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# Total Synthesis of Reveromycin B

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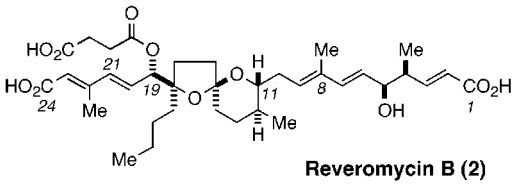
## ABSTRACT




**The stereoselective total synthesis of reveromycin B (2), a novel polyketide-type antibiotic, has been accomplished.**

Reveromycins A−D are novel polyketide-type antibiotics produced by *Streptomyces* sp. and inhibit mitogenic activity induced by the epidermal growth factor (EGF) in a mouse epidermal keratinocyte.[1] An inhibitor of mitogenic activity of EGF or TGF-α, which shares the same receptor with EGF, may be the focal point for the development of a novel range of antitumor drugs. Therefore, the reveromycins due to their pertinent bioactivity and low toxicity may be ideal drug candidates. Furthermore, reveromycins A, C, and D induced the morphological reversion of *src*$^{ts}$-NRK cells from spherical transformed cells to flat normal cells. In addition to the inhibition of mitogenic activity, the reveromycins showed antifungal activity and inhibition of protein synthesis and in the latter were selective toward eukaryotic cells only.

The characteristic structural features of the reveromycins include a 6,6- or a 5,6-spiroketal system, containing a hemisuccinate, two alkenyl carboxylic acids, and two alkyl groups.[2] The absolute configuration of reveromycin A (**1**; Figure 1) was determined on the basis of its chemical degradation and spectroscopic analysis,[3] while only the two-dimensional structure of reveromycin B (**2**) was reported. Their potent biological activity as potential drugs and their synthetically challenging, unique structure have attracted the attention of synthetic organic chemists.[4−6]

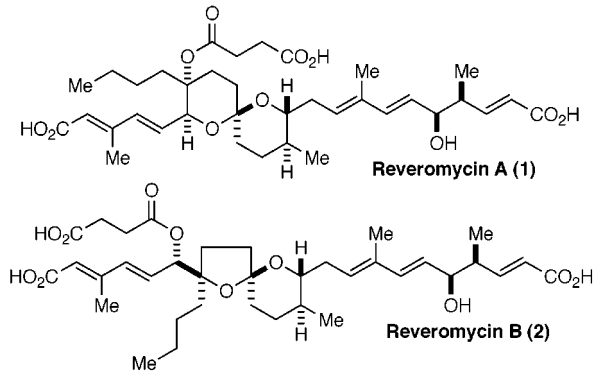



**Figure 1.** Structures of reveromycins A (**1**) and B (**2**).

Quite recently, Theodorakis et al.[6] reported the first total synthesis of **2**, which confirmed the absolute configuration of **2** as shown in Figure 1. We have also been investigating the total synthesis of reveromycins A (**1**) and B (**2**) and have already reported the stereoselective construction of the 6,6-

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(1) (a) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409−1413. (b) Takahashi, H.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414−1419.

(2) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 1420−1427.

(3) Ubukata, M.; Koshino, H.; Osada, H.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1877−1878.

(4) Shimizu, T.; Kobayashi, R.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6755−6758.

(5) McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196−1197.

(6) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 456−457.

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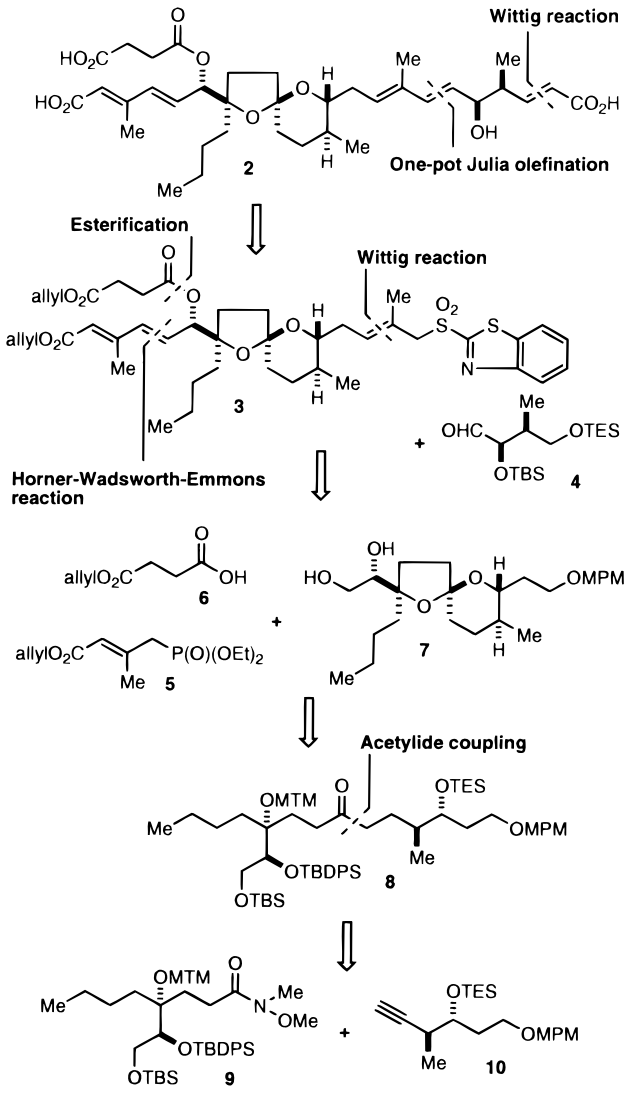
spiroketal part of **1**, confirming the absolute configuration.[4] We now report the stereoselective total synthesis of reveromycin B (**2**).

Our synthetic strategy for reveromycin B (**2**) is outlined in Scheme 1. It is postulated that a one-pot Julia olefination

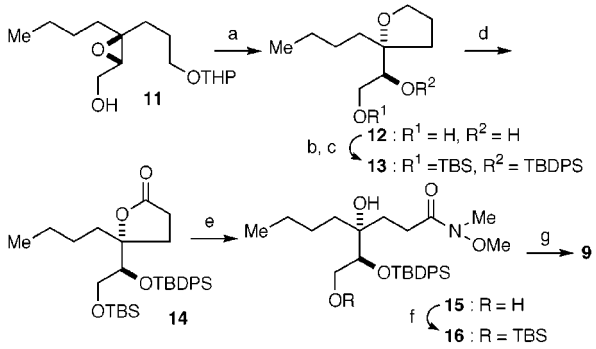
**Scheme 1**




employing sulfone **3** and aldehyde **4**, followed by a Wittig reaction, would lead to the stepwise elaboration of the labile polyunsaturated right chain.[7] Conversely, the left chain may be constructed via the Horner−Wadsworth−Emmons reaction using phosphonate **5**, following esterification with the *mono*(allyl succinate) **6**.[8] The 5,6-spiroketal core **7** would be synthesized via the coupling reaction of the Weinreb amide **9** and alkyne **10**.

The Weinreb amide **9** was prepared from the known epoxide **11**[4] (Scheme 2). Hydrolysis of the THP group in

**Scheme 2**[a]

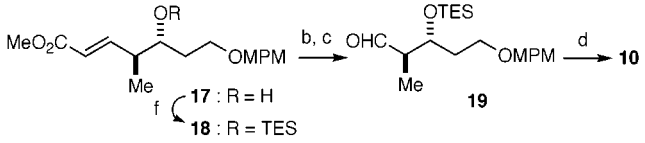


[a] Reagents and conditions: (a) AcOH, THF, $H_2O$, room temperature, then TsOH, MeOH, room temperature (88%); (b) TBSCl, $Et_3N$, DMAP, DMF, 0 °C to room temperature (96%); (c) TBDPSOTf, lutidine, $CH_2Cl_2$, 0 °C to room temperature (95%); (d) $RuCl_3$, $NaIO_4$, $CH_3CN$, $CCl_4$, phosphate buffer (pH 8), room temperature (92%); (e) $Me_2AlCl$, MeNHOMe·HCl, $CH_2Cl_2$, 0 °C to room temperature; (f) TBSCl, imidazole, DMAP, DMF, 0 °C to room temperature (65%, 2 steps; 11% of **14** was recovered); (g) DMSO, $Ac_2O$, room temperature (94%).

**11** with aqueous AcOH produced a simultaneous cyclization to give the tetrahydrofuran **12** in 88% yield.[9] After successive silylation of **12** with TBSCl and TBDPSOTf, oxidation with $RuCl_3$−$NaIO_4$[10] selectively afforded the $\gamma$-butyrolactone **14** in 84% yield over three steps. The aminolysis of **14** with $Me_2AlCl$−MeNHOMe·HCl,[11] an effective reagent for construction of Weinreb amides from sterically hindered lactones, cleanly proceeded to give the dihydroxy amide **15**, which was treated with TBSCl to produce the TBS ether **16** in 65% yield along with **14** (11%).[12] Protection of the tertiary alcohol in **16** with DMSO−$Ac_2O$ gave the desired Weinreb amide **9** in 94% yield.

The alkyne **10** was prepared from the known alcohol **17**[4] (Scheme 3). After protection of **17** with TESCl, successive

**Scheme 3**[a]



[a] Reagents and conditions: (a) TESCl, imidazole, DMAP, DMF, 0 °C to room temperature (96%); (b) $OsO_4$, NMO, acetone, $H_2O$, room temperature (87%); (c) $Pb(OAc)_4$, toluene, room temperature (97%); (d) $TMSCHN_2$, *n*BuLi, THF, −78 to 0 °C (70%).

treatment with $OsO_4$−NMO and $Pb(OAc)_4$ afforded the aldehyde **19** (81%), which was converted into the alkyne **10** (70%) by the Colvin rearrangement.[13]

(7) $\beta$-Elimination of the silylated C-5 hydroxy group occurred under various basic conditions.

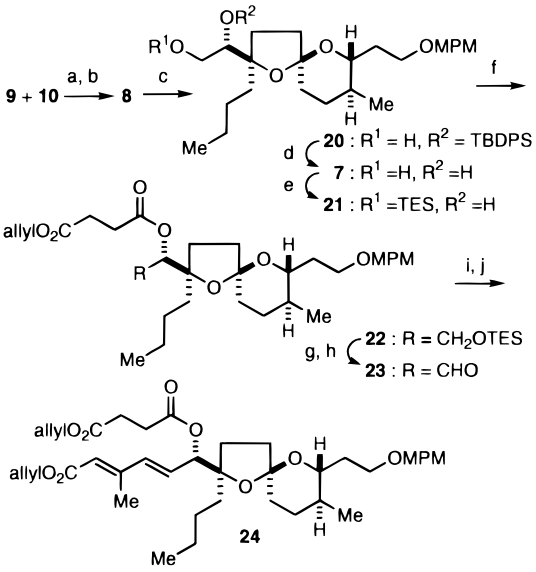
(8) The mono(allyl succinate) **6** was prepared by alcoholysis of succinic anhydride with allyl alcohol in 94% yield.

(9) During evaporation of the solvents, the resulting diol **12** was converted into the THP derivative, which was then treated with TsOH in MeOH to give **12**.

(10) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

With the desired Weinreb amide **9** and alkyne **10** in hand, we then investigated the union of these fragments leading to the spirocyclic core and incorporation of the dienyl carboxylic side chain (Scheme 4). The coupling reaction of

**Scheme 4**[a]




[a] Reagents and conditions: (a) *n*BuLi, THF, 0 °C; (b) Pd/C, $H_2$, AcOEt, room temperature (94%, 2 steps); (c) TsOH, $CHCl_3$, EtOH, 0 °C to room temperature (83%); (d) TBAF, THF, room temperature (86%); (e) TESCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (f) **6**, DIC, DMAP, $CH_2Cl_2$, room temperature (98%, 2 steps); (g) PPTS, $CHCl_3$, MeOH, 0 °C (92%); (h) TPAP, NMO, $CH_2Cl_2$, room temperature (93%); (i) **5**, LiHMDS, THF, HMPA, −78 to 0 °C; (j) **6**, DIC, DMAP, $CH_2Cl_2$, room temperature (77%, 2 steps).

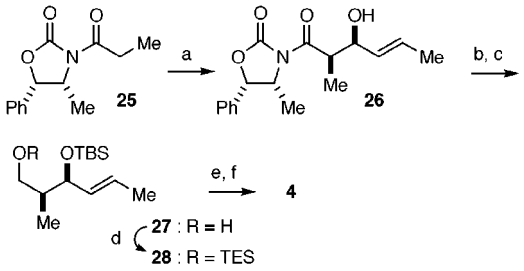
the lithio derivative of **10** and amide **9** followed by hydrogenation furnished the saturated ketone **8** in 94% yield. Treatment of **8** with TsOH in EtOH−$CHCl_3$ effected deprotection of the TES, TBS, and MTM groups and simultaneous 5,6-spiroketalization to give the thermodynamically stable isomer **20** in 83% yield. After deprotection of the TBDPS group with TBAF and silylation with TESCl, the resulting alcohol **21** was subjected to esterification with the mono(allyl succinate) **6** to give the succinate **22** in 84% yield. Desilylation of **22** with PPTS followed by TPAP oxidation gave the aldehyde **23** in 86% yield. The Horner−Wadsworth−Emmons reaction of **23** with phosphonate **5**[14] in the presence of HMPA at −78 to 0 °C[15] gave a ca. 7:3 inseparable mixture of dienoic esters and their des-succinate derivatives. This mixture was resubjected to esterification with **6** to give the desired (20*E*,22*E*)-**24** along with the 20*E*,-22*Z* isomer (77% yield; the ratio of **24** to its isomer is 14:1).

(11) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685−2688.

(12) Treatment of **15** with TBSOTf exclusively gave the lactone **14**.

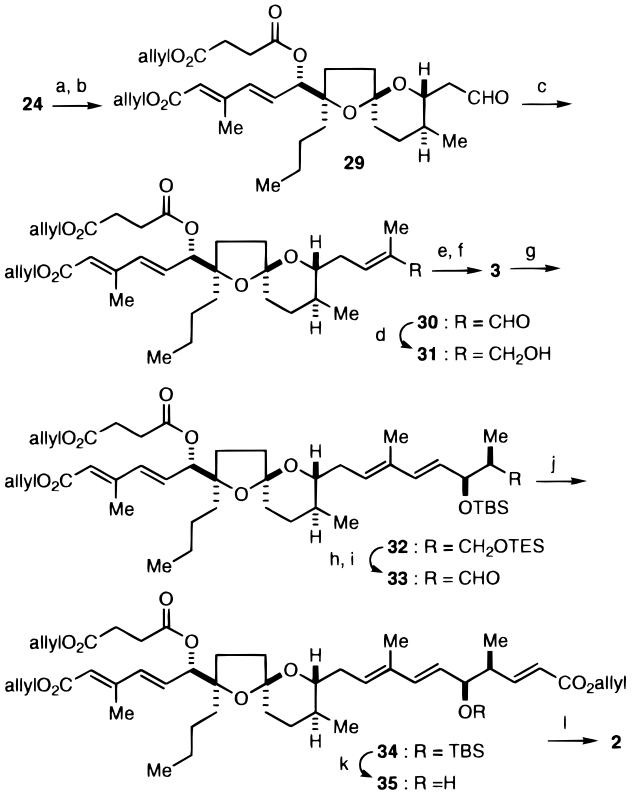
(13) (a) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151−152. (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869−874. (c) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107−108.

**Scheme 5**[a]




[a] Reagents and conditions: (a) *n*$Bu_2$BOTf, *i*$Pr_2$NEt, crotonaldehyde, $CH_2Cl_2$, −78 °C to room temperature (86%); (b) TBSOTf, lutidine, $CH_2Cl_2$, 0 °C (100%); (c) $NaBH_4$, THF, $H_2$, room temperature (87%); (d) TESCl, imidazole, DMF, 0 °C to room temperature (100%); (e) $OsO_4$, NMO, acetone, $H_2O$, room temperature (82%); (f) $Pb(OAc)_4$, toluene, room temperature (97%).

**Scheme 6**[a]




[a] Reagents and conditions: (a) DDQ, $CH_2Cl_2$, $H_2O$, room temperature (91%); (b) $SO_3$·Py, $Et_3N$, $CH_2Cl_2$, DMSO, 0 °C to room temperature (99%); (c) $Ph_3P$=C(Me)CHO, toluene, 110 °C (93%); (d) $Zn(BH_4)_2$, $Et_2O$, 0 °C; (e) 2-mercaptobenzothiazole, $Ph_3P$, DEAD, THF, room temperature; (f) $Mo_7O_{24}(NH_4)_6$·$4H_2O$, $H_2O_2$, EtOH, 0 °C to room temperature, (79% from **33**); (g) LiHMDS, **4**, THF, −78 to 0 °C (56%: 76% yield based on consumed **3**); (h) PPTS, $CHCl_3$, MeOH, 0 °C (95%); (i) Dess−Martin periodinane, $CH_2Cl_2$, room temperature (90%); (j) $Ph_3P$=$CHCO_2$(allyl), toluene, 80 °C (98%); (k) HF·Py, THF, 0 °C to room temperature (78%); (l) $Pd_2(dba)_3$·$CHCl_3$, *n*$Bu_3P$, $HCO_2H$, $Et_3N$, 1,4-dioxane, 50 °C (62%).

Two asymmetric centers in the right chain were set by Evans asymmetric aldol methodology[16] (Scheme 5). The

aldol reaction of the boron enolate of the oxazolidinone **25** with crotonaldehyde exclusively furnished the *syn*-alcohol **26** in 86% yield. Treatment of **26** with TBSOTf followed by $NaBH_4$ reduction in aqueous THF[17] produced the alcohol **27** in 87% yield. After protection of **27** with TESCl, the oxidative cleavage of the olefin by successive treatment with $OsO_4$−NMO and $Pb(OAc)_4$ afforded the desired aldehyde **4** in 80% yield.

The final elaboration of the dienyl alcohol side chain began with deprotection of the MPM group in **24** (Scheme 6). Treatment of **24** with DDQ followed by oxidation with $SO_3$·Py gave the aldehyde **29** (90%), which was subjected to the Wittig reaction to give the α,*β*-unsaturated aldehyde **30** in 93% yield. Reduction of **30** with $Zn(BH_4)_2$ afforded the allyl alcohol **31**, which was converted into the sulfone **3** in 79% yield by the Mitsunobu reaction with 2-mercaptobenzothiazole followed by Mo(VI)-mediated oxidation.[18] The one-pot Julia olefination of the sulfone **3** and the aldehyde **4** stereoselectively produced the (6*E*,8*E*)-diene **32** in 56% yield (76% yield based on the consumed **3**). After selective desilylation of **32** with PPTS followed by oxidation with the Dess−Martin periodinane, the resulting aldehyde **33** was subjected to a Wittig reaction employing the neutral phosphorane to afford the α,*β*-unsaturated ester **34** in 84% yield. Deprotection of the TBS group in **34** was achieved by HF·Py in THF; the use of TBAF caused decomposition of the substrate. Finally, removal of the three allyl groups in **35** by the Pd catalyst[19] cleanly proceeded to give reveromycin B (**2**). The spectral data ($^1$H NMR, $^{13}$C NMR, $[\alpha]_D$, IR, HRMS) of the synthetic **2** were identical with those of natural reveromycin B (**2**).

**Acknowledgment.** This work was supported in part by Special Project Funding for Basic Science (Multibioprobes) from RIKEN. We thank Dr. H. Koshino and Dr. H. Osada for supplying the spectra of the natural product and Ms. K. Harata for the mass spectral measurements.

**Supporting Information Available:** IR, $[\alpha]_D$, $^1$H NMR, $^{13}$C NMR, and mass spectroscopy data for compounds **3**−**5**, **7**, **9**, **10**, **22**, **24**, **32**, **34**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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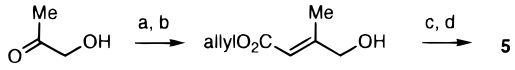
(14) The phosphonate **5** was prepared as follows:




Reagents and conditions: (*a*) $Ph_3P{=}CHCO_2Me$, benzene, 70 °C (81%); (*b*) allyl alcohol, $ClBu_2SnOSnBu_2OH$,[14a,b] toluene, 110 °C (85%); (*c*) $CBr_4$, $Ph_3P$, lutidine, $CH_3CN$, 0 °C (94%); (*d*) $P(OEt)_3$, 90 °C (90%). (a) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383−2386. (b) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307−5311.

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(16) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

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(19) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623−627.