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Synthetic study of polyoxypeptin: stereoselective synthesis of the acyl side-chain segment

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Abstract

The first synthesis of the acyl side-chain segment of polyoxypeptin, a potent inducer of apoptosis in human pancreatic carcinoma AsPC-1, was accomplished. The key feature of the present synthesis is the stereospecific palladium-catalyzed hydrogenolysis of (*Z*)-alkenyloxirane to *anti*-hydroxyalkenoate by an improved method. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: polyoxypeptin; Pd-catalyzed hydrogenolysis; alkenyl oxirane.

Polyoxypeptin (**1**) was isolated by Umezawa et al. as a potent inducer of apoptosis from a culture broth of *Streptomyces* sp. in 1998.[1] Polyoxypeptin has attracted a great deal of attention because it strongly induced apoptosis in human pancreatic carcinoma AsPC-1 with an IC_{50} of 80 ng/mL in 24 h.[1] The structure of polyoxypeptin was unambiguously established by X-ray crystallographic analysis to be a new 19-membered cyclic hexadepsipeptide[2] containing a novel acyl side-chain[3,4] and a hitherto unknown amino acid, (2*S*,3*R*)-3-hydroxy-3-methylproline. Therefore, polyoxypeptin is considered to be an interesting target molecule from a synthetic point of view[5] as well as from medicinal interest. We have investigated the total synthesis of polyoxypeptin, and we wish to report here the first synthesis of the acyl side-chain segment **2** (as a methyl ester) based on the Pd-catalyzed hydrogenolysis of 4,5-epoxy-2-alkenoate described in the preceding paper (Scheme 1).

Our retrosynthetic analysis of the acyl side-chain **2** is shown in Scheme 2. The α-hydroxy-β-ketoester moiety (C-1–C-3) including a quaternary center at C-2 might be most conveniently prepared by an asymmetric dihydroxylation of trisubstituted olefin **3** which, in turn, could be derived from unsaturated ester **4** by the conventional Wittig approach. Stereospecific Pd-catalyzed hydrogenolysis[6] of (*Z*)-epoxyalkenoate **5** into the requisite *anti*-isomer **4** is now possible by the modified Pd-catalyzed hydrogenolysis employing Ph_3P in DMF as described in the preceding paper. Finally, **5** could be obtained from allylic alcohol **6** by an asymmetric epoxidation and (*Z*)-selective Horner–Emmons reaction.

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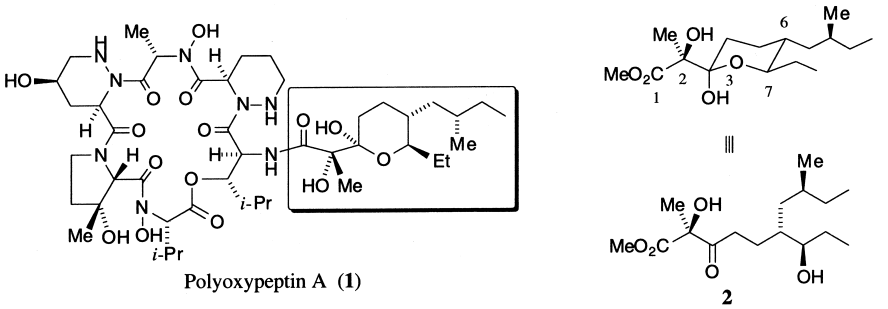
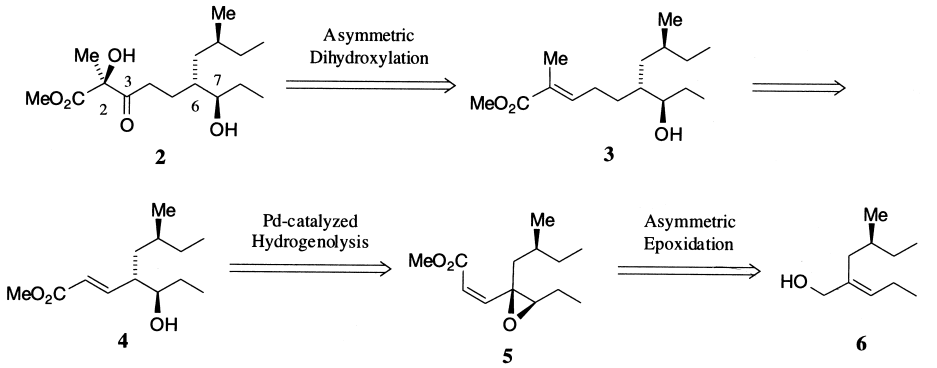
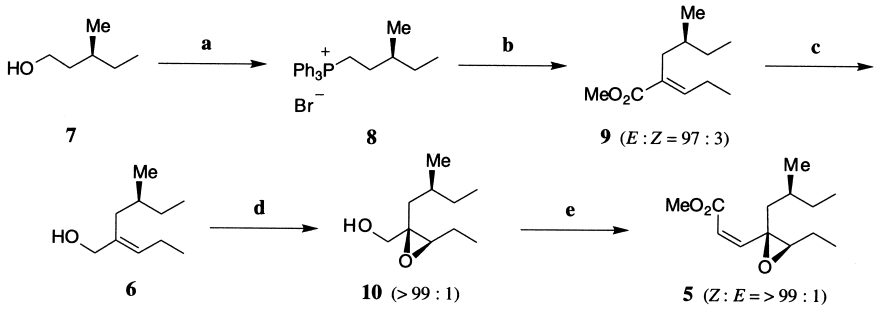


Scheme 1.



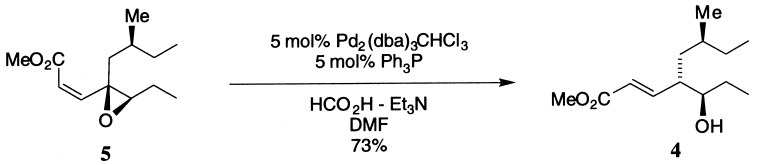
Scheme 2.

Epoxyalkenoate **5**, a substrate for Pd-catalyzed hydrogenolysis, was synthesized from a chiral alcohol **7**, readily prepared from L-(+)-isoleucine by a known procedure.[7] Thus, alcohol **7** was transformed into phosphonium bromide **8**, and its corresponding phosphonium ylide was treated with methyl chloroformate, followed by reaction with propionaldehyde to afford an (*E*)-alkenoate **9** in 40% yield based on chloroformate. After DIBAL reduction of unsaturated ester **9** (80% yield), the resulting allylic alcohol was subjected to Sharpless asymmetric epoxidation[8] using D-(−)-tartrate to give an epoxyalcohol **10** in 75% yield with a diastereomeric excess of over 99%. Epoxyalcohol **10** was oxidized by Swern oxidation, and the resulting aldehyde was reacted with (*Z*)-selective phosphonate[9] to obtain a (*Z*)-epoxyalkenoate **5** in 81% yield (two steps from **10**) in stereochemically pure form (Scheme 3).



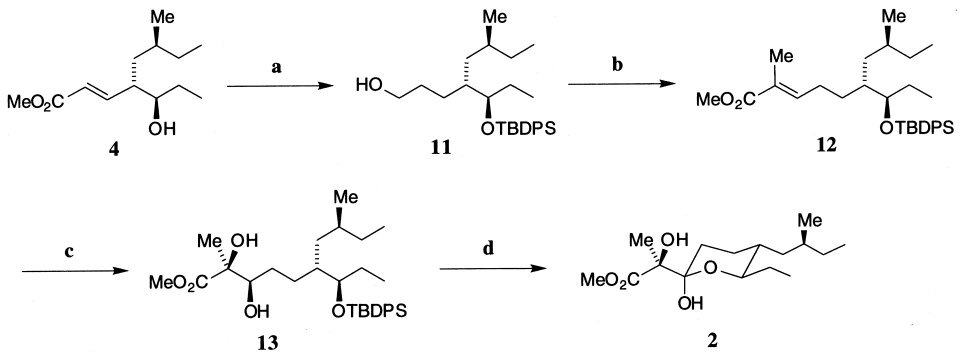
Scheme 3. *Reagents and conditions*: **a**: (i) 48% aq. HBr, H_2SO_4, reflux, 5 h, 73%. (ii) Ph_3P, 85°C, 4 days, 93%. **b**: (i) NaHMDS, THF, −78°C, 1.5 h. (ii) $ClCO_2Me$ (0.5 equiv.), −78°C to rt, 1 h. (iii) CH_3CH_2CHO, THF, rt, 5 days, 40% (based on $ClCO_2Me$). **c**: DIBAL, ether, 0°C, 1 h, 80%. **d**: TBHP, Ti(O-*i*-Pr)$_4$, D-(−)-DET, MS4A, CH_2Cl_2, −23°C, 1.5 h, 75%. **e**: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, rt, 1 h. (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −78°C, 1 h, 81% (two steps)

(*Z*)-Alkenyloxirane (**5**) was then subjected to hydrogenolysis employing the modified method described in the preceding paper. Thus, **5** was treated with 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 5 mol% Ph_3P, HCO_2H, and Et_3N in DMF at room temperature for 3 h to obtain the desired *anti*-isomer **4** in 73% yield with high stereospecificity (*anti*:*syn* = 96:4) (Scheme 4).



Scheme 4.

Transformation of **4** into the acyl side-chain segment **2** is summarized in Scheme 5. After protection of the hydroxyl group of **4** with TBDPS chloride, an unsaturated ester was reduced to a saturated alcohol **11** in high yield. The alcohol **11** was oxidized by Swern condition, and the resulting aldehyde was reacted with phosphorane to afford an unsaturated ester **12** as a single stereoisomer. Asymmetric dihydroxylation[10] of **12** was next carried out using AD-mix-β in the presence of $MeSO_2NH_2$ to obtain a diol **13**. The stereoselectivity of the present dihydroxylation was excellent, producing an almost single isomer.[11] The secondary hydroxyl group was then oxidized with $SO_3{\cdot}Py$, and finally deprotection of the silyl group with HF–CH_3CN[12] completed the synthesis of the acyl side-chain segment **2**.[13] The structure of **2** was confirmed by ^1H and ^{13}C NMR spectra which are in good accordance with those of natural polyoxypeptin.



Scheme 5. *Reagents and conditions*: **a**: (i) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 days, 83%. (ii) H_2, Pd–C, AcOEt, rt, 12 h, 98%. (iii) DIBAL, Et_2O, 0°C, 1 h, 97%. **b**: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, rt, 1 h. (ii) $Ph_3P{=}C(Me)CO_2Me$, benzene, reflux, 4 h, 68% (two steps). **c**: AD-mix-β, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0°C, 4 days, 54% (61% based on the recovered **12**). **d**: (i) $SO_3{\cdot}Py$, Et_3N, DMSO, rt, 3 h, 99%. (ii) HF, CH_3CN, rt, 12 h, 60%

In conclusion we were able to achieve the first synthesis of the acyl side-chain segment of polyoxypeptin. The stereochemistry at C-6 and C-7 was controlled by modified Shimizu–Tsuji reaction using Ph_3P in DMF, and the quaternary chiral center at C-2 was established by Sharpless asymmetric dihydroxylation. It is noteworthy that all reactions proceeded with high to excellent stereoselectivity. Preparation of other segments and the coupling toward the total synthesis of polyoxypeptin are now in progress.

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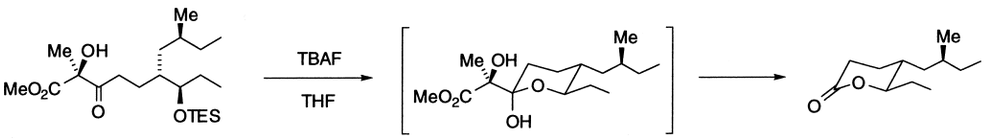
12. When desilylation was carried out using Bu_4NF in THF instead of HF–CH_3CN, retro-Claisen fragmentation occurred to give a substituted δ-lactone.



13. Mp 69–71°C. $[\alpha]_D^{23}$ +55° (*c* 0.36, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.79 (t, $J=7.3$ Hz, 3H), 0.81 (d, $J=6.4$ Hz, 3H), 0.86 (t, $J=7.3$ Hz, 3H), 0.97–1.07 (m, 2H), 1.14–1.30 (m, 4H), 1.33–1.41 (m, 2H), 1.42 (s, 3H), 1.62–1.70 (m, 2H), 1.75–1.79 (m, 1H), 1.84 (ddt, $J=13.1$, 4.3 and 2.7 Hz, 1H), 3.06 (s, 1H), 3.45 (dt, $J=9.5$ and 2.4 Hz, 1H), 3.81 (s, 3H), 4.23 (d, $J=2.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.63, 98.60, 78.93, 76.34, 52.77, 38.28, 36.87, 31.09, 30.95, 26.54, 25.36, 24.13, 19.50, 18.62, 11.57, 9.53. FAB-MS (pos.); *m*/*z* 325 $(M+Na)^+$. FAB-MS (neg.); *m*/*z* 301 $(M-H)^-$. FAB-HRMS (pos.) calcd for $C_{16}H_{30}NaO_5$ $(M+Na)^+$ 325.1984, found 325.1990.