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A practical synthesis of the lipophilic side chain of the polyoxypeptins

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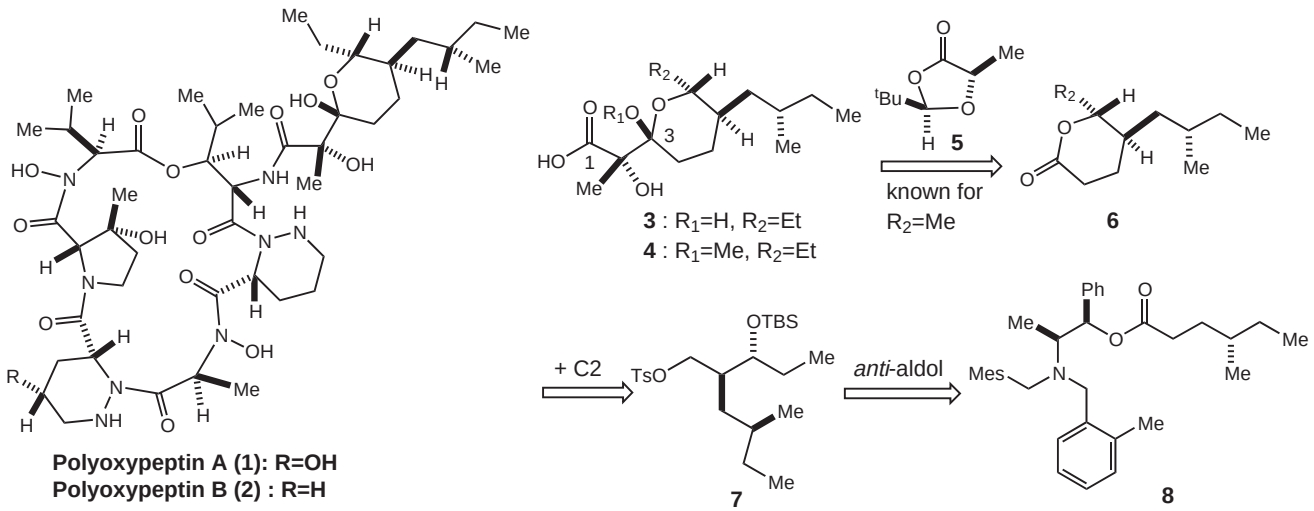
Abstract—The lipophilic side chain of the cyclic depsipeptide polyoxypeptin A (**1**) and B (**2**), strong apoptosis inducers, has been synthesised as an ester of mixed methyl ketal **18**. The key step is an asymmetric *anti*-aldol reaction of the designed 2-(*N*-2-methylbenzyl-*N*-2,4,6-trimethylbenzyl) amino-1-phenylpropyl ester **8** by means of a combination of LDA–Cp_2ZrCl_2 (0.3 equiv.) for enolation and transmetallation into the zirconium enolate for aldolization. By using a non-boron associated *anti*-aldol reaction, 10 g of the key lactone **6** were synthesised in six steps from **8** and in 48% overall yield. © 2001 Published by Elsevier Science Ltd.

Anticancer agents which induce apoptosis (programmed cell death) have a significant advantage over those which induce necrosis (accidental death caused by anticancer drugs). Thus, specific apoptosis inducers in cells expressing oncogenes will be useful for treating certain types of tumors. Polyoxypeptin A (**1**) and B (**2**), natural products isolated from the culture of broth of *Streptomyces* sp., induce apoptotic cell death in human pancreatic adenocarcinoma AsPC-1 cells, an apoptosis-resistant cell line, with ED_{50} values of 80 and 170 ng/mL, respectively. The relative and absolute stereochemistries of polyoxypeptin A were unambiguously determined through X-ray analysis and amino acids analyses. Polyoxypeptin A and B are 19-membered depsipeptides containing a lipophilic side chain, differ in the structure of the piperazic acid moiety (Scheme 1).[1]

While the side chain of polyoxypeptin is similar to that of antibiotic L-156602, the difference is the structure of the alkyl substituent on the tetrahydropyran ring (R_2 = Me in the structure **3**).[2] Because of its important biolog-



Scheme 1. The structure of polyoxypeptins and retrosynthesis of their lipophilic side chain **3**.

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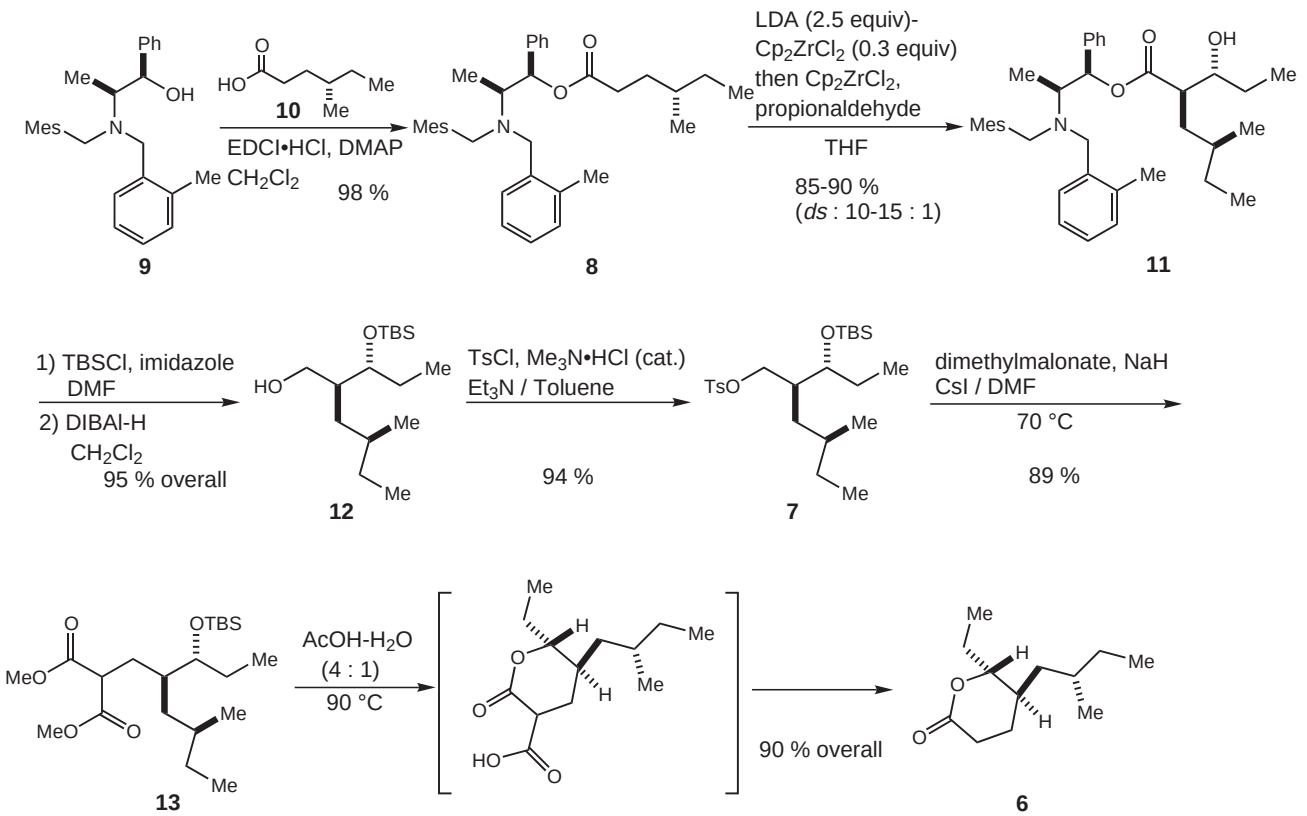
ical activity and unique structural features, we wanted to synthesize a relatively large quantity of such a molecule.[3]

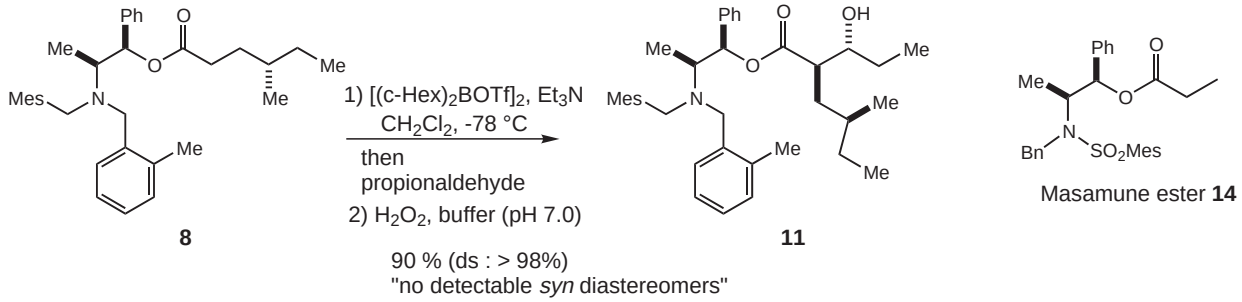
The transformation of lactone **6** (R_2 = Me) into **3** (R_2 = Me) with Seebach ester **5** has already been described by Caldwell and co-workers,[4] and it would be the shortest method for creating the C1–C3 chiral centres of the side chain. Therefore our strategy to access **3** (Scheme 1) required an efficient method to synthesize lactone **6** (R_2 = Et). We realised that an asymmetric *anti*-aldol reaction would be the most effective means for producing intermediate **7** (Scheme 1). We have recently developed a non-boron associated diastereselective *anti*-aldol reaction using a readily synthesized chiral template, 2-(*N*-2-methylbenzyl-*N*-2,4,6-trimethylbenzyl) amino-1-phenylpropyl ester.[5] Herein we report a practical synthesis of the lipophilic side chain of polyoxypeptins.

The synthesis of the key intermediate lactone **6** commenced with the known chiral carboxylic acid **10**[6] (Scheme 2). For use in the diastereselective *anti*-aldol reaction, alcohol **9** was converted into its ester **8** by reaction with water-soluble carbodiimide and DMAP. Selective generation of the *E*-enolate of **8** using LDA–Cp_2ZrCl_2 (0.3 equiv.), followed by transmetallation with Cp_2ZrCl_2 (2–3 equiv.) and aldolization with propionaldehyde afforded *anti*-aldol **9** in 85–90% yield with 98% *ds* (determined by HPLC).[5] Interestingly, the isolated *syn*-aldol product was a 1.5:1 mixture of diastereomers.[7] From a practical point of view, the *anti*-aldol reaction demonstrated herein has several advantages: (1) the high degree of diastereofacial selectivity; (2) all reagents for this chemistry are commercially available; (3) easy purification of *anti* and *syn* diastereomers; (4) quantitative recovery of the auxiliary. Because the structure of auxiliary **9** is similar to Masamune ester **14**, we applied the ester **8** to the Masamune's boron mediated aldol reaction condition.[8] By using $(c\text{-Hex})_2BOTf$ (2.4 equiv. as a monomer)[9] and 3 equiv. of Et_3N the aldol reaction of **8** with propionaldehyde afforded, after oxidative work-up, exclusively the *anti*-aldol product in 90% yield with greater than 98% *ds* (Scheme 3). For the reasons described above, we conducted the *anti*-aldol reaction of **8** on a 17 g scale using LDA–Cp_2ZrCl_2.

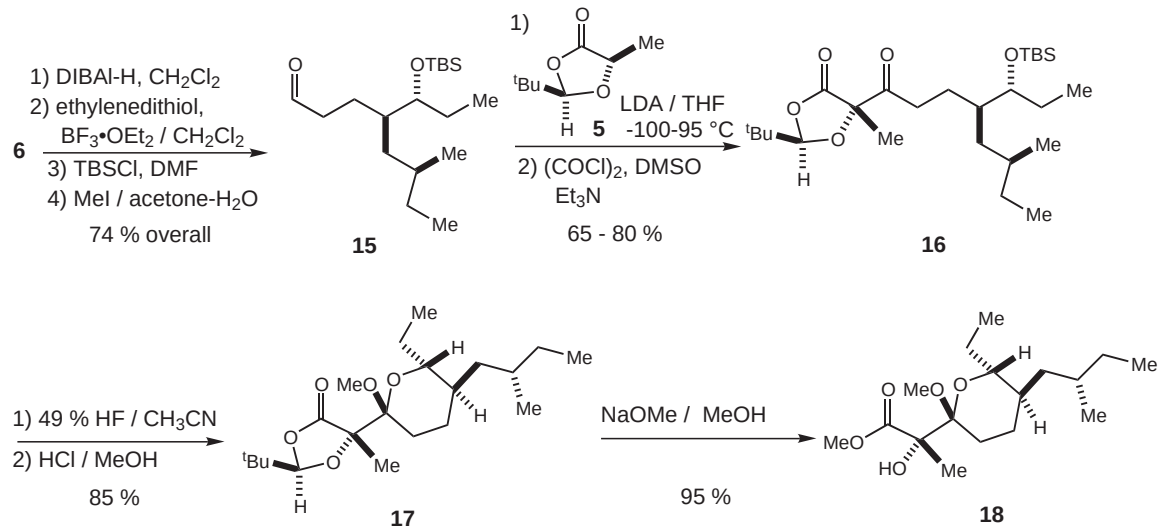
Protection of **11** as its TBS ether and reductive cleavage of the ester moiety yielded **12** in 95% yield, and auxiliary **9** was recovered almost quantitatively. For C2 elongation, the primary alcohol of **12** was activated as its tosylate.[10] The cesium malonate anion addition to tosylate **7** proceeded smoothly at 70°C in DMF within 5 h. The malonate adduct **13** could be transformed into the lactone **6** from **13** through the intermediate lactone–carboxylic acid in 90% yield by treatment with 80% AcOH at 90°C for 24 h. Thus, we were able to obtain more than 10 g of lactone **6** starting from 17 g of ester **8** in 43% overall yield.



Scheme 2. Synthesis of the lactone **6**.



Scheme 3. The *anti*-aldol reaction of **8** via Masamune's condition.



Scheme 4.

In our hands, introduction of a three-carbon unit by addition of lithium enolate of Seebach ester **5** to lactone **6** could not be reproducible. We have never obtained the coupling product under the condition described by Seebach.[11] In order to facilitate the coupling reaction with **5**, lactone **6** was converted into the acyclic aldehyde **15** via standard procedures (Scheme 4). Coupling of **15** with lithium enolate of **5** generated at −100 to −95°C followed by Swern oxidation gave β-keto ester **16**. Treatment of **16** with 49% HF in CH_3CN afforded hemiketal, which was then transformed into mixed methyl ketal **17**.[12] The transesterification of **17** with NaOMe in absolute MeOH yielded the stable compound **18**.[13]

In summary, the side chain of the polyoxypeptins has been synthesized very efficiently as a mixed methyl ketal ester **18** via a highly diastereoselective *anti*-aldol reaction as a key step.

Acknowledgements

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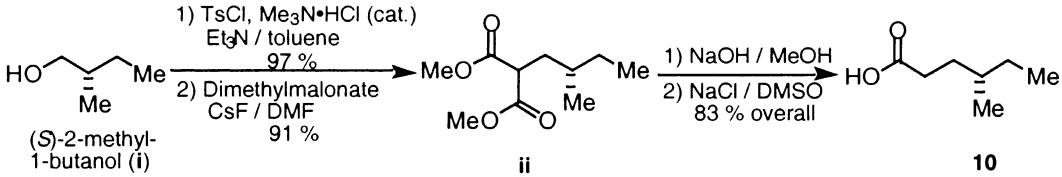
6. For example (*S*)-4-methylhexanoic acid (**10**) was utilised in Heathcock's zaragozic acid synthesis, see: Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115. Since in many cases the overall yield in the synthesis of **10** starting from commercially available (*S*)-2-methyl-1-butanol (**i**) was low and required multiple chromatographic purification, we developed a practical method for preparing **10** which does not require a silica gel purification. The procedure is the following. (1) For tosylation of **i** via Tanabe's condition (see Ref. 10): The reaction mixture was filtered through a glass-filter, and the crude mixture was distilled at 140°C/1 mmHg. (2) The cesium malonate addition to tosylate at 70°C: All volatiles were evaporated, and the crude mixture was distilled at 150°C/1 mmHg. (3) Saponification by NaOH in aqueous MeOH: The reaction mixture was acidified

and extracted with Et_2O, and the crude product was subjected to the next reaction. (4) Decarboxylation at 130°C: The reaction mixture was acidified and extracted with Et_2O. (*S*)-4-Methylhexanoic acid (**10**) was distilled at 92°C/1 mmHg.



7. This poor selectivity for *syn* diastereomers would be attributed to a boat-like transition structure that can accommodate two possible orientations of propionaldehyde.
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9. $(c\text{-Hex})_2BOTf$ was prepared from cyclohexene and $BH_3{\cdot}NEt_3$ followed by TfOH treatment. Procedure: (1) A mixture of $BH_3{\cdot}NEt_3$ (35 mL) and cyclohexene (95 mL, 4 equiv.) was stirred at 80°C for 24 h and at 100°C for 12 h. All volatiles (cyclohexene and NEt_3) were distilled off at 150°C and $(c\text{-Hex})_3B$ (very air sensitive) was distilled at 110°C at 1 mmHg. $(c\text{-Hex})_3B$ was then reacted with TfOH (15 mL) under Ar for 1 h. The reaction mixture was distilled at 118–120°C at 0.2 mmHg to afford $(c\text{-Hex})_2BOTf$ (39.5 g, ca. 60% overall) as a yellow solid. This was stored as a toluene solution (0.8 M).
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12. Data for **17**: ^1H NMR (300 MHz, $CDCl_3$): 5.25 ppm (1H, s), 3.37 (3H, s), 3.17 (1H, m), 1.86 (2H, td, $J=$ 13.5, 4.8 Hz), 1.74–1.53 (7H, m), 1.03–0.97 (6H, m), 0.93 (9H, s), 0.88 (3H, d, $J=2.7$ Hz), 0.82 (6H, t, $J=6.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 174.5 ppm, 108.3, 101.2, 84.9, 77.6, 50.2, 38.4, 36.0, 34.1, 30.9, 28.4, 25.6, 24.1, 18.8, 18.6, 11.5, 9.2. IR (neat): 2960 cm^{-1}, 2870, 1790, HRMS (ESI) $C_{21}H_{38}O_5$ ($M+Li^+$) calcd 377.19948, found 377.20020. $[\alpha]_D=+72.0$ (*c* 0.2, $CHCl_3$ at 25°C).
13. Compounds **3** and **4** are extremely sensitive to acids and strong bases. Side chain **3** was isolated and characterised as its protected form **18**. Data for **18**: ^1H NMR (300 MHz, $CDCl_3$): 3.78 ppm (3H, s), 3.76 (1H, s), 3.49 (3H, s), 3.47 (1H, m), 1.86 (2H, td, $J=13.2$, 4.8 Hz), 1.77–1.52 (2H, m), 1.44–1.11 (2H, m), 1.37 (9H, m), 1.09–0.78 (9H, m). IR (neat): 2970 cm^{-1}, 2880, 1780. HRMS (ESI) $C_{17}H_{32}O_5$ ($M+Li^+$) calcd 323.18542, found 323.18531. $[\alpha]_D=+82.0$ (*c* 0.1, $CHCl_3$ at 25°C).