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Synthesis of the acyl side chain segment of polyoxypeptins using regioselective ring-opening of chiral 2,3-epoxy alcohol

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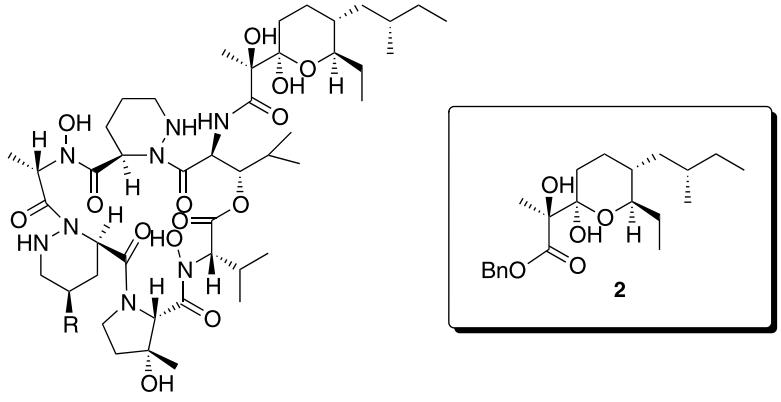
Abstract—The acyl side chain segment **2** contained in polyoxypeptins A (**1a**) and B (**1b**), apoptosis-inducing cyclodepsipeptides, was synthesized from chiral 2,3-epoxy alcohol (**6**), easily prepared by Sharpless asymmetric epoxidation, through a regioselective ring-opening reaction as the key step.

Polyoxypeptins A (**1a**) and B (**1b**) were isolated from the culture broth of *Streptomyces* species by Umezawa and co-workers.[1] They are known to exhibit potent apoptosis against human pancreatic adenocarcinoma AsPC-1 cells and have attracted attention as potential anticancer agents.[2] The structurally related cyclodepsipeptides have also become attractive targets for their unique structures and biological activities.[3] The relative and absolute stereostructure of polyoxypeptin A was determined by X-ray analysis and chemical degradation studies and revealed to bear a lipophilic acyl side chain segment and some unique amino acid residues, (2*S*,3*S*)-3-hydroxyleucine, (3*R*,5*R*)-5-hydroxypiperazic acid and (2*S*,3*R*)-3-hydroxy-3-methylproline ones. The intriguing biological activities coupled with the unique structure of polyoxypeptins prompted us to synthesize these novel cyclodepsipetides. As studies directed towards the total synthesis of the polyoxypeptins, we have already reported efficient synthesis of (2*S*,3*S*)-3-hydroxyleucine[2a] using dynamic kinetic resolution and (2*S*,3*R*)-3-hydroxy-3-methylproline using SmI_2-mediated cyclization.[2f] We describe here stereoselective synthesis of the acyl side chain segment **2** from chiral 2,3-epoxy alcohol **6**, easily prepared by Sharpless asymmetric epoxidation, through a regioselective ring-opening reaction. Kobayashi and Kurosu have indepen-



Polyoxypeptin A (**1a**) : R = OH
Polyoxypeptin B (**1b**) : R = H

Figure 1.

Keywords: polyoxypeptins; cyclodepsipeptide; regioselective ring-opening; 2,3-epoxy alcohol.

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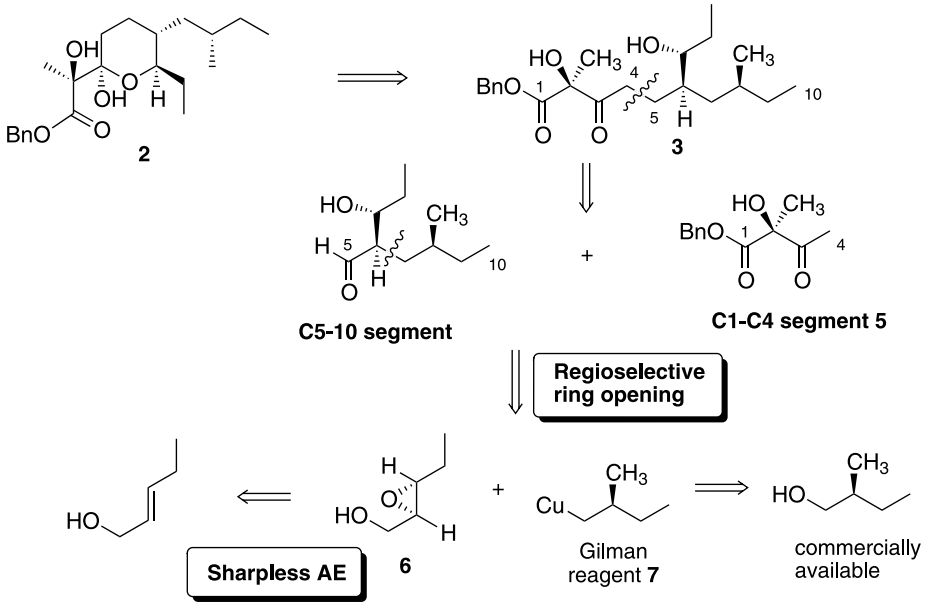
dently reported the stereoselective synthesis of the acyl side chain segment utilizing palladium-catalyzed hydrogenolysis and *anti*-aldol strategy, respectively (Fig. 1).[2d,e]

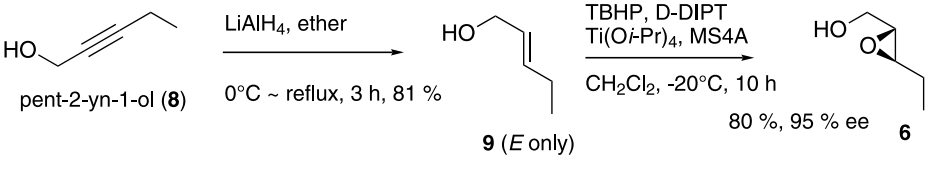
Our retrosynthetic analysis of the acyl side chain segment **2** is illustrated in Scheme 1. The segment **2** is equivalent to the open chain compound **3** which can be dissected into two segments, the C5–C10 segment and C1–C4 one. The latter segment **5** has already been synthesized by us and used in the synthesis of the acyl side chain segment of a structurally related cyclodepsipeptide, GE3.[3a] For the synthesis of the C5–C10 segment, we employed a regioselective ring-opening reaction of the chiral 2,3-epoxy alcohol **6** using the Gilman reagent **7**.

The required epoxide **6** was prepared from 2-pentyn-1-ol (**8**) by reduction of the triple bond with lithium aluminum hydride followed by Sharpless asymmetric epoxidation (Scheme 2).[4] Generally, this type of ring-opening reaction of 2,3-epoxy alcohols is known to be nonregioselective except the 2,3-epoxy alcohols branched at C4.[5,6] Especially, when the steric environment adjacent to an epoxide ring is similar to that of **6**, nucleophilic attack by an organocopper reagent competes at the C2 and C3 centers and gives equal amounts of 1,3-diol and 1,2-diol. We first investigated a model ring-opening reaction of the epoxide **6** using isobutylmagnesium bromide and copper salts because the preliminary experiment using lithium diisobutylcuprate, a homocuprate, was low regioselectivity and poor yield (entry 1). After extensive experiments, we found that the reaction was dependent on the solvent and the counter anion in the Grignard reagent and copper salts, as shown in Table 1. The reaction using the most effective combination, cuprous chloride (1 equiv.) and isobutylmagnesium bromide (4 equiv.) in ether, at −78°C for 15 h regioselectively proceeded and gave the 1,3-diol in 68% yield and a ratio of 96:4. Use of a catalytic amount of cuprous chloride was less effective than a stoichiometric amount in terms of yield and regioselectivity (entry 4). Next, using the optimized condition, ring-opening of the epoxide **6** with (*S*)-2-methylbutyl Grignard reagent derived from commercially available (*S*)-2-methylbutanol was investigated. Thus, the epoxide **6** was treated with a combination of (*S*)-2-methylbutylmagnesium bromide (**10**) and cuprous chloride in ether at −78°C for 6 h to afford the desired 1,3-diol **11** as a major product in 97% yield and a ratio of 95:5. Pure **11** was obtained in 63% yield after treatment of the mixture with sodium periodate for purification.[7] On the other hand, the corresponding iodide reagent, (*S*)-2-methylbutylmagnesium iodide and cuprous iodide, in ether yielded the products in a ratio of 67:33 (Scheme 3).

The 1,3-diol **11** was converted to aldehyde **15** in four steps as follows. Protection of the primary and sec-

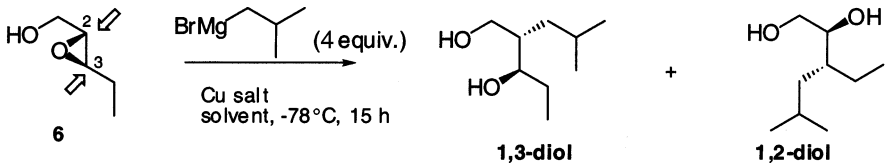


Scheme 1.



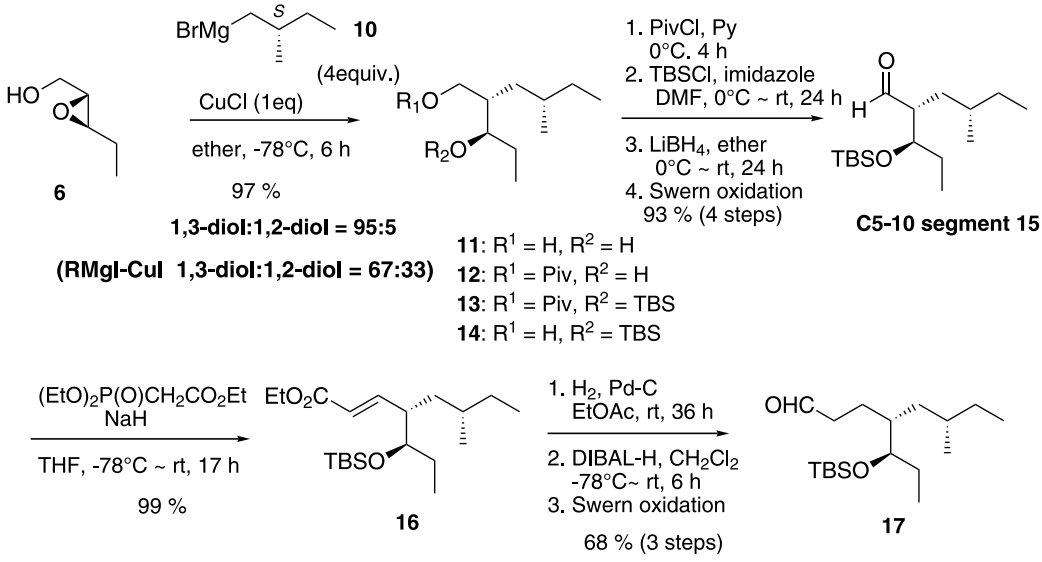
Scheme 2.

Table 1. Regioselective ring-opening reaction of chiral 2,3-epoxy alcohol



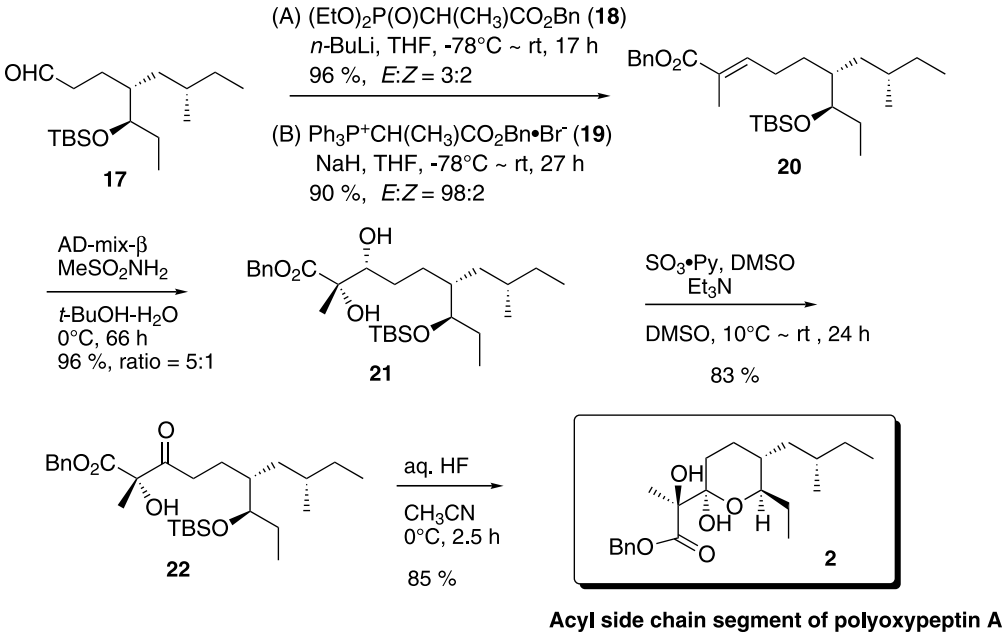
Entry	Solvent	Cu salts (1 equiv.)	Ratio of 1,3- and 1,2-diol[a]	Yield (%)
1	Ether	–[b]	73:27	20
2	Ether	–[c]	–	–[d]
3	Ether	CuCl	96:4	68
4	Ether	CuCl (0.2 equiv.)	93:7	58
5	Ether	CuBr	94:6	66
6	Ether	CuI	91:9	41
7	Ether	CuCN	87:13	52
8	THF	CuCl	91:9	75
9	DME	CuCl	84:16	76

[a] Determined by GLC.
[b] Lithium diisobutylcuprate was used.
[c] No copper salt.
[d] No reaction was observed.



Scheme 3.

ondary alcohols with pivaloyl and *tert*-butyldimethylsilyl groups, respectively, gave ester **13** in excellent yield. Removal of the pivaloyl group from **13** with lithium borohydride yielded alcohol **14**, which was oxidized under Swern oxidation to produce the C5–C10 segment **15**. Coupling of the thus obtained aldehyde **15** was first attempted with the C1–C4 segment **5**. The reaction with the lithium enolate (1.1 equiv.) prepared from **5** at $-78\sim0$°C for 7 h, however, failed probably due to the steric bulkiness of the aldehyde **15** which was recovered without epimerization. The alkylation of the C1–C4 segment **5** using the corresponding iodide reagent derived from **15** caused complete decomposition of the iodide. Therefore, we were forced to change the route to a stepwise elongation approach. The aldehyde **15** was homologated by Horner–Emmons olefination to produce α,β-unsaturated ester **16**, which was converted to aldehyde **17** by hydrogenation of the double bond, reduction of the ester, and Swern oxidation of the resulting alcohol in 68% yield. The reaction of **17** using the phosphonate reagent **18** (method A) afforded α,β-unsaturated ester **20** in 96% yield but nonstereoselectively. Fortunately, the phosphorane reagent generated from phosphonium salt **19** by treatment with sodium hydride in THF (method B) produced **20** in 90% yield and an E/Z ratio of 98:2. After separation of the undesired isomer by column chromatography, the (*E*)-α,β-unsaturated ester was asymmetrically dihydroxylated with AD-mix-β[8] in the presence of methanesulfonamide to afford dihydroxy ester **21** in 96% yield and a ratio of 5:1. The undesired isomer was found to be separated in a later step. Oxidation of the



Scheme 4.

dihydroxy ester **21** by the Parikh–Doering method[9] followed by acid treatment of the resulting keto ester **22** with aqueous hydrofluoric acid in acetonitrile furnished the acyl side chain segment **2** of polyoxypeptins as a nice crystalline in 70% yield (Scheme 4). The C-2 epimer derived from the AD-mix-β dihydroxylation was removed by simple recrystallization. The structure of **2** was confirmed by comparison of the spectral values of natural polyoxypeptin A[10] and the synthetic acyl side chain.[2d,e] Incidentally, the route from **16** was similar to the reported one[2d] except the protecting groups and the efficiency.

In conclusion, we have achieved the stereoselective synthesis of the acyl side chain segment **2** of polyoxypeptins. In this route, we have demonstrated the highly regioselective C-2 ring-opening reaction of 2,3-epoxy alcohol **6**, derived from Sharpless asymmetric epoxidation, by carbon nucleophiles. Further investigation directed towards the total synthesis of polyoxypeptins is under way.

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7. Procedure for **11**: To a stirred suspension of cuprous chloride (99.0 mg, 1.00 mmol) and **6** (103 mg, 1.00 mmol) in ether (5 mL) at −78°C was added dropwise (*S*)-2-methylbutylmagnesium bromide (5.00 mL, 4.00 mmol) over 5 min and the mixture was stirred at −78°C for 1 day. After quenching with saturated aqueous ammonium chloride (50 mL), the resulting mixture was vigorously stirred for 1 day. The mixture was extracted with ethyl acetate (20 mL×3). The organic extracts were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give a mixture of 1,3-diol and 1,2-diol (170 mg, 97%) as a slightly yellow oil in a ratio of 95:5. For removal of the unwanted 1,2-diol, the product was dissolved in methanol (10 mL) and water (2 mL) and treated with sodium periodate (200 mg, 0.935 mmol) at 0°C. After stirring at 0°C for 1 day, the reaction mixture was quenched with saturated aqueous sodium sulfite and the volatiles were removed in vacuo. The residue was extracted with ethyl acetate (20 mL×3). The organic extracts were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel chromatography (*n*-hexane:ethyl acetate = 1:1) to give **11** (110 mg, 63%) as a colorless oil: $[\alpha]_D^{24} = +47.69$ (*c* 0.84, $CHCl_3$); IR (neat, cm^{-1}) 3363, 2961, 2929, 2876, 1654, 1462; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, $J = 6.4$ Hz, CH_3), 0.88 (t, 3H, $J = 7.2$ Hz, CH_3), 0.98 (t, 3H, $J = 7.2$ Hz, CH_3), 1.02–1.73 (m, 8H, CH, CH_2), 2.38 (bs, 1H, OH), 2.71 (bs, 1H, OH), 3.50–3.59 (m, 1H, CH), 3.62 (dd, 1H, $J = 10.0$, 6.4 Hz, CH_2), 3.91 (d, 1H, $J = 11.2$ Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 11.4, 19.0, 28.3, 30.3, 31.9, 35.5, 41.4, 64.1, 78.2; HRMS (FAB) calcd for $C_{10}H_{22}O_2$ (M+H) 175.1620, found: 175.1650.

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10. **2**: mp 67–68°C; $[\alpha]_D^{23} = +80.5$ (*c* 0.32, $CHCl_3$); IR (neat, cm^{-1}) 3533, 3409, 2958, 2910, 2873, 1741, 1454; ^1H NMR (600 MHz, $CDCl_3$) δ 0.75 (t, $J = 7.4$ Hz, 3H, CH_3), 0.80 (d, $J = 6.3$ Hz, 3H, CH_3), 0.86 (t, $J = 7.4$ Hz, 3H, CH_3), 0.94–1.07 (m, 2H, CH_2), 1.12–1.31 (m, 4H, CH, CH_2), 1.32–1.41 (m, 2H, CH_2), 1.43 (d, $J = 0.8$ Hz, 3H, CH_3), 1.55–1.63 (m, 1H, CH), 1.68 (ddd, $J = 13.2$, 4.1, 3.0 Hz, 1H, CH), 1.76 (ddd, $J = 12.9$, 7.4, 3.8 Hz, 1H, CH), 1.84 (ddt, $J = 13.2$, 4.4, 2.5 Hz, 1H, CH), 3.09 (s, 1H, OH), 3.45 (ddd, $J = 10.2$, 8.4, 2.4 Hz, 1H, CH), 4.18 (d, $J = 3.0$ Hz, 1H, OH), 5.22 (s, 2H, CH_2), 7.31–7.39 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 11.6, 18.6, 19.5, 24.1, 25.2, 26.6, 31.0, 31.0, 36.5, 38.2, 67.7, 76.2, 78.9, 98.7, 128.4, 128.6, 128.7, 134.9, 175.9; HRMS (FAB) calcd for $C_{22}H_{34}NaO_5$ (M+Na) 401.2304, found: 401.2309. Anal. calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.88; H, 8.73%.