Enantioselective Total Synthesis of Reveromycin B

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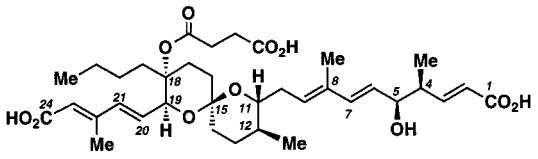
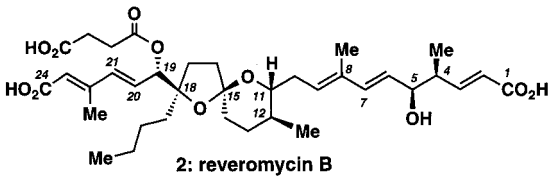
The reveromycins A (**1**) and B (**2**) belong to a new family of natural products that have been isolated from a soil actinomycete of the genus *Streptomyces*.[1] Both compounds inhibit eukaryotic cell growth presumably by interfering with an element associated with the epidermal growth factor receptor pathway.[2,3] The molecular structures of **1** and **2** are characterized by a [6,6] or [5,6] spiroketal core respectively, decorated with two highly unsaturated side-chains ending in carboxylic acid units. The relative and absolute configuration of **1** was determined by chemical degradation and spectroscopic analysis, while the structure of **2** was proposed by analogy to **1**.[4] Herein, we would like to disclose a route to the chemical synthesis of **2**, which may also be amenable to the synthesis of other members of this family.[5] This reaction sequence constitutes the first total synthesis of a member of the reveromycin family and unambiguously confirms the proposed structures for **2** and **1**.



1: reveromycin A



2: reveromycin B

The strategic bond disconnections of reveromycin B (**2**) are outlined in Figure 1. Our plan was based on the use of Negishi[6] and Kishi-Nozaki[7] coupling reactions for the construction of the reveromycin framework. The key components of our strategy were thus defined as vinyl iodide **3**, vinyl iodide **4**, and alkyne **5**. Compound **5** was further disconnected, revealing aldehyde **6** and iodide **7** as potential precursors. Application of this plan to the synthesis of **2** is shown below.[8]

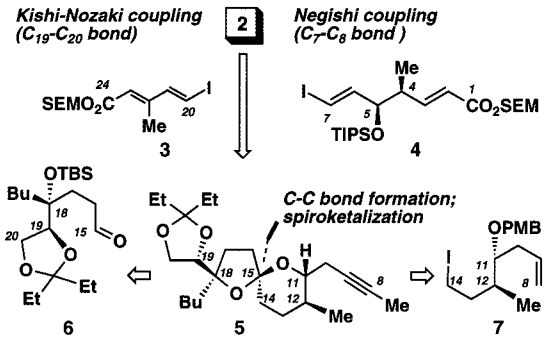
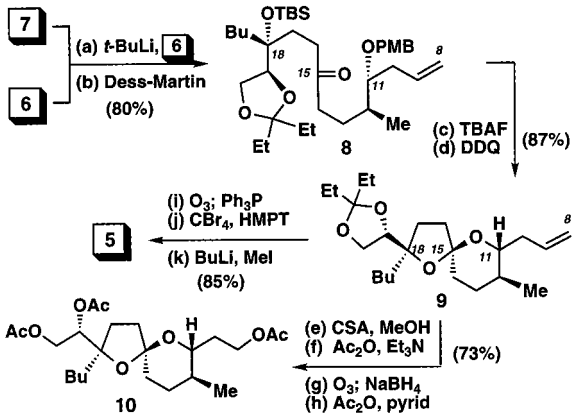


Figure 1. Strategic bond disconnections of reveromycin B (**2**).

Scheme 1. Synthesis of the C8−C20 Fragment **5**[a]



[a] Reagents and conditions: (a) 1.0 equiv **7**, 2.1 equiv *t*-BuLi, −78 °C, Et_2O, 0.5 h, then 1.4 equiv **6**, 0.5 h, 84%; (b) 1.2 equiv Dess−Martin periodinane, CH_2Cl_2, 25 °C, 1 h, 95%; (c) 1.5 equiv TBAF·THF, THF, 50 °C, 2 h; (d) 1.5 equiv DDQ, wet CH_2Cl_2, 15 min, 25 °C, 87% (over two steps); (e) 0.1 equiv CSA, CH_2Cl_2/MeOH, 9:1, 25 °C, 3 h, 80%; (f) 3.5 equiv Ac_2O, 7.0 equiv Et_3N, CH_2Cl_2, 0 °C, 3 h, 97%; (g) O_3, CH_2Cl_2, −78 °C, then 5.0 equiv $NaBH_4$, MeOH, 25 °C, 1 h, 97%; (h) 1.5 equiv Ac_2O, 3.0 equiv pyridine, CH_2Cl_2, 25 °C, 15 min, 97%; (i) O_3, CH_2Cl_2, −78 °C, then 1.5 equiv Ph_3P; (j) 5.0 equiv CBr_4, 10 equiv HMPT, THF, −30 °C, 30 min, 89% (over two steps); (k) 2.1 equiv BuLi, THF, −78 to −20 °C, 20 min, then 5.0 equiv MeI, THF, −78 to 0 °C, 2 h, 95%.

The synthesis of fragment **5** is illustrated in Scheme 1 and requires union of aldehyde **6**[9] with iodide **7**.[9] To this end, lithiation of **7** (*t*-BuLi, −78 °C) followed by addition of **6** and subsequent Dess−Martin periodinane oxidation of the resulting C15 hydroxyl group afforded ketone **8** (2 steps, 80% overall yield). Sequential deprotection of C18 and C11 hydroxyl groups (TBAF, DDQ) furnished spiroketal **9** (2 steps, 87% overall). The structure of **9** was unambiguously confirmed by its conversion to triacetate **10**, which exhibited identical spectroscopic and analytical data with the known **10**, obtained by degradation of the natural reveromycin.[5a] Compound **9** was then transformed to the desired alkyne **5** via ozonolysis of the terminal olefin and treatment of the resulting aldehyde under the modified Corey−Fuchs conditions (three steps, 85% overall yield).[10]

The synthesis of the C1−C7 fragment **4** proceeded as depicted in Scheme 2. Evans' aldol methodology[11] was employed to set the stereochemistry at the C4 and C5 carbons, and thus, aldehyde

(1) Osada, H.; Koshino, H.; Isono, K.; Takahashi, H.; Kawanishi, G. *J. Antibiot.* **1991**, *44*, 259. Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiotics* **1992**, *45*, 1420. Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409.

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(3) For a recent review on the control of cell cycle using natural products see: Hung, D. T.; Jamison, T. F.; Schreiber S. L. *Chem. Biol.* **1996**, *3*, 623.

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

(5) For synthetic studies from other laboratories, see: (a) Shimizu, T.; Kobayashi, R.; Osako, K.; Osada, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6755. (b) McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196.

(6) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.

(7) Kishi Y. *Pure Appl. Chem.* **1992**, *64*, 343. Cintas, P. *Synthesis* **1992**, 248.

(8) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

(9) Experimental details for the synthesis of **3**, **6**, and **7** are included in Supporting Information.

(10) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(11) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

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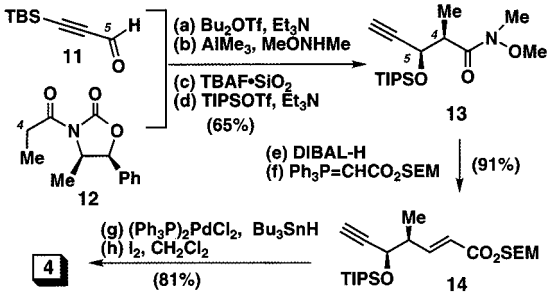
Scheme 2. Synthesis of the C1−C7 Fragment **4**[a]



[a] Reagents and conditions: (a) 1.0 equiv **12**, 1.0 equiv Bu_2BOTf, 1.2 equiv Et_3N, then 1.3 equiv **11**, CH_2Cl_2, −78 to 0 °C, 2 h, 80%; (b) 9.0 equiv $AlMe_3$, 9.0 equiv MeO−NHMe·HCl, THF, −30 to 0 °C, 2 h; (c) 2.0 equiv TBAF·SiO_2, THF, 25 °C, 3 h; (d) 1.5 equiv TIPSOTf, 3.0 equiv 2,6−lutidine, CH_2Cl_2, 25 °C, 15 min, 81% (over three steps); (e) 2.5 equiv DIBAL-H, THF −78 °C, 0.5 h; (f) 2.5 equiv $Ph_3P{=}CH{-}CO_2SEM$, CH_2Cl_2, 25 °C, 15 h, 91% (over two steps); (g) 0.02 equiv $(Ph_3P)_2PdCl_2$, 1.5 equiv Bu_3SnH, benzene, 5 °C, 10 min, 91%; (h) I_2, CH_2Cl_2, 0 °C, 5 min, 90%.

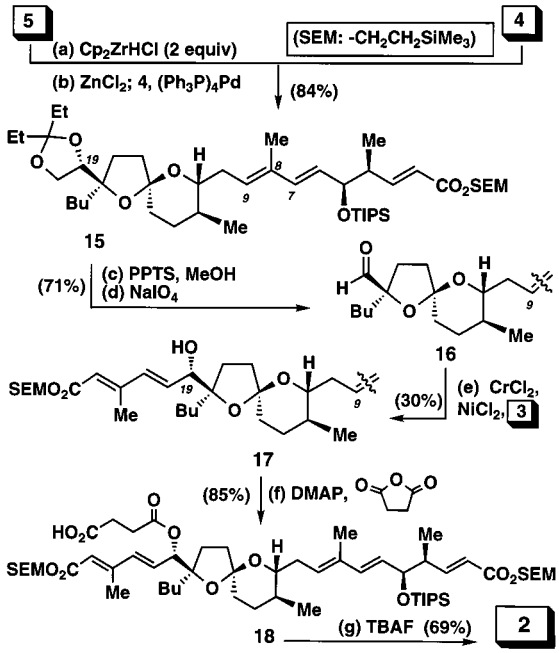
11 gave rise to alkyne **14**, via amide **13** (6 steps, 59% overall yield). Hydrostannylation of **14** using catalytic Pd(II) afforded the vinyl stannane, which upon treatment with iodine generated the desired vinyl iodide **4** (81% overall).[12]

Having completed the synthesis of the C8−C20 and C1−C7 fragments, our attention was focused on the construction of a sterically hindered C7−C8 bond. This was successfully achieved with the utilization of the modified Negishi coupling conditions, recently reported by Panek and Hu.[6,13] Thus, hydrozirconation of **5**, followed by treatment with $ZnCl_2$ and subsequent addition of vinyl iodide **4** and $Pd(PPh_3)_4$, afforded the desired cross-coupled product **15** in one pot and 84% yield (Scheme 3). It is worthwhile to comment on the efficiency and superiority of the above coupling as compared to the Stille-type reaction for the formation of the C7−C8 bond.[14]

The final steps of the reveromycin B (**2**) synthesis are described in Scheme 3. Acid-catalyzed deprotection of the acetonide functionality of **15**, followed by oxidative cleavage of the resulting diol, gave rise to aldehyde **16** in 71% overall yield. This set the stage for the crucial Kishi−Nozaki coupling[7] of **16** with **3**,[9] which afforded alcohol **17** (1.2:1 ratio at C19, 65% combined yield). Despite several attempts to increase the yield and d.e. of this reaction, we observed no significant improvement. Nonetheless, it is important to recognize the remarkable selectivity of the organochromium species for a hindered aldehyde in the presence of other potent electrophilic carbon centers.[15]

NOE experiments indicated that the minor diastereomer, formed via the Kishi−Nozaki reaction, had the correct (*S*) stereochemistry at the C-19 carbon center. This compound was subsequently esterified with succinic anhydride to yield the fully protected reveromycin B (**18**) (85% yield). Finally, TBAF-induced deprotection[16] of **18** generated synthetic reveromycin B (**2**) (69% yield). Synthetic compound **2** exhibited spectroscopic and analytical properties identical to those of the natural product.[17]

Scheme 3. Synthesis of Reveromycin B (**2**)[a]



[a] Reagents and conditions: (a) 1.0 equiv **5**, 2.0 equiv Cp_2ZrHCl, THF, 50 °C, 2 h; (b) 3.0 equiv $ZnCl_2$, THF, 5 min, 25 °C; then 1.1 equiv **4**, 0.05 equiv $(Ph_3P)_4Pd$, THF, 2 h, 25 °C, 84%; (c) 3.0 equiv PPTS, MeOH, 3 h, 40 °C, 75%; (d) 6.0 equiv $NaIO_4$, THF:H_2O (2:1), 2 h, 0 °C, 95%; (e) 4.0 equiv **3**, 24 equiv $CrCl_2$ (with 0.5% $NiCl_2$), DMF, 25 °C, 3 h, 65% (1.2:1 ratio at C19); (f) 10 equiv succinic anhydride, 12 equiv DMAP, 25 °C, 3 h, 85%; (g) 10 equiv TBAF·THF, THF, 2 h, 25 °C, 69%.

In summary, the first total synthesis of reveromycin B (**2**) has been designed and accomplished. Crucial steps of our strategy included a modified Negishi coupling[6,14] and a Kishi−Nozaki coupling,[7] that were applied for the installation of the polyene-containing side chains of **2**. Our synthesis demonstrates the utility of the above methodologies for the construction of complex, polysubstituted dienes. The highly convergent route with the longest sequence of 21 steps could provide access to a variety of potentially bioactive analogues. Our synthesis also confirms the proposed stereochemistry of the reveromycins.

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Supporting Information Available: Selected experimental procedures and spectral data for compounds **2**−**18** (PDF). See any current masthead page for Web access instructions.

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(13) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914.

(14) Our earlier attempts to exploit Stille cross-coupling chemistry for this transformation proved to be either unsuccessful or produced **15** in low yields.

(15) For a recent impressive demonstration of the application of the Kishi−Nozaki coupling to the synthesis of complex spiroketals, see: McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(16) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711. Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1989**, *30*, 7149.

(17) We thank Professor H. Osada (RIKEN Institute, Japan) for providing us with the NMR data of natural reveromycin B.