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Synthetic Studies on Reveromycin A: Stereoselective Synthesis of the Spiroketal System

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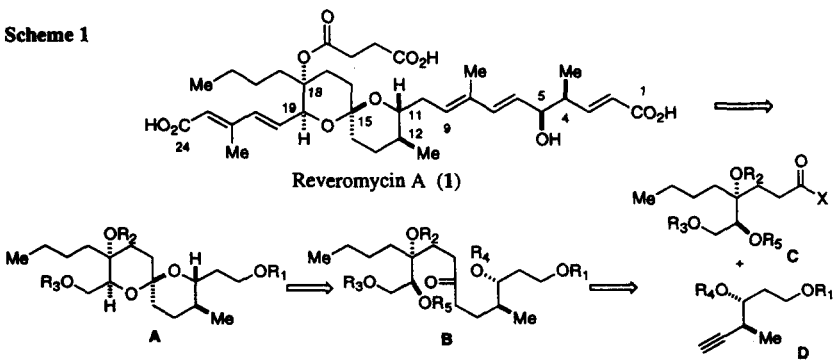
Abstract : The 6,6-spiroketal system of reveromycin A (**1**), corresponding to the C_9-C_{20} part, was stereoselectively synthesized and the absolute configuration at C_{11}, C_{12}, C_{15}, C_{18} and C_{19} of **1** was confirmed by the synthesis of the 5,6-spiroketal derivative degradated from **1**.

Reveromycin A (**1**) is a novel polyketide-type antibiotic produced by *Streptomyces sp.* and inhibits mitogenic activity induced by the epidermal growth factor in a mouse epidermal keratinocyte.[1] The characteristic structural features of **1** include a 1,7-dioxaspiro[5.5]undecane moiety, that is, the 6,6-spiroketal system comprising a hemisuccinate, two alkenyl carboxylic acids, and methyl and *n*-butyl groups.[2] Recently, the absolute configuration of **1** was determined on the basis of chemical degradation and spectroscopic evidence.[3] In this paper, we report the stereoselective synthesis of the 6,6-spiroketal system **A** (=**17**) in **1**, the key synthetic intermediate corresponding to the C_9-C_{20} part, and the elucidation of the absolute configuration at C_{11}, C_{12}, C_{15}, C_{18} and C_{19} through the synthesis.

Scheme 1

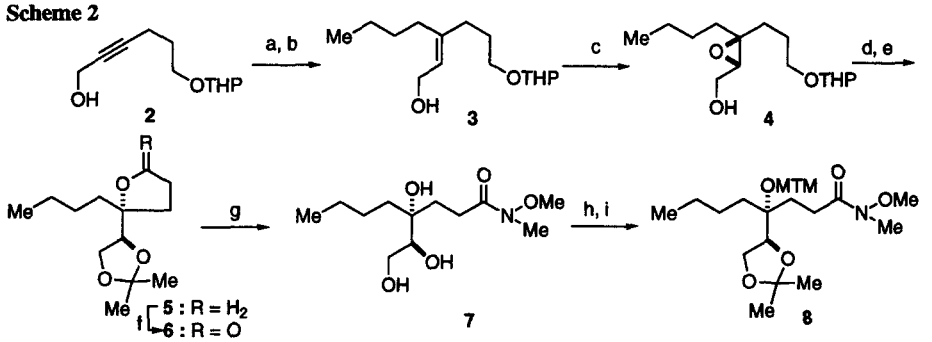


Our synthetic strategy for the 6,6-spiroketal system **A**, having the requisite functional groups for the synthesis of **1**, involves the coupling of two segments, **C** and **D**, followed by ring closure of ketone **B** to the 6,6-spiroketal.

Propargyl alcohol **2**, prepared from 4-pentyn-1-ol,[4] was chosen as the starting material for the synthesis

of segment **C**. The successive treatment of **2** with LAH-NaOMe and I_2 furnished the iodide, which was alkylated by treatment with *n*-Bu_2CuLi and then *n*-BuI[5] to give allyl alcohol **3** (88%). The Sharpless asymmetric epoxidation[6] of **3** with *t*-BuOOH in the presence of (+)-DET and Ti(O*i*-Pr)$_4$ afforded the β-epoxide **4** (92%). Hydrolysis of the THP group in **4** with AcOH effected simultaneous cyclization to give the tetrahydrofuran derivative (92% ee based on the ^{1}H-NMR spectra of the corresponding MTPA ester), whose hydroxyl groups were protected as the acetonide to afford **5** (69% from **4**). The oxidation of **5** with $RuCl_3$-$NaIO_4$[7] selectively gave γ-butyrolactone **6** (92%). The direct introduction of several alkyl groups to the lactone **6** gave unsatisfactory results. We therefore investigated the route via *N*-methoxy-*N*-methyl amide for the effective addition of segment **D**.[8a,b] Treatment of **6** with (MeO)MeNH·HCl-Me_3Al, however, resulted in low yield of the desired *N*-methoxy-*N*-methyl amide **7**. After several attempts, we found that (MeO)MeNH·HCl-Me_2AlCl exclusively underwent ring opening to give **7**.[9] The hydroxyl groups in **7** were protected as the acetonide and MTM ether by successive treatment with $Me_2C(OMe)_2$ and DMSO-Ac_2O to give the fully protected amide **8** (57% from **6**) corresponding to segment **C**.

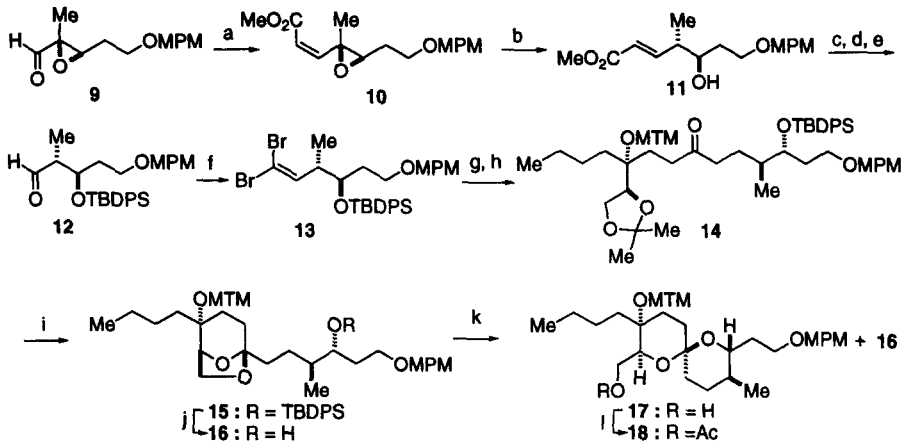
Scheme 2



Reagents and conditions: a) LAH, NaOMe, THF, reflux , then I_2, -78 °C ~ rt; b) *n*-Bu_2CuLi, Et_2O, -30 °C, then *n*-BuI, -30 °C ~ rt (88% from **2**); c) *t*-BuOOH, (+)-DET, Ti(O*i*-Pr)$_4$, 4A-MS, CH_2Cl_2, -23 °C (92%); d) AcOH, THF, H_2O, rt; e) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt (69% from **4**); f) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, rt (92%); g) (MeO)MeNH·HCl, Me_2AlCl, CH_2Cl_2, rt; h) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt; i) DMSO, Ac_2O, rt (57% from **6**).

The construction of segment **D** and subsequent coupling with **C** were then carried out. The epoxy aldehyde **9**[10] was converted into the (*Z*)-olefinic ester **10** with $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ 18-crown-6 and $KN(TMS)_2$[11] (73%). The palladium-catalyzed hydrogenolysis of the (*Z*)-alkenyloxirane **10** was performed with $Pd_2(dpa)_3$·$CHCl_3$ in the presence of *n*-Bu_3P-HCO_2H-Et_3N[12] to stereoselectively afford the *anti*-alcohol **11** (84%). After protection of the hydroxyl group as the TBDPS ether (100%), the olefin was oxidatively cleaved by successive treatment with OsO_4-NMO and $Pb(OAc)_4$ to afford the aldehyde **12** (84%), which was then treated with CBr_4-Ph_3P to give the dibromoolefin **13** (94%) corresponding to segment **D**. Treatment of **13** with 2 equiv of *n*-BuLi followed by the addition of **8** afforded the coupling product[13] which was hydrogenated on Pd/C to give the saturated ketone **14** (80%). Selective cleavage of the acetonide in **14** was performed with PPTS in MeOH to give the bicyclic ketal **15** (34%) along with the recovered **14** (22%). The TBDPS group in **15** was deprotected with *n*-Bu_4NF to give the alcohol **16** (80%). The bicyclic ketal **16** was easily converted into a 1:1 equilibrium mixture of 6,6-spiroketal **17** and **16** upon standing in $CDCl_3$ at rt. The stereostructure of **17**, corresponding to **A**, was confirmed by the NMR analysis (^{1}H NMR and NOE) of the corresponding acetate **18**[14], which proved to have the same conformation as that of reveromycin A (**1**) as shown in Fig. 1.

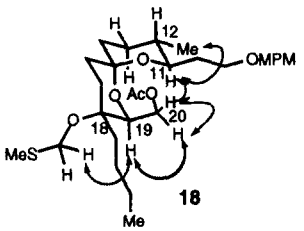
Scheme 3



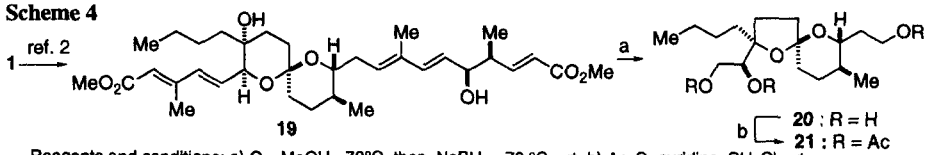
Reagents and conditions: a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-Crown-6, $KN(TMS)_2$, THF, -78 °C (73%); b) $Pd_2(dba)_3{\cdot}CHCl_3$, *n*-Bu_3P, HCO_2H-Et_3N, dioxane, rt (84%); c) TBDPSCl, imidazole, DMF, rt (100%); d) OsO_4, NMO, *t*-BuOH, acetone, H_2O, rt (97%); e) $Pb(OAc)_4$, toluene, rt (87%); f) CBr_4, Ph_3P, CH_2Cl_2, 0 °C (94%); g) *n*-BuLi, THF, -78 °C ~ rt, then **8**, 0 °C ~ rt (82%); h) H_2, Pd/C, AcOEt, rt (97%); i) PPTS, MeOH, rt (34% for **15** and 22% for **14**); j) *n*-Bu_4NF, THF, rt (80%); k) $CDCl_3$, rt (100%, **16**:**17** =1:1); l) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt (99%).

Here, the absolute configuration of the spiroketal system of **1** was reconfirmed through the following synthesis (Scheme 4).[3] The ozonolysis of the desuccinated ester **19**,[2] prepared from **1**, followed by $NaBH_4$ reduction produced the 5,6-spiroketal **20**, which was then acetylated to give the triacetate **21**,[15] $[\alpha]_D$ +44.3 (c 0.18, $CHCl_3$). The authentic triacetate **21** was also synthesized from a mixture of **16** and **17**. Treatment of the mixture with *p*-TsOH exclusively gave the 5,6-spiroketal **22** (90%) which was converted into the triacetate **21**,[15] $[\alpha]_D$ +39.1 (c 0.13, $CHCl_3$), by acetylation, deprotection of the MPM group, and acetylation. The spectral data and optical rotation of **21** prepared from natural **1** were identical with those of the synthetic **21**. Thus, the absolute configuration of the 6,6-spiroketal system in **1** was unequivocally reconfirmed through the synthesis as shown in the structure **1**, that is, 11*R*, 12*S*, 15*S*, 18*R* and 19*S* configuration.

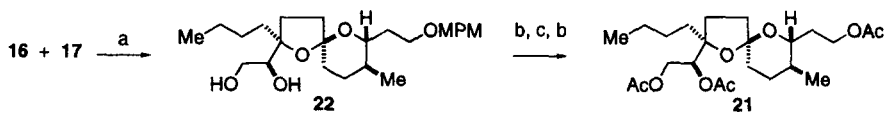
Fig. 1 NOE Data of Acetate **18**



Scheme 4



Reagents and conditions: a) O_3, MeOH, -78°C, then $NaBH_4$, -78 °C ~ rt; b) Ac_2O, pyridine, CH_2Cl_2, rt.



Reagents and conditions: a) *p*-TsOH, $CHCl_3$, rt (90%); b) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt; c) DDQ, CH_2Cl_2, H_2O, 5 °C ~ rt; b) Ac_2O, pyridine, CH_2Cl_2, rt (86% from **22**).

In conclusion, we have accomplished the stereoselective synthesis of the 6,6-spiroketal system **17** in reveromycin A (**1**), corresponding to the C_9-C_{20} part, and confirmed its absolute configuration through the synthesis of the spiroketal **21**. The total synthesis of reveromycin A is now in progress.[16]

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4. The propargyl alcohol **2** was obtained from 4-pentyn-1-ol in two steps: a) DHP, *p*-TsOH, Et_2O, rt (99%); b) *n*-BuLi, $(HCHO)_n$, THF, rt (90%).
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9. (MeO)MeNH·HCl-Me_2AlCl gave the *N*-methoxy-*N*-methyl amide in good yield even in the case of the hindered lactones and esters. The results will be reported in due course.
10. The epoxy aldehyde **9** was prepared from 1,3-propanediol. Private communication from Prof. I. Shimizu (Waseda University).
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13. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769-3772.
14. Data for **18**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.85 (d, J = 6.4 Hz, C_{12}-Me), 0.91 (t, J = 7.0 Hz, H_{28}), 2.05 (s, Ac), 2.21 (s, SMe), 3.55 (ddd, J = 6.4, 8.9, 8.9 Hz, H_9x1), 3.62 (ddd, J = 5.2, 8.9, 8.9 Hz, H_9x1), 3.68 (ddd, J = 2.7, 7.9, 7.9 Hz, H_{11}), 3.80 (s, OMe), 3.91 (dd, J = 3.4, 8.5 Hz, H_{19}), 4.15 (dd, J = 8.5, 11.3 Hz, H_{20}x1), 4.35 (dd, J = 3.6, 11.3 Hz, H_{20}x1), 4.42 (d, J = 11.3 Hz, ArCH), 4.45 (d, J = 11.3 Hz, ArCH), 4.52 (d, J = 10.4 Hz, OCHS), 4.55 (d, J = 10.4 Hz, OCHS). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 14.07 (C_{28}), 14.58 (SMe), 18.01 (C_{12}-Me), 20.99 (MeCO), 23.17 (C27), 24.60 (CH_2), 25.34 (C_{26}), 27.48 (CH_2), 32.44 (CH_2), 32.76 (CH_2), 32.98 (CH2), 33.39 (CH_2), 34.67 (C12), 55.26 (OMe), 64.37 (C_{20}), 66.42 (OCH_2S), 67.01 (C_9), 72.67 ($ArCH_2$), 73.66 (C_{11}), 74.74 (C_{18}, C19), 96.21 (C_{15}), 113.68 (Ar), 129.20 (Ar), 130.87 (Ar) , 159.03 (Ar), 170.87 (MeCO) .
15 The structure of **21** was elucidated from the chemical shift of C_{15} (106.9 ppm) and the NOE between H_{11} and H_{20}. Data for **21**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (d, J = 6.4 Hz, C_{12}-Me), 0.91 (t, J = 6.8 Hz, H_{28}), 2.03 (s, Ac), 2.04 (s, Ac), 2.07 (s, Ac), 3.49 (ddd, J = 2.6, 8.0, 10.4 Hz, H11), 4.17 (ddd, J = 6.8, 8.1, 10.7 Hz, H_9x1), 4.24 (dd, J = 8.6, 12.0 Hz, H_{20}x1), 4.32 (ddd, J = 5.1, 8.6, 10.7 Hz, H_9x1), 4.51 (dd, J = 2.1, 12.0 Hz, H_{20}x1), 5.17 (dd, J = 2.1, 8.6 Hz, H_{19}).
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