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An efficient enantioselective synthesis of the acyl side chain of polyoxypeptins

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Abstract—An enantioselective synthesis of the acyl side-chain **3** of polyoxypeptins **1** and **2** was achieved by the Sharpless AE, with subsequent regioselective opening of the epoxyalcohol using a Grignard reagent in the presence of CuI, and an aldol condensation using Seebach's ester. The method reported has the advantage of a concise route and excellent enantiomeric purity, as well as starting from readily available chemical substrates and the use of inexpensive reagents.

Nature is still the major resource of new biologically active and diverse chemical agents, which are contributing greatly to the modern drug discovery and related medical sciences. In 1998, two new cyclic hexadepsipeptides belonging to the azinothricin/A83586C/L-156,602 family[1] were isolated from fermentation broths of *Streptomyces* MK 498-98F14 by Umezawa and coworkers.[2] They named these compounds polyoxypeptins A (**1**) and B (**2**), respectively (Fig. 1). Both were believed to be potent inducers of apoptosis in human pancreatic adenocarcinoma AsPC-1 cells, an apoptosis-resistant human solid tumor cell line.[3] The depsipeptins contain a novel (2*S*,3*R*)-3-hydroxy-3-methylproline (3-OH MePro),[4] a complex acyl side chain, and several other non-proteinogenic amino acids that include (3*R*)-piperazic acid[5] and (3*R*,5*R*)-5-hydroxypiperazic acid.[6] Due to their unique structures and the interesting biological properties of the polyoxypeptin/L-156,602/A83586C/GE3 class, a significant effort has been directed towards their chemical synthesis.[4,7–10] Recently, Kobayashi[10a] and Kurosu[10b] reported the stereoselective synthesis of the acyl chain using a stereospecific Pd-catalyzed hydrogenolysis of a (*Z*)-alkenyloxirane, and a diastereoselective *anti*-aldol reaction as the key steps. As a part of our recent progress on this target,[4b] we wish to report a new short and efficient synthetic route towards the acyl side chain of polyoxypeptins with excellent stereochemical control.

The strategy for accessing the acyl chain is outlined retrosynthetically in Figure 2. The structure of the acyl chain **3** is very similar to that of antibiotic L-156,602,[1c]

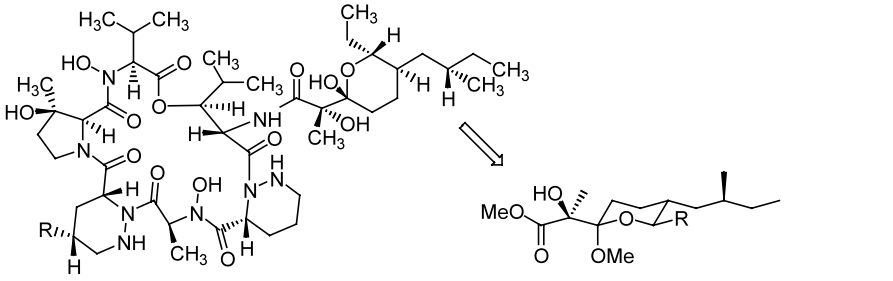

Figure 1. Chemical structures of polyoxypeptin A and B.

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the only difference between them being the substitution status of the tetrahydropyran ring (Fig. 1, R = Et instead of Me in L-156602). Caldwell et al. reported[7b] the first synthesis of the side chain **3A**, using a reaction between a lactone and Seebach's ester[12] **4** in the total synthesis of L-156602. To date, it is still the most efficient established means of producing the tertiary hydroxyl stereogenic center of these side chains. In our synthesis, this disconnection leads to Seebach's ester **4** and the lactone **5**.[11] The lactone **5** could be conveniently prepared from the linear α,β-unsaturated ester **6** by catalytic hydrogenation. Further retrosynthetic analysis of this intermediate reveals that the precursor aldehyde may be prepared by a regioselective opening of epoxyalcohol **7** using a Grignard reagent and subsequent oxidation. Finally, the epoxyalcohol **7** could be readily derived from *trans*-2-pentenol **8**, a commercially available chemical, by a Sharpless AE reaction.[13] Based on this strategy, all the stereochemistry in this molecule should be highly controlled. The details of this successful synthetic route for the acyl chain are outlined in Schemes 1 and 2.

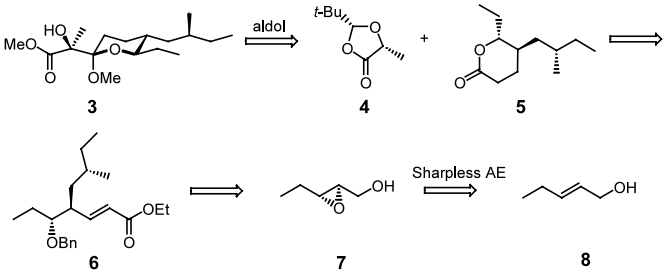
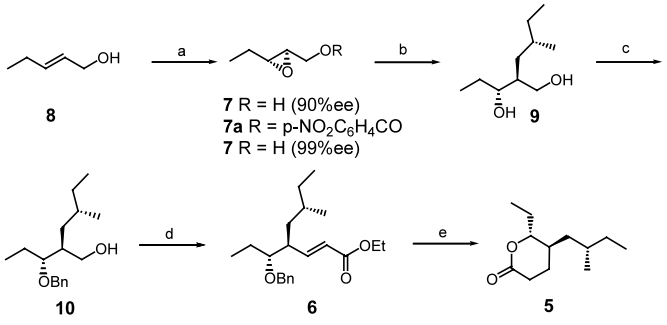
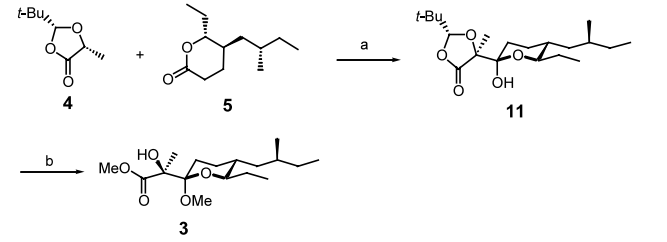


Figure 2. Retrosynthetic analysis of the side chain **3**.



Scheme 1. *Reagents and conditions*: (a) i. TBHP, $Ti(OiPr)_4$, D-(−)-DET, 3 Å MS, CH_2Cl_2, −25°C; (ii) pyridine, *p*-nitrobenzoyl chloride, CH_2Cl_2, 0°C; recrystallization, >99% ee (by HPLC), iii. 1N NaOH, MeOH/H_2O (1:1), 65% from **8**; (b) (2*S*)-methylbutyl-1-magnesium bromide, CuI, THF, −30°C, 8 h, 60%; (c) i. $PhCH(OMe)_2$, CSA, CH_2Cl_2, ii. DIBAL-H in cyclohexane, 0°C to rt, 95%; (d) i. $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, rt, ii. $(EtO)_2P(O)(CH_2COOEt)$, NaH, THF, 0°C to rt, 82%; (e) i. 20% $Pd(OH)_2/C$, MeOH, ii. 6N HCl, SiO_2, 96%.

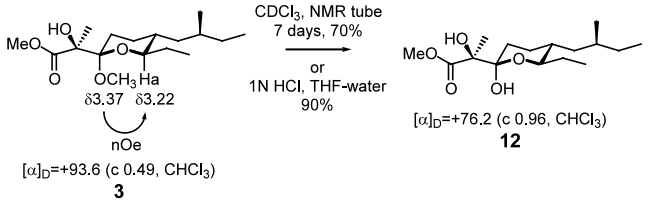


Scheme 2. *Reagents and conditions*: (a) LDA, −78°C, then **5**, −30°C, 8 h, 76%; (b) i. AcCl, MeOH, 0°C to rt, ii. NaOMe, MeOH, rt, 2 days, 70%.

Firstly, Sharpless asymmetric epoxidation[13] of *trans*-2-pentenol **8** using diethyl *D*-(−)-tartrate yielded the crude epoxyalcohol **7** (ca. 90% ee, 90% yield), which was further purified as its *p*-nitrobenzoate derivative **7a**[14] in up to >99% ee (determined by HPLC analysis) by a single recrystallization. Alkaline hydrolysis of the *p*-nitrobenzoate afforded pure **7** (>99% ee) in 65% overall yield based on **8**. When diisopropyl D-(−)-tartrate was used as the chiral ligand in the first step, a lower ee resulted for **7** (85% ee). Regioselective epoxide opening of **7** by the Grignard reagent derived from (*S*)-1-bromo-2-methylbutane in the presence of CuI at −30°C gave 1,3-diol **9** in 60% yield and its regioisomer (15% yield, separated by flash chromatography). The diol **9** was protected as an acetal using benzaldehyde dimethyl acetal and DIBAL-H reduction gave the primary alcohol **10** in 95% yield. The alcohol **10** was oxidized under Swern conditions, and the resulting aldehyde was reacted with triethyl phosphonoacetate in the presence of NaH to afford the *trans*-α,β-unsaturated ester **6** in 82% yield. Reduction of the double bond and removal of the benzyl protecting group were achieved by hydrogenation in the presence of a catalytic amount of $Pd(OH)_2$ on charcoal, and treatment with 6N HCl on SiO_2 gave the desired lactone **5** in 96% yield.

With the lactone **5** in hand, the remaining three carbon atoms of the acyl side chain were introduced by the addition of the lithium enolate of Seebach's ester[12] **4** in THF at −78 to −30°C (Scheme 2), affording **11** as a single diastereomer in 76% isolated yield. In this step, 2 equiv. of the lithium enolate of **4** were required to achieve the maximum yield of product **11**. It was observed that the diastereoselectivity of **11** was barely reduced even if the temperature was raised during the reaction after 2 h of standing at −78°C. On the contrary, it was necessary to raise the temperature from −78 to −30°C to drive the reaction to completion. Treatment of **11** with methanolic HCl accomplished the smooth conversion into the methyl pyranoside intermediate, and subsequent transesterification of the resulting dioxalanone with an excess of sodium methoxide was used to remove the acetal protection and giving **3** as a very stable ester derivative in 70% yield $[\alpha]_D^{25} = +93.6$ (*c* 0.49, $CHCl_3$), lit.[10b] $[\alpha]_D^{25} = +82.0$ (*c* 0.1, $CHCl_3$).

Although its rotation is close to that reported,[10b] the synthetic sample **3** showed differences in its ^1H NMR spectrum to that reported.[10b] Meanwhile, it was found that our ^1H NMR spectrum of **3**[15] conforms well to that of the side chain (**3A**) of L-156,602,[7b] even though there are a minor structural differences between them



Scheme 3.

(Fig. 1, R = Me instead of Et). Fortunately, the methyl acetal **3** was accidentally transformed into the semi-acetal **12**, which was also reported[10a] recently, after 7 days standing in a NMR tube, in 70% yield (Scheme 3). The ^1H and ^{13}C NMR spectra of the purified diol **12**[16] coincide with those reported by Kobayashi et al.,[10a] while the rotation ($[\alpha]_D^{25} = +76.2$ (*c* 0.96, $CHCl_3$)) is higher than that reported (lit.[10a] $[\alpha]_D^{25} = +55$ (*c* 0.36, $CHCl_3$)). Based on this evidence, it is believed our samples **3** and **12** are correct albeit with higher enantiomeric purities, and there are probably some unsolved structural questions associated with compound **3** obtained by Kurosu et al.[10b] In order to confirm the orientation of the acetal OCH_3, a NOESY spectrum of **3** was measured and clearly showed a strong NOE between the methyl group and Ha (Scheme 3). Thus, our sample **3** has the unambiguous stereochemical configuration as shown in Scheme 3.

In summary, an enantioselective synthesis of the 15-carbon tetrahydropyranyl side chain of polyoxypeptins is reported in 15.5% overall yield. It provides an attractive effective synthesis of this lactone and also provides a short route potentially amenable to preparation of the related compounds such as antibiotic L-156,602. Further studies toward the total synthesis of polyoxypeptins are now in progress.

Acknowledgements

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15. Data for **3**: $[\alpha]_D^{25} = +93.6$ (*c* 0.49, $CHCl_3$). IR (neat, cm^{-1}): 3526, 2960, 2878, 1739, 1463, 1380, 1151, 1055. ^1H NMR ($CDCl_3$, 600 MHz): δ 3.78 (s, 3H), 3.37 (s, 1H), 3.37 (s,

3H), 3.22 (1H, dt, $J=3.2$, 9.0 Hz), 1.89 (dt, 1H, $J=13.8$ Hz, 3.0 Hz), 1.65–1.78 (m, 3H), 1.44 (s, 3H), 1.37–1.46 (m, 2H), 1.14–1.33 (m, 4H), 1.05 (dt, 1H, $J=3.3$, 10.2 Hz), 0.97 (dd, 1H, $J=3.9$, 10.2 Hz), 0.96 (t, 3H, $J=7.2$ Hz), 0.87 (t, 3H, $J=7.2$ Hz), 0.82 (d, 3H, $J=6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.19, 99.56, 80.33 76.56, 52.37, 50.91, 38.31, 35.75, 30.95, 30.90, 28.77, 25.35, 24.23, 22.21, 18.55, 11.52, 9.20 ppm. MS (ESI, m/z): 339.3 $(M+Na)^+$. HRMS (ESI) calcd for $C_{17}H_{32}O_5Na$ $(M+Na)^+$: 339.2147, found: 339.2142.

16. Data for **12**: mp 68–69°C. $[\alpha]_D^{25}=+76.2$ (c 0.96, $CHCl_3$). IR (neat, cm^{-1}): 3463, 2963, 2919, 1709, 1453, 1376, 1274, 1054. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.22 (d, 1H, $J=3.0$ Hz), 3.81 (s, 3H), 3.45 (dt, 1H, $J=3.0$, 9.3 Hz), 3.06 (s, 1H), 1.84 (ddt, 1H, $J=13.2$, 4.2, 2.4 Hz), 1.77 (ddd, 1H, $J=13.2$, 7.2, 2.4 Hz), 1.69 (dt, 1H, $J=13.2$, 3.3 Hz), 1.65 (ddd, 1H, $J=13.2$, 7.2, 2.4 Hz), 1.42 (s, 3H), 1.39 (dq, 2H, $J=4.2$, 7.2 Hz), 1.14–1.30 (m, 4H), 0.97–1.07 (m, 2H), 0.86 (t, 3H, $J=7.5$ Hz), 0.81 (d, 3H, $J=6.6$ Hz), 0.79 (t, 3H, $J=7.2$ Hz). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 176.62, 98.62, 78.94, 76.35, 52.73, 38.31, 36.89, 31.13, 30.94, 26.57, 25.38, 24.18, 19.50, 18.63, 11.54, 9.51. MS (ESI, m/z): 325.3 $(M+Na)^+$.