of apoptosis in human pancreatic carcinoma AsPC-1, was accomplished. The key feature of the synthesis is the palladium-catalyzed intramolecular *N*-allylation of alkenyloxirane to the pyrrolidine ring.

Polyoxypeptin A (**1**),[1] isolated by Umezawa et al. has attracted a great deal of attention due to its significant apoptosis-inducing activity in human pancreatic carcinoma AsPC-1. Structurally, polyoxypeptin is a unique hexadepsipeptide containing novel subunits such as the acyl side-chain moiety and (2*S*,3*R*)-3-hydroxy-3-methylproline (**2**) (Scheme 1). Therefore, polyoxypeptin is considered to be an interesting target molecule from a synthetic point of view as well as from medicinal interest.

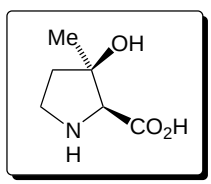
During the course of our investigation towards the total synthesis of polyoxypeptin, we recently reported the first stereoselective synthesis of the acyl side-chain segment.[2] Here we wish to report the first stereoselective synthesis of **2** based on palladium-catalyzed cyclization as the key-step.

Our strategy for the synthesis of the (2*S*,3*R*)-3-hydroxy-3-methylproline (**2**) is shown in Scheme 2. We were interested in the possibility of the palladium-catalyzed cyclization of alkenyloxylane **4**. There is no precedent for such pyrrolidine formation.[3] Alkenyloxirane **4**, in turn, might be prepared in an enantioselective manner from geraniol using asymmetric epoxidation.[4]

Alkenyloxirane **4**, a substrate for Pd-catalyzed cyclization, was synthesized from known aldehyde **6**, readily prepared from geraniol in three steps.[5] The aldehyde **6** was oxidized to carboxylic acid **7**, and the latter was



Polyoxypeptin A (1)



(2*S*, 3*R*)-3-Hydroxy-3-methylproline (**2**)

Scheme 1. The structure of polyoxypeptin A and (2*S*,3*R*)-3-hydroxy-3-methylproline.

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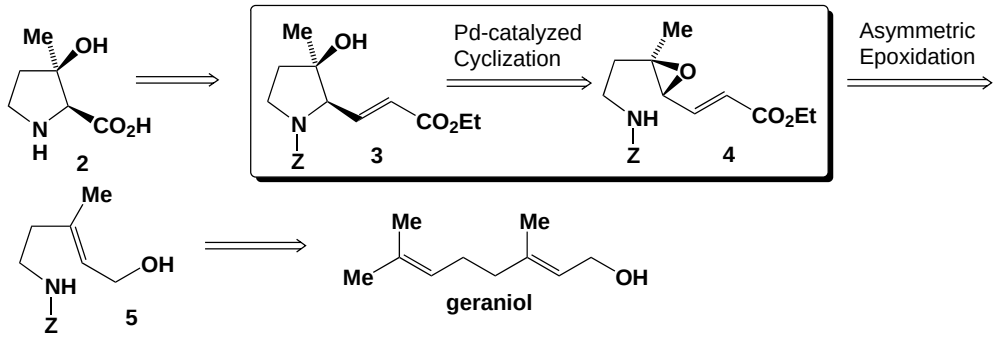
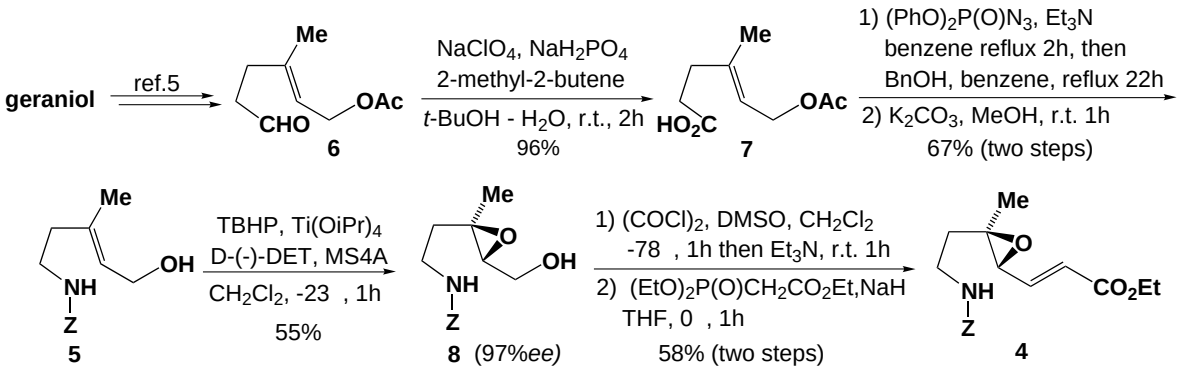


Scheme 2. Retrosynthetic analysis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**2**).

subjected to a modified Curtius rearrangement using $(PhO)_2P(O)N_3$[6] and benzyl alcohol, followed by deacetylation to afford an allylic alcohol **5** in 67% yield (two steps). The allylic alcohol **5** was next subjected to Sharpless asymmetric epoxidation[4] using D-(−)-tartrate to give epoxyalcohol **8** in 55% yield with 97% ee.[7] Epoxyalcohol **8** was oxidized by Swern oxidation, and the resulting aldehyde was reacted with triethyl phosphonoacetate to obtain (*E*)-alkenyloxirane **4** in 58% yield (two steps from **8**) in stereochemically pure form (Scheme 3). The key reaction, Pd-catalyzed cyclization of **4**, was next examined (Table 1).

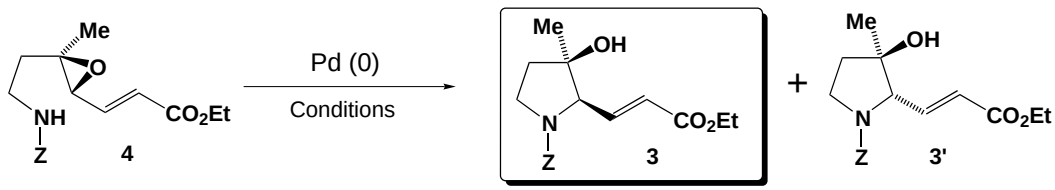
When **4** was treated with a catalytic amount (5 mol%) of $Pd(PPh_3)_4$ in THF at room temperature in the presence of NaH, no reaction occurred, and **4** was recovered in 60% yield. When the above reaction was carried out under reflux, a complex mixture of products was formed. On the other hand, cyclization proceeded smoothly in THF under reflux without a base affording a mixture of pyrrolidine derivative **3** and **3′** in total 74% yield (90:10).

The stereochemistry of the major isomer **3** was tentatively assigned as shown based on the mechanism (Fig.



Scheme 3. Synthesis of the alkenyloxirane **4**.

Table 1. Pd-catalyzed cyclization



Entry	Pd Cat.	Base	Conditions	Yield	Ratio **3**:**3′**
1	5 mol% $Pd(PPh_3)_4$	NaH	THF, rt, 24 h	N.R.[a]	–
2	5 mol% $Pd(PPh_3)_4$	NaH	THF, reflux, 5 h	Complex mixture	–
3	5 mol% $Pd(PPh_3)_4$	NaH	DMF, rt, 24 h	Complex mixture	–
4	**5 mol% $Pd(PPh_3)_4$**	**None**	**THF, reflux, 5 h**	**74%**	**90:10**
5	None	None	THF, reflux, 24 h	N.R.[b]	–

[a] **4** was recovered in 60% yield.
[b] **4** was recovered in quantitative yield.

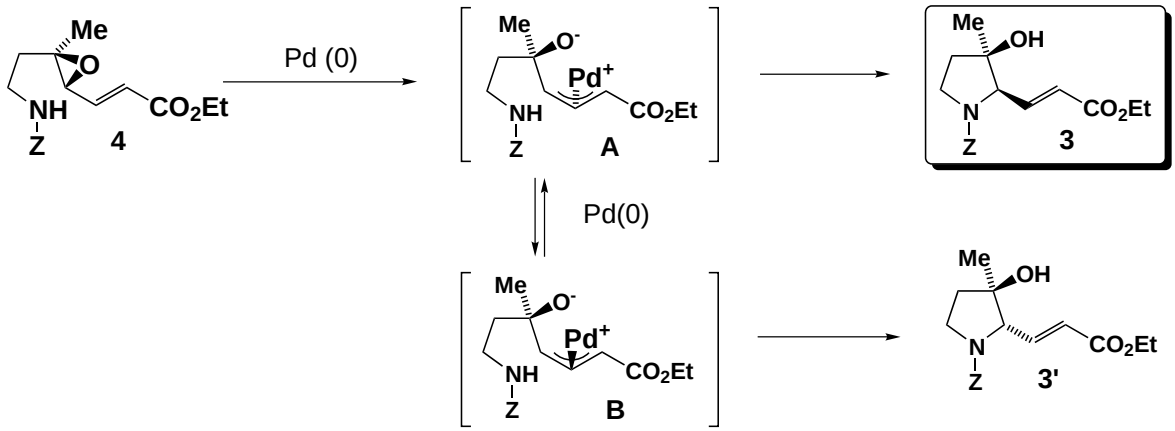
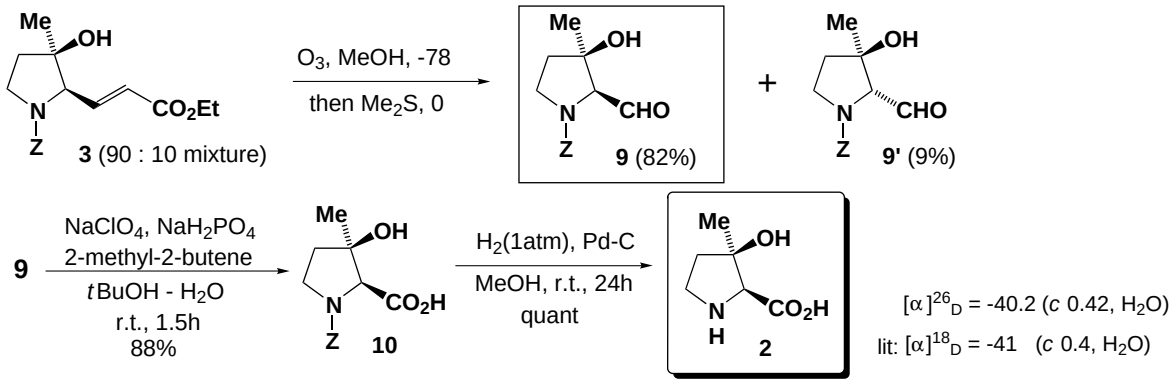


Figure 1. Mechanism of the Pd-catalyzed cyclization.



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

1), and was unambiguously confirmed by successful correlation to **2**. The isomeric **3′** might be derived from π-allyl palladium **B** formed by an intermolecular S_N2-type attack of Pd(0) to π-allyl palladium **A**. The formation of **3′** is also possible by the direct epoxide opening by 5-*endo* mode. However, this seems unlikely because no reaction occurred without $Pd(PPh_3)_4$ in refluxing THF.

Transformation of **3** into (2*S*,3*R*)-3-hydroxy-3-methylproline (**2**) is summarized in Scheme 4. Cleavage of the double bond using O_3 oxidation gave the desired aldehyde **9** in 82% yield. The C2-epimer **9′**, which was derived from **3′**, was separated from **9** by silica gel column chromatography (9% yield). The aldehyde **9** was then oxidized with $NaClO_2$, and finally deprotection of the benzyloxycarbonyl group with H_2–Pd/C completed the first synthesis of **2**.[8] Spectral data as well as the optical rotation value of the synthetic **2** were in good accordance with those of the natural (2*S*,3*R*)-3-hydroxy-3-methylproline reported by Umezawa's group.[1b]

In conclusion we were able to achieve the first synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline **2**. The key feature of the present synthesis is that the stereochemistry at C-2 and C-3 was controlled by Pd-catalyzed cyclization of alkenyloxirane without a base. Preparation of other segments and the coupling toward the total synthesis of polyoxypeptin are now in progress.

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7. The enantiomeric excess of **8** was determined after conversion to (+)-MTPA ester by chiral HPLC analysis [column, Chiralcel AD (4.6ϕ×250 mm); eluent, 20:1 *n*-hexane:EtOH mixture; flow rate, 0.8 ml/min; temperature 35°C; wavelength, 254 nm].
8. Data for **2**: mp 198–201°C. $[\alpha]_D^{26}$ −40.2 (*c* 0.42, H_2O). ^1H NMR (D_2O, 500 MHz): δ 1.60 (s, 3H), 2.13–2.16 (m, 2H), 3.45 (ddd, $J=11.6$, 7.0 and 4.6 Hz, 1H), 3.55 (ddd, $J=$ 11.6, 10.7 and 7.9 Hz, 1H), 3.86 (s, 1H). ^{13}C NMR (D_2O, 125 MHz): δ 171.21, 78.83, 70.09, 43.70, 39.84, 24.26. FAB-MS (pos.); m/z 146 $(M+H)^+$. FAB-HRMS (pos.) calcd for $C_6H_{12}NO_3$ $(M+H)^+$ 146.0817, found 146.0815.