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Total Synthesis of (−)-Reveromycin B

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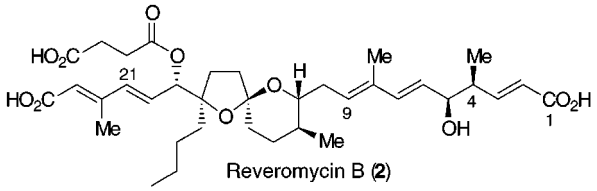
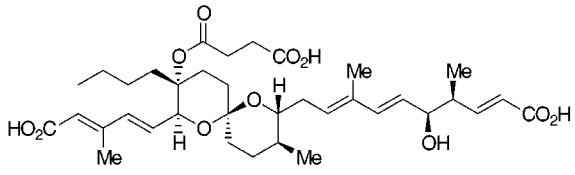
ABSTRACT

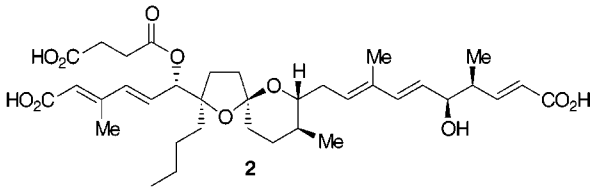


The total synthesis of the epidermal growth factor inhibitor reveromycin B (2) is described. A novel, convergent, and stereoselective reaction sequence was utilized to construct the 5,6-spiroketal system 10 which was converted into the natural product 2 by a 16-step sequence.

The reveromycins A (**1**) and B (**2**) are members of a novel family of bioactive spiroketal-containing natural products isolated from a soil actinomycete belonging to the *Streptomyces* genus.[1,2] These compounds were found to act as inhibitors of the mitogenic activity of epidermal growth factor (EGF) and may represent a new class of antitumor agents.[3] The structures of **1** and **2** were deduced by spectroscopic analysis while the absolute configuration depicted was inferred from chiroptical and spectroscopic analysis of various degradation products.[4] Synthetic studies toward these compounds have been initiated by several groups,[5,6] and the first total synthesis of reveromycin B (**2**) was recently reported by Theodorakis and Drouet.[7] A second total synthesis of **2** has also been communicated by Shimizu, Nakata, and co-workers.[8] We now report the asymmetric total synthesis of (−)-reveromycin B (**2**) which utilizes a novel convergent approach to the spiroketal segment.



1



2

Our retrosynthetic analysis of **2** is shown in Figure 1. It was envisaged that the C21−C22 bond could be constructed by a Pd(0)-mediated cross-coupling reaction while the C2−C3 and C8−C9 bonds might both be formed by Wittig reactions using the appropriate stabilized ylides to control the double-bond geometry. An asymmetric *syn*-aldol reaction could be utilized to form the C4−C5 bond and stereogenic centers and esterification at the C19 hydroxyl group would introduce the succinate half-ester. This analysis leads to the intermediate **3**, the synthesis of which has been reported by us using a hetero-Diels−Alder approach[9] to construct the

(1) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409−1413.
(2) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 1420−1427.
(3) Takahashi, H.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414−1419.
(4) Ubukata, M.; Kishino, H.; Osada, H.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1877−1878.
(5) Shimizu, T.; Kobayashi, R.; Osako, K.; Osado, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6755−6758.
(6) McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196−1197.
(7) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 456−457.
(8) Masuda, T.; Osako, K.; Shimizu, T.; Nakata, T. *Org. Lett.* **1999**, *1*, 941−944.

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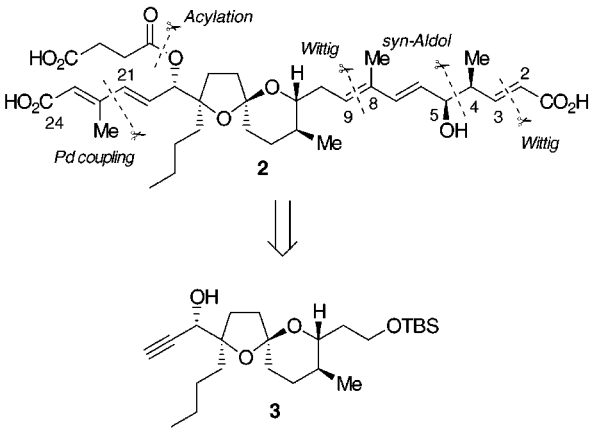
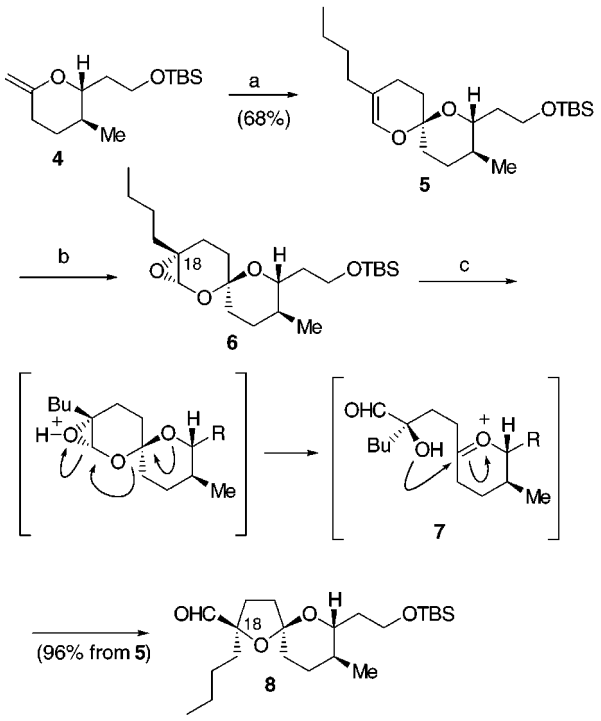


Figure 1. Retrosynthetic analysis of reveromycin B (**2**).

spiroketal system.[6] This sequence has now been modified and the key steps are shown in Schemes 1 and 2.

Scheme 1[a]

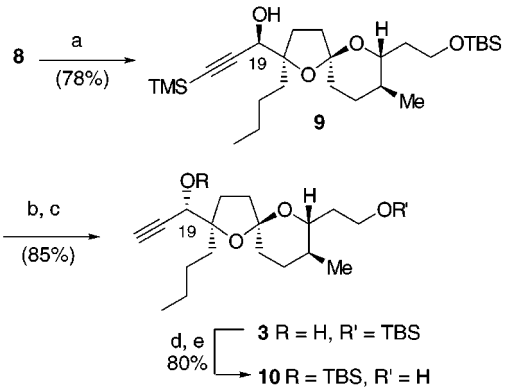


[a]Reagents and conditions: (a) 5 eq. butylacrolein, K_2CO_3, 110°C, 48h; (b) dimethyldioxirane, CH_2Cl_2, 0°C, 10 min; (c) cat. camphorsulfonic acid, rt, CH_2Cl_2, 20 min.

A [4 + 2] cycloaddition reaction between the methylenepyran **4** and freshly distilled butylacrolein in the presence of K_2CO_3 proceeded smoothly at a slightly higher temperature (110 °C) than reported previously[6] to give the 6,6-spiroketal **5** in good yield as one diastereoisomer (Scheme 1). The stereocontrol in the cycloaddition arises from axial approach of the aldehyde oxygen atom in the transition state due to the anomeric effect. Oxidation of the enol ether **5** with dimethyldioxirane[10] occurs exclusively from the face opposite the axial spiro-oxygen atom to provide the labile epoxide **6** which rearranges to aldehyde **8** upon treatment with CSA. Presumably, protonation of the 6,6-spiroketal epoxide results in formation of the intermediate oxonium ion **7** as shown, which cyclizes to the thermodynamically most stable 5,6-spiroketal **8** with the desired C18 stereochemistry.

Stereoselective addition of lithium trimethylsilylacetylide to aldehyde **8** provided the alkyne **9** (Scheme 2) with the incorrect stereochemistry at C19 as the only product.[6]

Scheme 2[a]



[a]Reagents and conditions: (a) TMSC≡CLi, THF, -78°C; (b) (i) Dess-Martin periodinane, CH_2Cl_2; (ii) L-selectride, THF, -78°C (α:β selectivity 9:1); (c) K_2CO_3, MeOH, rt, 3h; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, -40°C; (e) HF.pyridine/pyridine, THF, rt, 5h.

Oxidation followed by reduction of the resultant ketone with L-selectride and removal of the TMS group then afforded the alcohol **3** as a 9:1 mixture at C19, favoring the desired isomer. Silylation and selective desilylation of the primary TBS group gave the alcohol **10** which was easily separated from the small amount of undesired C19 isomer by flash chromatography.

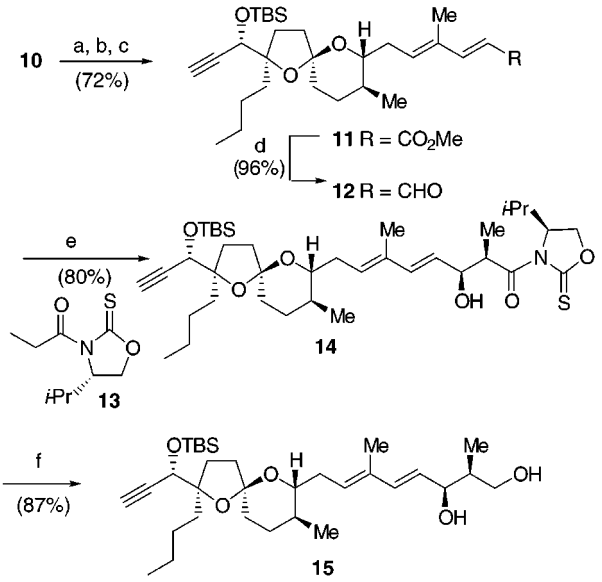
Oxidation of **10** with Dess−Martin reagent and sequential Wittig reactions gave the diene ester **11** in good overall yield (Scheme 3). The aldehyde derived from **10** was quite unreactive toward 2-(triphenylphosphoranylidene)propionaldehyde in a number of solvents; however, condensation proceeded smoothly in chlorobenzene at 100 °C. Attempts at producing the diene **11** in one step using a conjugated

(9) (a) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1954**, 672−678. (b) Ireland, R. E.; Häbich, D. *Chem. Ber.* **1981**, *114*, 1418−1427. (c) Sauvé, G.; Schwartz, D. A.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 2929−2935. (d) Tietze, L. F.; Schneider, C. *J. Org. Chem.* **1991**, *54*, 2476−2481.

(10) Murray, R. W.; Jeyaraman, R. J. *J. Org. Chem.* **1985**, *50*, 2847−2853.

stabilized ylide[11] were not fruitful. Reduction of ester **11** followed by buffered Dess−Martin oxidation[12] then afforded the labile aldehyde **12** ready for aldol condensation. After some experimentation, a tin-mediated asymmetric aldol reaction with a 1,3-oxazolidine-2-thione as the chiral auxiliary proved to be the method of choice.[13] Condensation of the aldehyde **12** with the tin enolate derived from optically pure oxazolidine-2-thione **13**[13c] provided the *syn*-adduct **14** in excellent overall yield for the three steps. Removal of the chiral auxiliary was then easily achieved by treatment of **14** with sodium borohydride in wet THF.

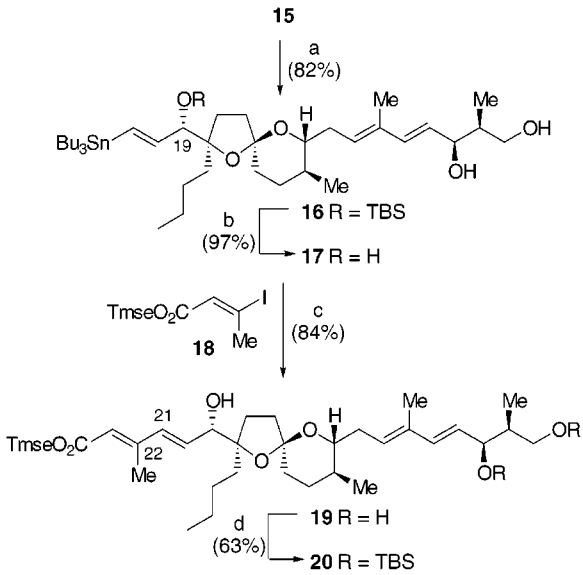
Scheme 3[a]



[a]Reagents and conditions: (a) Dess-Martin periodinane, CH_2Cl_2; (b) Ph_3P=C(Me)CHO, C_6H_5Cl, 100°C, 72h; (c) Ph_3P=$CHCO_2Me$, benzene, reflux, 24h; (d) (i) DiBALH, CH_2Cl_2, -78°C; (ii) Dess-Martin periodinane, pyridine, CH_2Cl_2; (e) oxazolidine-2-thione **13**, $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, –55°C, then aldehyde **12**, -78°C; (f) $NaBH_4$, THF, H_2O.

A number Pd(0)-mediated methods for C21−C22 bond construction were tried in model systems,[14] and the Stille protocol[15] was found to be the most effective. Thus, the diol **15** was first converted into stannane **16** by palladium-catalyzed hydrostannylation[16] (Scheme 4). Removal of the

Scheme 4[a]

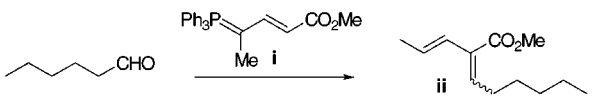


[a]Reagents and conditions: (a) Bu_3SnH, cat. $(Ph_3P)_2PdCl_2$, CH_2Cl_2, 0°C, 1h; (b) TBAF, THF, 50°C, 16h; (c) cat. $Pd_2(dba)_3$, TFP, NMP, 60°C, 30 min; (d) TBSCl, imidazole, DMF, 50°C, 3h. Tmse = -$CH_2CH_2SiMe_3$

hindered C19 OTBS group with TBAF in warm THF then furnished triol **17** which was immediately subjected to Stille cross-coupling with the vinyl iodide **18**[17] under conditions reported by Farina[18] to give tetraene **19** in excellent yield. The order of the reaction sequence to provide intermediate **19** was crucial. Hydrostannylation in the presence of the C19 OTBS group was necessary to achieve good yields and regioselectivity while the Stille coupling was most effective with the C19 alcohol free. The steric hindrance at the C19 hydroxy group eventually proved useful as triol **19** could be converted into the bis-TBS ether **20** under standard silylation conditions.

The final sequence to reveromycin B (**2**) is shown in Scheme 5 and begins with a DCC-mediated succinoylation of **20** with the Tmse half-ester **21**[19] derived from succinic anhydride to yield ester **22**. The primary TBS group in **22** was then selectively removed by the action of HF·pyridine

(11) (a) Buchta, E.; Andree, F. *Chem. Ber.* **1959**, *92*, 3111−3116. (b) Le Corre, M. *Tetrahedron Lett.* **1974**, 1037−1040. We found that the conjugated ylide **i** reported by Buchta reacted with aliphatic aldehydes such as hexanal to give an undesired isomeric diene **ii** as the major product:



(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. Unbuffered Dess−Martin oxidation resulted in formation of a small amount of another aldehyde tenatively assigned as the C8−C9 geometric isomer of **12**.

(13) (a) Nagao, Y.; Hagiwara, Y.; Kumagi, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393. (b) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418−1419. (c) Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E.; Inoue, Y.; Nagase, Y.; Aoyagi, S.; Abe, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2361−2367.

(14) Details of this study will appear in a full account of this work.

(15) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Farina, V.; Krishnamurthy V. Scott W. J. In *Organic Reactions*; Paquette, L. A., Ed.; J. Wiley and Sons: New York, 1997; pp 1−652.

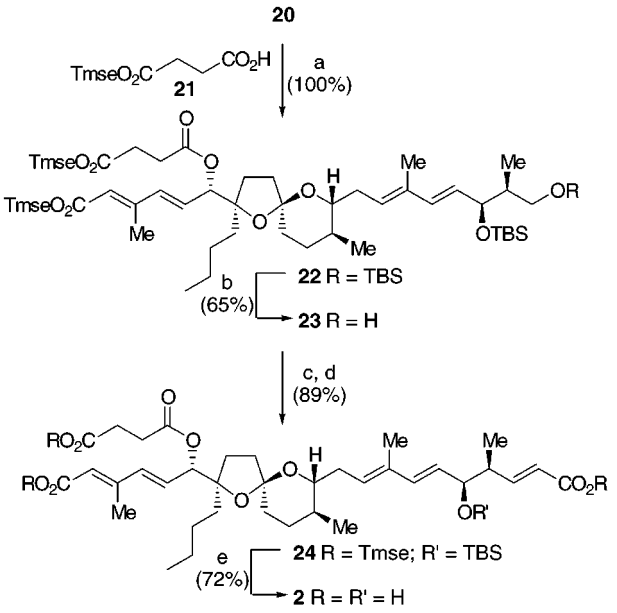
(16) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

(17) The iodide **18** was prepared by esterification ($Me_3SiCH_2CH_2OH$, DCC, DMAP, CH_2Cl_2) of the known acid: LeNoble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897−3899.

(18) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(19) Acid **21** was synthesized in quantitative yield by treament of succinic anhydride with $Me_3SiCH_2CH_2OH$, NEt_3, DMAP, and *N*-hydroxysuccinimide: Guzzo, P. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862−4867.

Scheme 5[a]



[a]Reagents and conditions: (a) DCC, cat. DMAP, 35°C, 24h; (b) HF.pyridine/pyridine, THF, rt, 7h; (c) Dess-Martin periodinane, pyridine, CH_2Cl_2, rt, 1h; (d) $Ph_3P{=}CHCO_2Tmse$, CH_2Cl_2, rt, 24h; (e) 12 eq. TBAF, DMF, rt, 48h. Tmse = $-CH_2CH_2SiMe_3$

buffered with pyridine[20] to give alcohol **23**, and subsequent oxidation followed by final Wittig extension[21] then afforded the fully protected reveromycin B derivative **24**. Global deprotection[7,22] of **24** with TBAF in DMF and purification by reverse-phase chromatography (C18 silica, 40−20% H_2O/MeOH eluent) yielded reveromycin B (**2**) which was identical in all respects to the natural product.[2,23]

In summary, the total synthesis of reveromycin B (**2**) was achieved in 25 steps from methylenepyran **4**. The key features of this route include a hetero-Diels−Alder reaction followed by oxidation and subsequent acid-induced ring contraction to construct the 5,6-spiroketal system in a highly convergent and stereoselective manner, a Stille cross-coupling to form the C21−C22 bond and a tin-mediated asymmetric aldol reaction to introduce the C4−C5 *syn*-propionate. Finally, it should be noted that only one type of alcohol protecting group (TBS ether) was utilized throughout the synthesis.

Acknowledgment. We thank the Australian Research Council for financial support.

Supporting Information Available: Characterization data for compounds **10**, **11**, **14**−**16**, **19**, **20**, **22**−**24**, and synthetic reveromycin B (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The Tmse esters were stable to these conditions. A Tmse phosphonate ester has been shown to be stable to HF·pyridine/pyridine; see: Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.

(21) Tmse ylide preparation: Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1981**, *64*, 1467−1487.

(22) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711−2716. When TBAF in THF was utilized for the deprotection, the Tmse groups were removed rapidly but some C5 OTBS reveromycin B remained even after prolonged exposure. Deprotection was more effective with TBAF in DMF.

(23) We thank Dr. Hidetoshi Takahashi (Research Institute of Life Science, Snow Brand Milk Products Co. Ltd., Japan) for copies of the NMR spectra of reveromycin B.