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An effective extension of the polyacetate chain in the polyene macrolide antibiotic filipin III, based on chiral oxazaborolidinone-promoted asymmetric aldol reactions

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Abstract

The enantioselective construction of the iterative polyacetate unit **3** in filipin III has been accomplished, essentially by an aldol strategy based on chiral oxazaborolidinone-promoted asymmetric aldol reactions.

A variety of approaches have been reported for the stereoselective construction of the 1,3-polyacetate moiety in polyene macrolide antibiotics.[1] The access using asymmetric aldol reactions is now limited, in spite of it being a straightforward means of stereoselectively introducing the β-hydroxy function. It was considered that this tactic suffers from the iterative nature required to set each stereogenic center correctly.[1f] By taking advantage of the iterative nature found in 1,3-polyols, however, our aldol strategy using chiral oxazaborolidinone, (*S*)-**1** or (*R*)-**1**, -promoted asymmetric aldol reaction under promoter control on enantioselective acyclic stereoselection (Fig. 1) is not necessarily the case.[2] We disclose herein a versatile approach to the 1,3-polyacetate units using our aldol reaction.

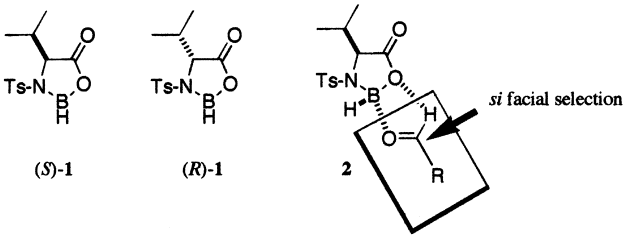

Figure 1. Chiral oxazaborolidinones and facial selection

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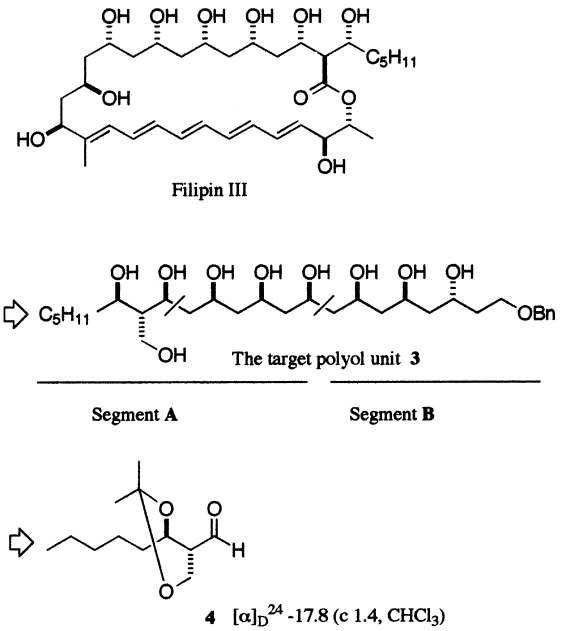
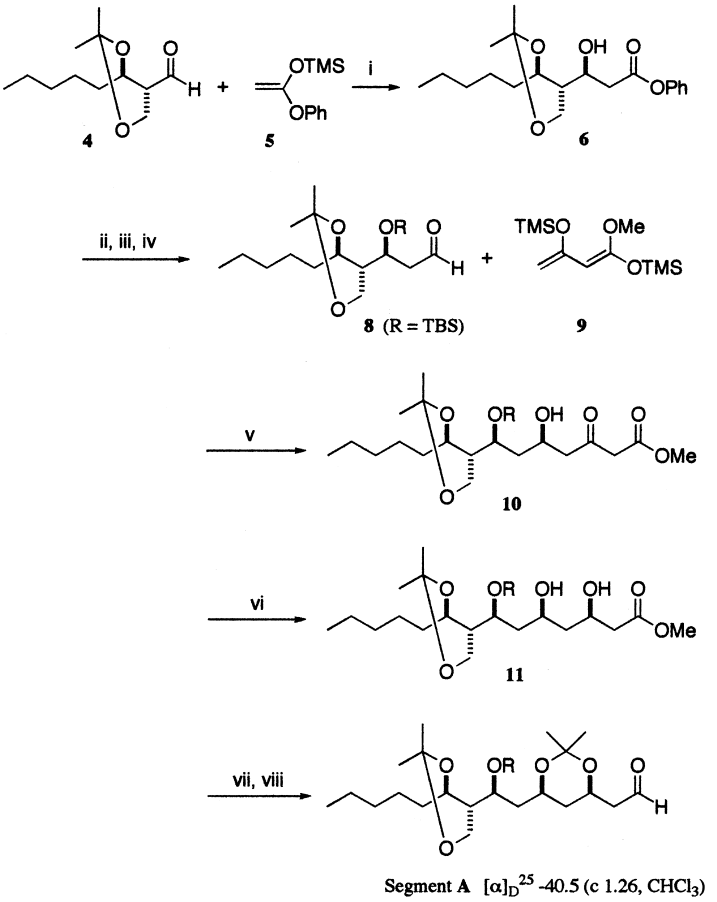
Filipin III, a polyene macrolide antibiotic which is a membrane disrupter that selectively binds cholesterol, was isolated from cell culture filtrates of *Streptomyces filipinensis*.[3] The structure determination[4] and the first total synthesis were achieved by the same group.[5] The iterative nine 1,3-polyol unit involved in filipin III is a synthetic target suitable for the purpose of examining the viability of our aldol strategy. The tactic using our aldol reaction repeatedly, applied to the synthesis of an enantiopure 1,3-polyacetate unit in bryostatins, is possibly available for this 1,3-polyol unit. However, such a linear approach is not feasible in the case of so much iteration. As shown in Scheme 1, the target polyol unit **3** was retrosynthetically planned to be divided into two parts; segments **A** and **B**. The starting aldehyde **4**, $[\alpha]_D^{24}$ −17.8 (*c* 1.4, $CHCl_3$), toward the preparation of segment **A** has been synthesized and reported in an enantiopure form by a method using our asymmetric aldol reaction.[6]



Scheme 1. Retrosynthesis of filipin III

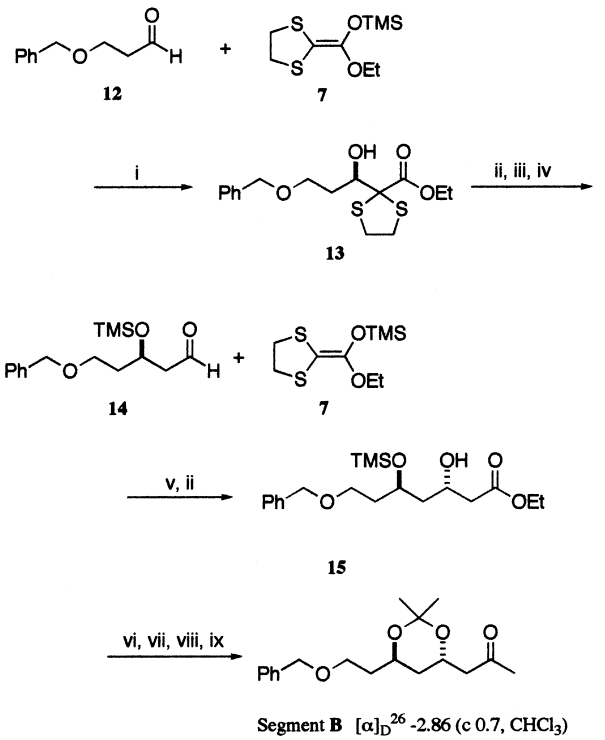
The synthesis of segment **A** is summarized in Scheme 2, which is basically realized by applying the enantioselective aldol reaction with two different silyl nucleophiles and the following *syn* selective reduction. The first aldol reaction with acetonide aldehyde **4** was carried out in the presence of chiral oxazaborolidinone (*S*)-**1** using silyl nucleophile **5**, derived from α-unsubstituted acetate, to give the expected aldol **6** in moderate diastereoselection (75% de). In this reaction dithiolane silyl nucleophile **7**,[7] developed by us and which promises quite high enantioselection, did not work because of the excessive steric hindrance in aldehyde **4**. Subjection of aldol **6** to a typical reaction sequence (DIBALH reduction and Swern oxidation), after protection of the free hydroxy group as TBS ether, afforded the second aldehyde **8**. In the presence of the same promoter (*S*)-**1**, aldehyde **8** participated in the second aldol reaction with disilyl nucleophile **9**[2d,8] resulting in *syn* diastereoselection (92% de) to hydroxy keto ester **10**. A complete *syn* reduction of the keto function in **9** could, as expected, be achieved with Et_2BOMe and $NaBH_4$[9] to give compound **11** having the four successive hydroxy functions as a 1,3-poly-



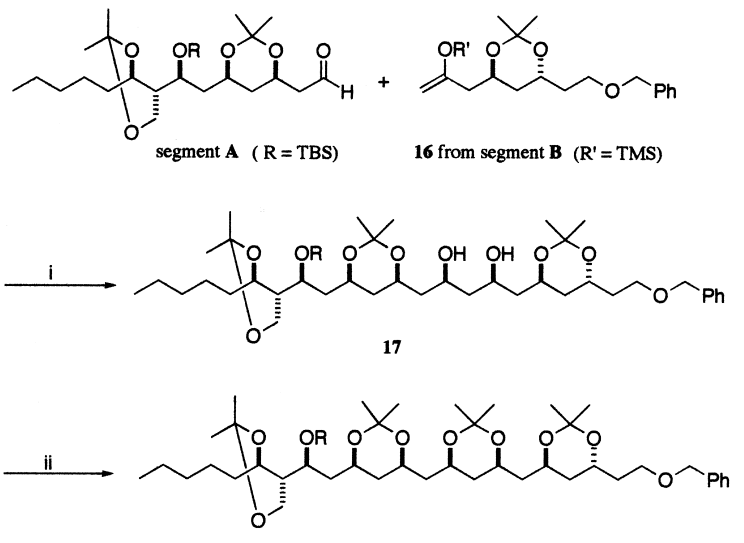
Scheme 2. Enantioselective synthesis of segment **A**. *Reaction conditions*: (i) (*S*)-**1** (BH_3·THF, *N*-Ts-L-valine), CH_2Cl_2, −78°C, 3 h, 72%, 75% de; (ii) TBSCl, DMF, >95%; (iii) DIBALH, CH_2Cl_2, −78°C to rt, 84%; (iv) Swern oxid., 78%; (v) (*S*)-**1** (BH_3·THF, *N*-Ts-L-valine), CH_2Cl_2, −78°C, 6 h, 65%, 92% de; (vi) Et_2BOMe, $NaBH_4$, MeOH, >95%, >98% de; (vii) CSA, $Me_2C(OMe)_2$, acetone, >95%; (viii) DIBALH, CH_2Cl_2, −78°C, 85%

acetate mode in excellent yield. After protection as acetonide, the following DIBALH reduction at −78°C directly gave segment **A**, $[\alpha]_D^{25}$ −40.5 (*c* 1.26, $CHCl_3$), as an aldehyde available for the last condensation reaction.

The synthesis of segment **B** is very simple, demonstrating plainly the advantage of our aldol strategy for constructing the 1,3-*anti* diol system which is obtainable only by using promoter (*S*)-**1** and its reverse (*R*)-**1** twice with essentially complete selection, as depicted in Scheme 3. Although the action of silyl nucleophile **7** on benzyl aldehyde **12** effected the desired, highly enantioselective aldol reaction in the presence of (*S*)-**1** to afford aldol **13** (through the *si* facial selection), the dithiolane moiety in the product must be eliminated. The desulfurization procedure was accelerated on treatment with *n*-Bu_3SnH and AIBN[10] in a quantitative yield. After protection with TMSOTf and 2,6-lutidine, aldehyde **14** was obtained from the precursor ester by direct DIBALH reduction. In the presence of chiral borane (*R*)-**1**, the next aldol reaction of **14** with **7** took place in an essentially complete diastereo-controlled manner allowing the *re* facial selection of the nucleophile independently of the pre-existing chiral center so as to afford only *anti* isomer **15**, as expected. After desilylation and acetalization, segment **B**, $[\alpha]_D^{26}$ −2.86 (*c* 0.7, $CHCl_3$), was prepared through a Weinreb amide.[11]



Scheme 3. Enantioselective synthesis of segment **B**. *Reaction conditions*: (i) (*S*)-**1** (BH_3·THF, *N*-Ts-L-valine), CH_2Cl_2, −78°C, 20 h, 68%, 98% ee; (ii) *n*-Bu_3SnH, AIBN, >95%; (iii) TMSOTf, 2,6-lutidine, 85%; (iv) DIBALH, CH_2Cl_2, −78°C, 72%; (v) (*R*)-**1** (BH_3·THF, *N*-Ts-D-valine), CH_2Cl_2, −78°C, 20 h, 65%, >98% de; (vi) citric acid, MeOH, >95%; (vii) CSA, $Me_2C(OMe)_2$, acetone, >95%; (viii) Me(MeO)NH·HCl, *i*-PrMgBr, 84%; (v) MeMgI, 92%



Scheme 4. Condensation of segments **A** and **B**. *Reaction conditions*: (i) (*S*)-**1** (BH_3·THF, *N*-Ts-L-valine), C_2H_5CN, −78°C, 5 h, 64%, *syn*/*anti*=>98% de; (ii) CSA, $Me_2C(OMe)_2$, acetone, >95%

The last step toward the target polyol unit **3** was addressed to the chiral oxazaborolidinone-promoted aldol reaction accompanying the sequential asymmetric *syn* reduction with the same oxazaborolidinone. It was known from our previous work that the coupled asymmetric reactions proceed in one pot in the system using silyl enol ethers, not ketene silyl acetals.[12] Indeed, the expected aldol reaction of segment **A** with silyl enol ether **16**, prepared from segment **B** in the usual manner, furnished the desired *syn*-1,3-diol **17** with >98% de in 64% yield, together with a small amount of the corresponding aldol product (ca. 10%) (in Scheme 4). Acetalization of **17** accomplished the effective synthesis of the protected compound of **3**.[13]

The construction of the nine contiguous hydroxy stereocenters in the protected compound of **3** is now complete. Each selectivity obtained in the reaction sequence is presented in Fig. 2; excellent to good enantioselectivities in the eight aldol reactions and one reduction were achieved. Thus, our aldol strategy based on chiral oxazaborolidinone-promoted asymmetric aldol reactions turned out to be quite reliable as a general way of constructing a variety of iterative 1,3-polyacetate systems.

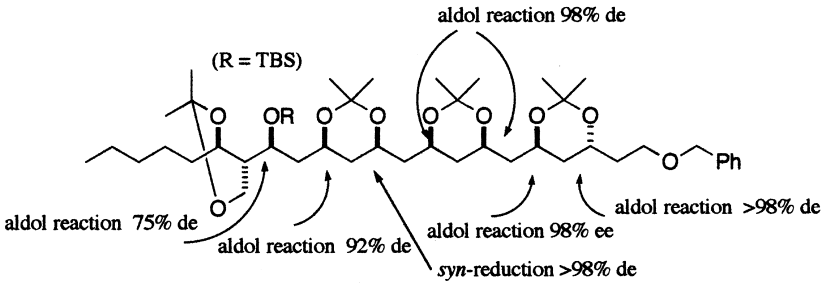


Figure 2. Each selectivity found in the reaction sequence

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References

1. (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (b) Rychonovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (c) Schneider, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1375. (d) Enders, D.; Hundertmark, T. *Tetrahedron Lett.* **1999**, *40*, 4169. (e) Garner, P.; Anderson, J. T. *Org. Lett.* **1999**, *1*, 1057. (f) Smith III, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001. (g) Trieselmann, T.; Hoffmann, R. W. *Org. Lett.* **2000**, *2*, 1209.
2. (a) Kiyooka, S.-i. *Rev. Heteroatom. Chem.* **1997**, *17*, 245. (b) Kiyooka, S.-i.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett.* **1997**, *38*, 3553. (c) Kiyooka, S.-i.; Madeda, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3371. (d) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511.
3. Isolation: (a) Whitfield, G. B.; Brock, T. D.; Ammann, A.; Gottlieb, D.; Carter, M. E. *J. Am. Chem. Soc.* **1955**, *77*, 4799. (b) Bergy, M. E.; Eble, T. E. *Biochemistry* **1968**, *7*, 653.
4. Structure Elucidation: (a) Rychnovsky, S. D.; Richardson, T. I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1227. (b) Richardson, T. I.; Rychonovsky, S. D. *J. Org. Chem.* **1996**, *61*, 4219.
5. Total synthesis: Richardson, T. I.; Rycohnovsky, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 12360.
6. Kiyooka, S.-i.; Hena, M. A.; Goto, F. *Tetrahedron*: Asymmetry **1999**, *10*, 2871.
7. Kiyooka, S.-i.; Hena, M. A. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2181.

8. (a) Yamamoto, K.; Suzuki, S.; Tsuji, J. *Chem. Lett*. **1978**, 649. (b) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull*. **1994**, *42*, 839. (c) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc*. **1995**, *117*, 12360.
9. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett*. **1987**, *28*, 155.
10. Boaz, N. W. *J. Org. Chem*. **1992**, *57*, 4289.
11. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461.
12. (a) Kaneko, Y.; Matsuo, T.; Kiyooka, S.-i. *Tetrahedron Lett*. **1994**, *35*, 4107. (b) Kiyooka, S.-i.; Kaneko, Y.; Harada, Y.; Matsuo, T. *Tetrahedron Lett*. **1995**, *36*, 2821.
13. On analysis of ^{13}C NMR correlations of 1,3-diol acetonide: see Rychonovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem*. **1993**, *58*, 3511. Selected physical data of the protected compound of **3**: $[\alpha]_D^{23}$ −122.2 (*c* 0.20, $CHCl_3$); IR (neat) 2942, 1379, 1263, 1199, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.30–7.35 (m, 5H), 4.50 (s, 2H), 4.21 (d, 2H, $J=11.95$ Hz), 4.05–4.12 (m, 2H), 3.95–4.05 (m, 6H), 3.90 (dd. 2H, $J=3.68$, 12.0 Hz), 3.55 (dddd, 2H, $J=5.70$, 6.20, 8.81, 14.0 Hz), 2.05 (ddd, 1H, $J=2.01$, 6.25, 11.4 Hz), 1.99 (ddd, 1H, $J=3.52$, 7.31, 11.6 Hz), 1.83 (dd, 2H, $J=6.43$, 13.6 Hz), 1.77 (dd, 2H, $J=6.21$, 12.4 Hz), 1.60–1.63 (m, 2H), 1.42 (s, 3H), 1.41 (s, 6H), 1.37 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.33 (s, 6H), 1.25–1.55 (m, 13H), 1.18 (t, 2H, $J=11.7$), 0.90 (t, 3H, $J=6.44$), 0.88 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 138.5, 128.4 (×2), 127.7 (×2), 127.6, 100.3, 98.3, 98.2, 98.1, 77.2, 73.1, 69.8, 66.6 (×2), 66.5, 65.6, 65.2, 63.6, 62.8, 59.0, 42.9, 42.2, 42.0, 41.6, 38.5, 36.4 (×2), 36.0, 32.4, 31.8, 30.3, 30.2, 29.5, 25.8 (×3), 25.4, 24.8, 24.7, 22.6, 20.0, 19.8, 18.8, 18.0, 14.1, −4.2, −4.5. FABMS calcd for $C_{48}H_{84}O_{10}Si$: 848.58 found: 848.87 [M^+].