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Total Synthesis of Reveromycin A

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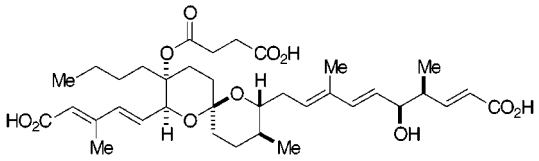
ABSTRACT



Reveromycin A (**1**)

The stereoselective total synthesis of reveromycin A (1), a potent inhibitor of eukaryotic cell growth, has been accomplished on the basis of the stereocontrolled construction of the 6,6-spiroketal system, efficient succinylation of the *tert*-alcohol under high pressure, and the introduction of the unsaturated side chains.

Reveromycins A−D (**1**−**4**, Figure 1) are novel polyketide-type antibiotics isolated from the genus *Streptomyces* as inhibitors of mitogenic activity induced by the epidermal growth factor (EGF) in a mouse epidermal keratinocyte.[1] Reveromycins A, C, and D exhibit the morphological reversion of *src*^{ts}-NRK cells, the antiproliferative activity against human tumor cell lines and antifungal activity. Furthermore, reveromycin A is a selective inhibitor of protein synthesis in eukaryotic cells.

The characteristic structural features of reveromycins include a 6,6- or a 5,6-spiroketal system bearing a hemisuccinate, two unsaturated side chains, and two alkyl groups.[2,3] Their strong biological activity as potential drugs and their synthetically challenging, unique structure have attracted the attention of synthetic organic chemists, and the total synthesis of reveromycin B (**2**) has been independently accomplished by three groups.[4−6] Despite some synthetic efforts, however, no synthesis of reveromycin A (**1**), which is the major and most bioactive compound of the reveromycins, has been accomplished to date.[7−9] We now report the first asymmetric total synthesis of **1**.

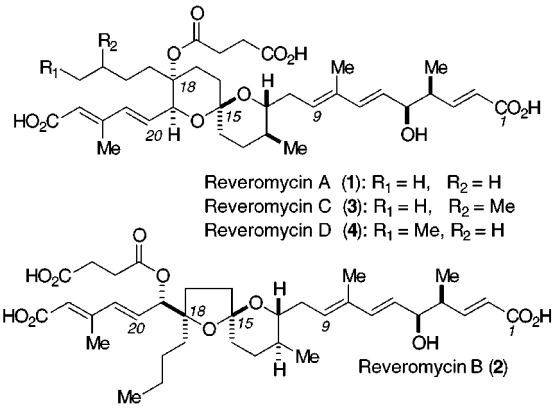


Figure 1. Structures of reveromycins.

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Our retrosynthetic analysis of reveromycin A (**1**) is shown in Figure 2. The unsaturated left and right side chains should

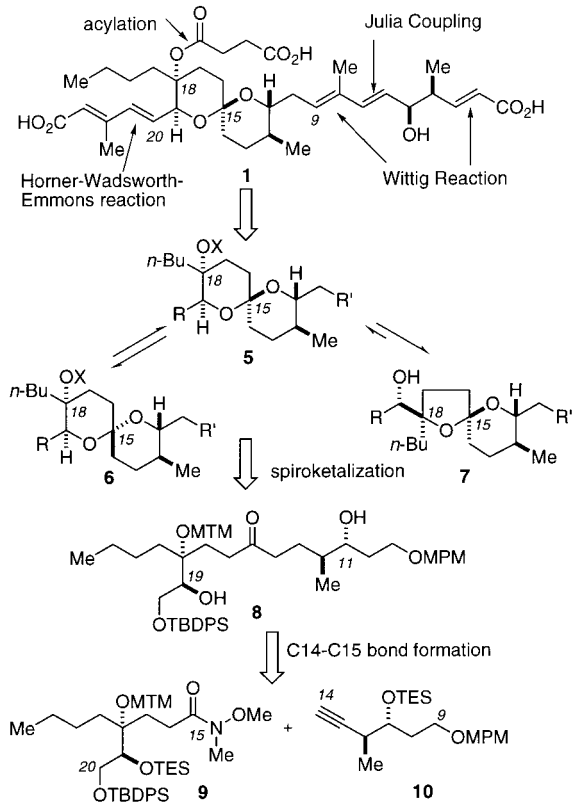
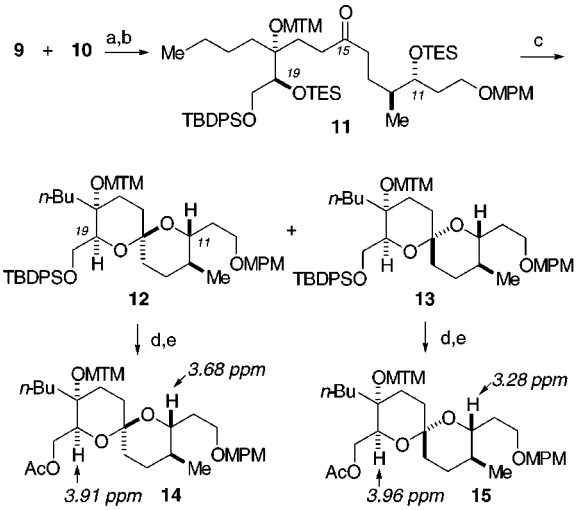


Figure 2. Retrosynthetic analysis of reveromycin A (**1**).

be produced by the Horner−Wadsworth−Emmons reaction, Julia coupling, and Wittig reaction during the later stage as a result of their instabilities. The construction of the hemisuccinate of the C18 *tert*-hydroxyl group, which is one of the difficult tasks in the synthesis of **1**, might be achieved by acylation under high pressure.[10] The main problem should be the construction of the 6,6-spiroketal core **5** in which the C18 *tert*-hydroxyl group and C19 side chain are axially oriented**.** The inherent instability of the 6,6-spiroketal system in **5** may cause some difficulties during the synthetic studies, e.g., easy transketalization of **5** (X = H) into the stable 5,6-spiroketal **7**,[7−9] transformation of **5** into the undesired 6,6-spiroketals **6** in the unnatural form via an equilibration (Figure 3),[11] and so on. The construction of **5** could be achieved by the intramolecular ketalization of the ketone **8**, in which the C18 hydroxyl group is protected as the MTM ether. The ketone **8** would be synthesized via the coupling reaction of the Weinreb amide **9** and alkyne **10**.[5]

We first investigated the union of the Weinreb amide **9**[12] and alkyne **10**[12] leading to the spiroketal core (Scheme 1).

Scheme 1. Synthesis of Spiroketals **12** and **13**[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, 0 °C to room temperature (93%); (b) H_2, Pd/C, AcOEt, room temperature (99%); (c) CSA, $CHCl_3$, MeOH, 0 °C to room temperature (**12**, 54%; **13**, 27%); (d) TBAF, THF, room temperature; (e) Ac_2O, Py, CH_2Cl_2, room temperature (98%, two steps).

The coupling reaction of **9** and the lithio derivative of **10** followed by hydrogenation furnished the saturated ketone **11** in 92% yield. The stage is now set for the construction of the 6,6-spiroketal. The MM2 calculation of the spiroketals **5** and **6** (R = R′ = CH_2OMe, X = Me), corresponding to **12** and **13**, revealed an energy difference of only 0.44 kcal/mol, which means a 2.3:1 ratio of **5** and **6**.[13] The deprotection of the two TES groups in **11** with CSA in $CHCl_3$−MeOH effected, as expected, the simultaneous intramolecular ketalization to give the 6,6-spiroketals **12** and **13** in 54% and 27% yields, respectively. The stereochemistry of **12** and **13** was determined by extensive NMR analysis of the corresponding acetates **14** and **15**; the NOEs between H11 and H20 in **14** and NOEs between H11 and H16eq in **15** were observed (Figure 4).

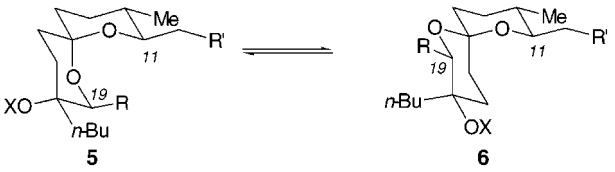


Figure 3. Conformations of 6,6-spiroketals **5** and **6**.

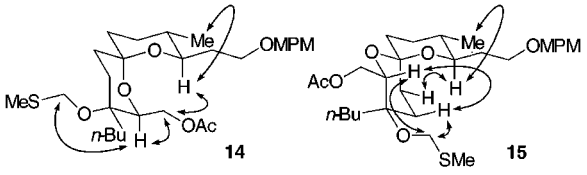
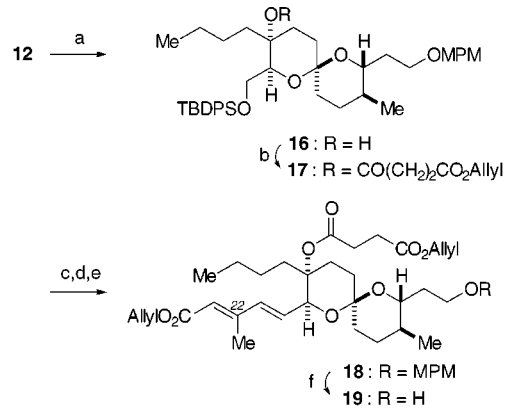


Figure 4. NOE observed in spiroketals **14** and **15**.

The 6,6-spiroketal **12** in the natural form was first subjected to the introduction of succinate and dienoic ester (Scheme 2). Deprotection of the MTM group in **12** with MeI

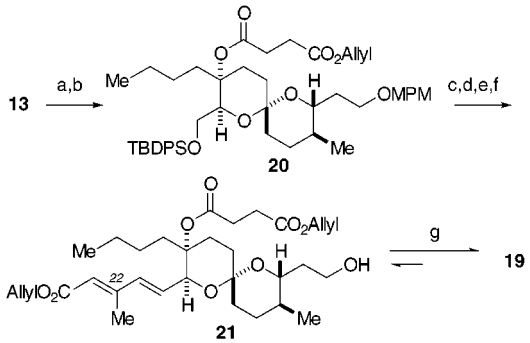
Scheme 2. Synthesis of Spiroketal **19**[a]



[a] Reagents and conditions: (a) MeI, $NaHCO_3$, acetone, H_2O, 60 °C (96%); (b) *mono*-allyl succinate, DCC, DMAP, CH_2Cl_2, 1.5 GPa, room temperature, 24 h (83%); (c) HF·Py−Py (1:4), THF, room temperature (92%); (d) Dess−Martin periodinane, MS4A, CH_2Cl_2, room temperature (e) diethyl (2*E*)-3-(allyloxycarbonyl)-2-methylprop-2-enylphosphonate, LHMDS, HMPA, THF, −78 to 0 °C (82%, two steps; 22*E*:22*Z* = 14:1); (f) DDQ, CH_2Cl_2, H_2O, room temperature (89%).

in the presence of $NaHCO_3$ proceeded without transketalization leading to the undesired 5,6-spiroketal to afford the alcohol **16** in 91% yield.[14] The next crucial step is the introduction of the hemisuccinate of the *tert*-hydroxyl group in **16**. The initial attempt using our reported procedure under high pressure (succinic anhydride in pyridine in the presence of DMAP at 1.5 GPa)[10] resulted in the recovery of **16**. After

Scheme 3. Conversion of Spiroketal **13** into **19**[a]

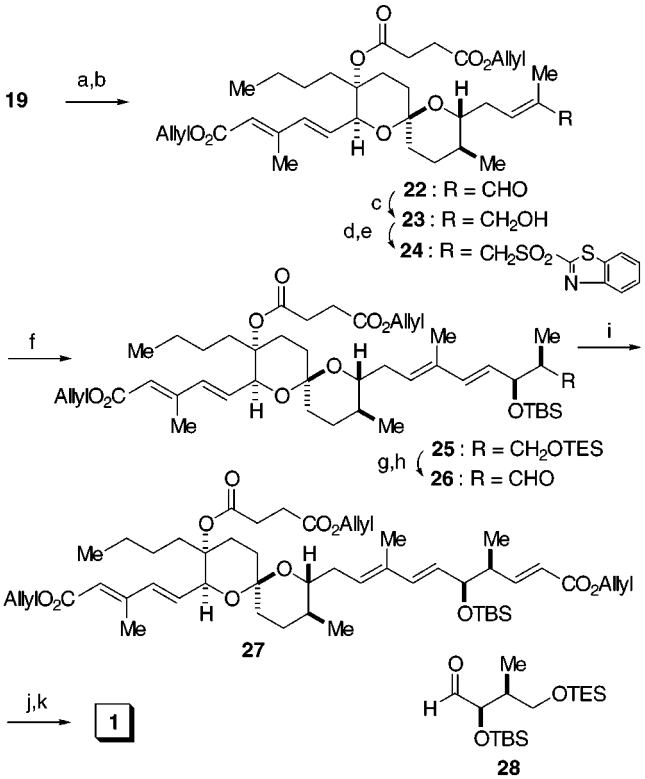


[a] Reagents and conditions: (a) MeI, $NaHCO_3$, acetone, H_2O, 60 °C (91%); (b) *mono*-allyl succinate, DCC, DMAP, CH_2Cl_2, 1.5 GPa, room temperature, 24 h (76%); (c) HF·Py−Py (1:4), THF, room temperature (95%); (d) Dess−Martin periodinane, MS4A, CH_2Cl_2, room temperature; (e) diethyl (2*E*)-3-(allyloxycarbonyl)-2-methylprop-2-enylphosphonate, LHMDS, HMPA, THF, −78 to 0 °C (88%, two steps; 22*E*:22*Z* → 50:1); (f) DDQ, CH_2Cl_2, H_2O, room temperature (88%); (g) 0.1 equiv CSA, $CHCl_3$, MeOH, room temperature, 24 h; 2 times repeated (**19**, 82%; **21**, 8%).

several attempts, we found that the succinylation of **16** with *mono*-allyl succinate and DCC at 1.5 GPa efficiently proceeded to give the succinate **17** in 83% yield. Desilylation of **17** with HF·Py (92%)[15] followed by the Dess−Martin oxidation gave the aldehyde, which was subjected to the Horner−Wadsworth−Emmons reaction with $(EtO)_2P(O)$-$CH_2C(Me)$=$CHCO_2Allyl$[5] and LHMDS in the presence of HMPA[16] to give the desired (20*E*,22*E*)-dienoic esters **18** along with the (20*E*,22*Z*)-isomer (**18**:22*Z*-isomer = 14:1; 82% yield, two steps). Deprotection of the MPM group in **18** with DDQ afforded the alcohol **19** in 89% yield.

Next, the conversion of the 6,6-spiroketal **13** in the unnatural form into the desired **19** was examined (Scheme 3). We anticipated that this problem should be overcome by an equilibration after the introduction of the unsaturated ester, because the MM2 calculation of the spiroketals **5** and **6** having the C19 dienoic ester (R = CH=CH−C(Me)=$CHCO_2Me$, R′ = CH_2OMe, X = Me) suggested a large energy difference (4.68 kcal/mol) in favor of **5**.[13] Being encouraged by these studies, the isomer **13** was thus

Scheme 4. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, MS4A, CH_2Cl_2, room temperature; (b) Ph_3P=C(Me)CHO, toluene, 110 °C (88%, two steps); (c) $Zn(BH_4)_2$, Et_2O, 0 °C (99%); (d) 2-mercaptobenzothiazole, *n*-Bu_3P, TMAD, benzene, 5 °C to room temperature (87%); (e) $Mo_7O_{24}(NH_4)_6$·$4H_2O$, H_2O_2, EtOH, 0 °C to room temperature (79%); (f) LHMDS, **28**, THF, −78 °C to room temperature (90%); (g) PPTS, $CHCl_3$, MeOH, 0 °C; (h) Dess−Martin periodinane, MS4A, CH_2Cl_2, room temperature (91%, two steps); (i) Ph_3P=$CHCO_2Allyl$, toluene, 80 °C (98%); (j) $Pd(Ph_3P)_4$, Ph_3P, pyrrolidine, CH_2Cl_2, 0 °C to room temperature; (k) TBAF·$3H_2O$, DMF, room temperature (71%, two steps).

converted into **21** having the C19 dienoic ester via **20** in 54% overall yield, under the same procedure for the preparation of **19** from **12**. During these steps, no equilibration was observed. Upon treatment with 0.1 equiv of CSA in $CHCl_3$−MeOH, the spiroketal **21** was, as expected, epimerized into the desired spiroketal **19** in the natural form (82% of **19** and 8% of **21** after twice repeated treatments).

The final elaboration of the labile unsaturated right side chain was accomplished in a stepwise procedure (Scheme 4). The Dess−Martin oxidation of **19** followed by the Wittig reaction gave the α,β-unsaturated aldehyde **22** (88%), which was reduced with $Zn(BH_4)_2$ to give the allyl alcohol **23** in 99% yield. The treatment of **23** with 2-mercaptobenzothiazole under the modified Mitsunobu conditions with TMAD and *n*-Bu_3P[17] gave the sulfide (87%),[18] which was subjected to the Mo(VI)-mediated oxidation to give the sulfone **24** in 79% yield. The one-pot Julia olefination[19] of **24** and the aldehyde **28** stereoselectively produced the (6*E*,8*E*)-diene **25** in 90% yield. After selective deprotection of the TES group in **25** with PPTS followed by the Dess−Martin oxidation (91% yield, two steps), the resulting aldehyde **26** was treated with $Ph_3P{=}CHCO_2Allyl$[5] to afford the α,β-unsaturated ester **27** in 98% yield. Deprotection of the three allyl groups in **27** was cleanly achieved by treatment with $Pd(Ph_3P)_4-Ph_3P$ in the presence of pyrrolidine.[20] Finally, the removal of the TBS group with TBAF in DMF gave reveromycin A (**1**) in 71% yield over two steps. The spectral data (^1H NMR, ^{13}C NMR, $[\alpha]_D$, IR, HRMS) of the synthetic **1** were identical with those of the natural reveromycin A (**1**).

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Supporting Information Available: Synthetic schemes of **9** and **10** and ^1H and ^{13}C NMR data for compounds **9**, **10**, **12**, **13**, **19**, **21**, **27**, and the synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The acid-catalyzed equilibration of spiroketal **5** (R = acetyleneTMS, R′ = CH_2OH, X = TBS) was reported to provide a mixture of **5** and **6** in a 1.5:1 ratio.[9]

(12) The synthetic schemes of **9** and **10** are included in Supporting Information.

(13) The computational calculations were performed using MM2*/MacroModel 6.0.

(14) The other conditions ($HgCl_2$, $CdCO_3$ or $AgNO_3$, 2,6-lutidine) induced transacetalization to give the corresponding 5,6-spiroketal.

(15) Deprotection of the TBDPS group in **17** or **20** with TBAF in THF at room temperature afforded the C20-succinate via the migration.

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(18) Treatment of **23** with 2-mercaptobenzothiazole−PPh_3−DEAD, which was effective for the synthesis of reveromycin B,[5] resulted in the recovery of **23**. This result would be due to the steric hindrance of the C19 dienoic ester.

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(20) Treatment of **27** with HF·Py in THF or TBAF in DMF resulted in the recovery or decomposition, respectively.