

Enantioselective Synthesis of the [6,6]
Spiroketal Core of Reveromycin A

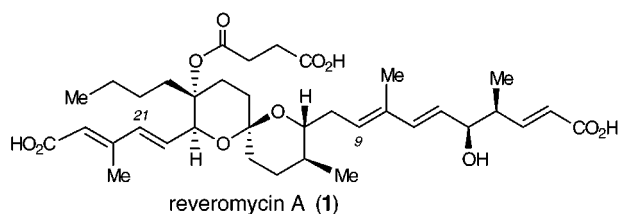
Keith E. Drouet, Taotao Ling, Hung V. Tran, and Emmanuel A. Theodorakis*

Department of Chemistry and Biochemistry, University of California, San Diego,
9500 Gilman Drive, La Jolla, California 92093-0358

etheodor@ucsd.edu

Received November 30, 1999

ABSTRACT



Reveromycin A (1) belongs to a family of microbial polyketides with unusual structural features and biological activities. The structure of 1 is composed of a [6,6] spiroketal core decorated with highly unsaturated side chains. As a prelude to the synthesis of 1, we present herein a short, efficient, and enantioselective synthesis of the C9–C21 fragment 5 (spiroketal core) of reveromycin A.

Reveromycins A–D (1–4, Figure 1) constitute a novel class of polyketide-type natural products that have recently been isolated from *Streptomyces* sp. and display intriguing biological¹ and structural features.² From a biological standpoint, these compounds exhibit strong antiproliferative activities,

which presumably derive from inhibition of the mitogenic activity of the epidermal growth factor (EGF).^{3,4} Moreover, reveromycins A, C, and D inhibit protein synthesis selectively in eukaryotic cells and induce morphological reversion of *scr^{ts}*-NRK cells.¹

From a structural standpoint, the reveromycins are triacids composed of a [6,6] or [5,6] spiroketal core bearing a hemisuccinate ester, two highly unsaturated side chains, and two alkyl groups. The combination of exquisite structure and

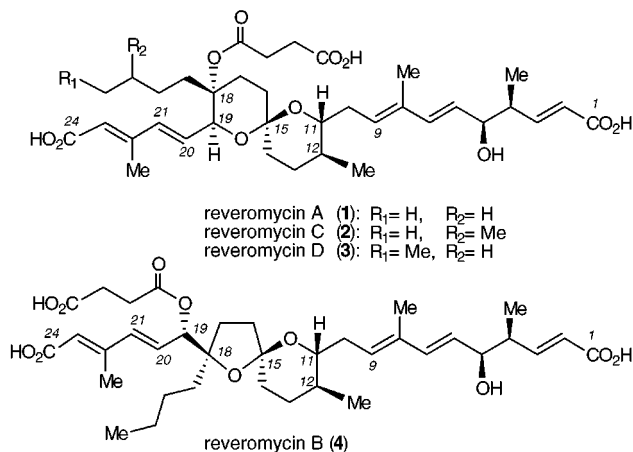


Figure 1. The reveromycin family of natural products.

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(2) (a) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409–1413. (b) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 1420–1427. (c) Ubukata, M.; Koshino, H.; Osada, H.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1877–1878.

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(4) For selected references on the importance of EGF receptor in anticancer drug design, see: Stearns, M. E.; Stearns, M. *Cancer Metastasis Rev.* **1993**, *12*, 39–52. Klijn, J. G. M.; Berns, P. M. J. J.; Schmitz, P. I. M.; Foekens, J. A. *Endocrine Rev.* **1992**, *13*, 3–17. Modjtahedi, H.; Dean, C. *Intern. J. Oncol.* **1994**, *4*, 277–296.

biological activity displayed by these compounds has attracted the interest of the synthetic community and has led recently to the development of two independent total syntheses of reveromycin B (**4**).^{5,6} Despite some reported efforts, however, no synthesis of reveromycin A (**1**) has been accomplished to date.⁷

Structural inspection of reveromycin A (**1**) and B (**4**) reveals that these molecules are constructed by a different folding of an identical C1–C24 backbone. In the case of reveromycin A, this folding creates a unique mosaic composed of a [6,6] spiroketal core,⁸ in which the C18 tertiary hydroxyl group and C20–C24 side chain are axially oriented.^{2c} The strain associated with such an arrangement is at least partially alleviated in reveromycin B, in which the C18 hydroxyl group is engaged in the spiroketal formation. Respectful of the inherent instability of the [6,6] core of **1**,⁷ we set out to approach its synthesis keeping the C18 hydroxyl group protected as a robust silyl ether. Moreover, we projected that functionalization of the C20 carbon center with an acetylene unit could provide the flexibility needed for further construction of the C20–C24 side chain. These considerations led us to define compound **5** as our synthetic target (Figure 2). Disassembly of the

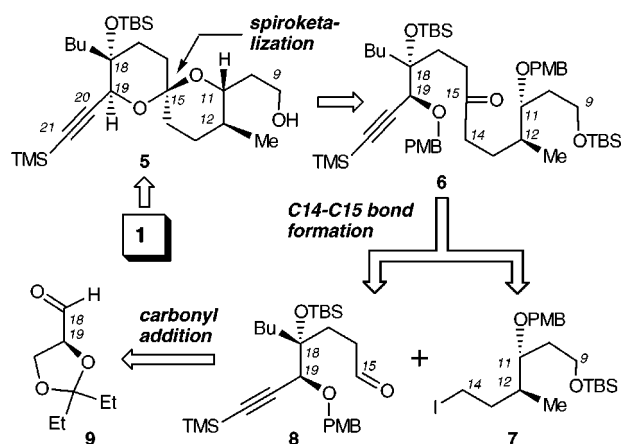
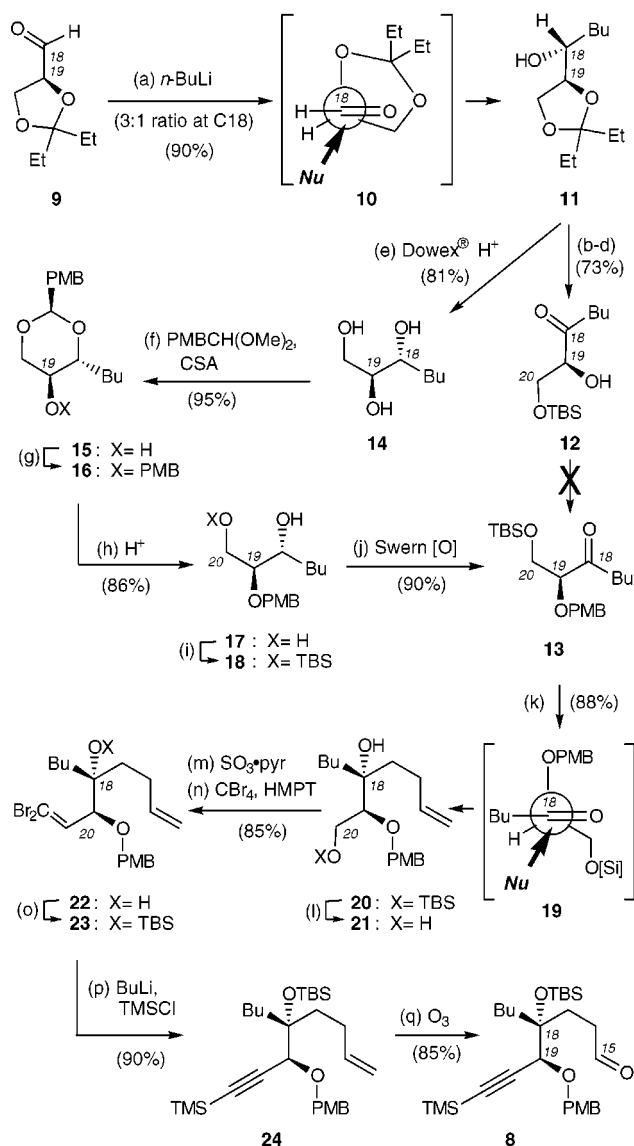


Figure 2. Retrosynthetic analysis of the [C9–C21] spiroketal fragment of reveromycin A (**1**).

spiroketal unit of **5** unveiled ketone **6** as a putative precursor. In the synthetic direction, we envisioned that concurrent release of the C11 and C19 hydroxyl groups would lead to the desired spiroketal **5** without any interference from the C18 silyl ether. Further disconnection across the C14–C15 bond revealed iodide **7**⁹ and aldehyde **8** as coupling partners, the latter being synthetically accessible from compound **9**.¹⁰ Our venture to bring this strategy to fruition is described below.

The synthesis of fragment **8** proceeded as shown in Scheme 1. Treatment of the readily available aldehyde **9**¹⁰ with *n*-BuLi at -78°C afforded a 3:1 mixture of alcohols at the newly installed C18 center in favor of compound **11** (85% combined yield). The observed stereochemical outcome

Scheme 1. Synthesis of Aldehyde **8**^a



^aReagents and conditions: (a) 1.25 equiv *n*-BuLi (1.6 M), THF, -78°C , 30 min, 90%; (b) 2.5 equiv $(\text{COCl})_2$, 3.0 equiv Me_2SO , CH_2Cl_2 , -78°C , 2.5 h, then 5.0 equiv Et_3N , -78 to 25°C , 88%; (c) 10% Dowex[®] 50WX4-400, $\text{MeOH}/\text{THF}/2/1$, 60°C , 12 h, 91%; (d) 2.5 equiv imid, 1.0 equiv TBSCl, CH_2Cl_2 , 0°C , 1 h, 91%; (e) 10% Dowex[®] 50WX4-400, $\text{MeOH}/\text{THF}/2/1$, 60°C , 15 h, 81%; (f) 1.2 equiv $\text{PMBCH}(\text{OMe})_2$, 0.1 equiv CSA, CH_2Cl_2 , 25°C , 1 h, 95%; (g) 1.2 equiv NaH, 1.2 equiv $\text{PMBCH}(\text{OMe})_2$, THF, 0°C , 3 h, 90%; (h) 10% Amberlyst[®] 15 (wet), THF/ MeOH : 2/1, 50°C , 3 h, 86%; (i) 2.5 equiv imid, 1.0 equiv TBSCl, CH_2Cl_2 , 0°C , 1 h, 95%; (j) 2.5 equiv $(\text{COCl})_2$, 3.0 equiv Me_2SO , CH_2Cl_2 , -78°C , 2.5 h, then 5.0 equiv Et_3N , -78 to 25°C , 90%; (k) 4.5 equiv Li, sand, 1.5 equiv $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{Br}$, Et_2O , -40°C ; 1.0 equiv **13**, THF, -78°C , 4 h, 88%, 8:1 ratio at C18; (l) 1.1 equiv TBAF \cdot THF, THF, 25°C , 15 min, 97%; (m) 4.0 equiv Me_2SO , 5.0 equiv Et_3N , 3.0 equiv $\text{SO}_3\cdot\text{pyr}$, CH_2Cl_2 , 0°C , 2 h; (n) 5.0 equiv CBr_4 , 10 equiv HMPT, THF, -30°C , 1 h, 85% (over two steps); (o) 3.0 equiv 2,6-lutid, 1.5 equiv TBSOTf, CH_2Cl_2 , 25°C , 24 h, 98%; (p) 2.1 equiv *n*-BuLi (1.6 M), 5.0 equiv TMSCl, THF, -78 to 25°C , 7 h, 90%; (q) O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{pyr}$: 5/5/1, -78°C , 30 min, then 2.0 equiv Ph_3P , -78°C to 25°C , 2 h, 85%.

of this reaction was consistent with addition of the nucleophile according to the modified Felkin–Ahn model **10**.¹¹ Formation of the above diastereomeric mixture was inconsequential for our synthetic plan, since both compounds were eventually converted to a single ketone, **13**. Nonetheless, to obtain analytical and spectroscopic data after each step, we separated a small amount of these alcohols and carried out the transformation to ketone **13** with the predominant diastereomer.¹²

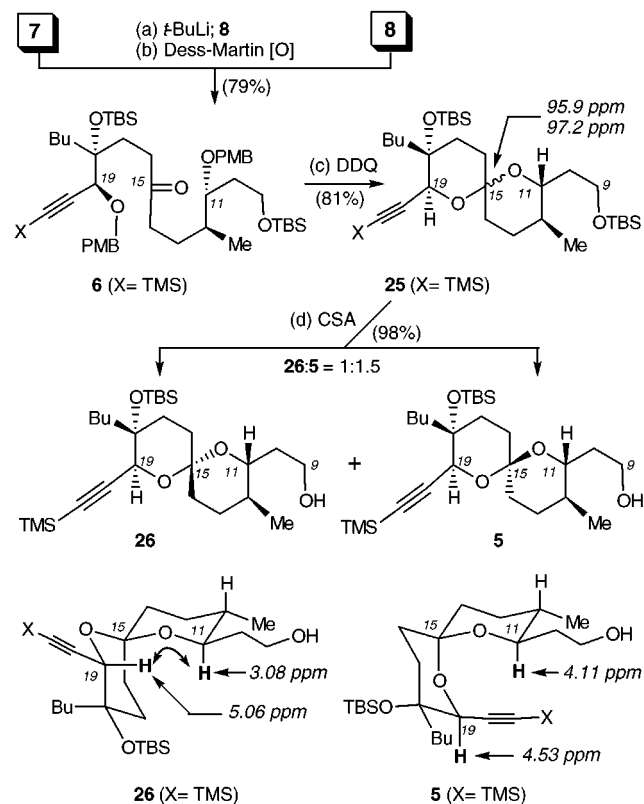
In our initial trial we attempted to produce ketone **13** from alcohol **12**, the latter being easily obtained from **11** via a sequence of three steps involving: oxidation of the C18 hydroxyl group to the corresponding ketone, acid-catalyzed removal of the acetonide unit, and selective monoprotection of the resulting diol at the primary C20 hydroxyl center (73% overall yield). However, our efforts to protect the C19 hydroxyl group of **12** as a *p*-methoxybenzyl ether met with failure, due to a concomitant scrambling and removal of the primary silyl group that occurred under both acidic (PM-BONHCCl₃, CSA) and basic (PMBCl, NaH) treatment. To overcome this problem, we pursued a synthetic maneuver, which began with exposure of compound **11** to Dowex 50WX4-400 resin to afford triol **14** (81% yield). Treatment of **14** with *p*-methoxybenzaldehyde dimethyl acetal under acid catalysis produced the six-membered acetal **15** in 95% yield, thereby rendering the C19 hydroxyl group available for further functionalization. Treatment of **15** with *p*-methoxybenzyl chloride, followed by removal of the acetal unit under carefully controlled acidic conditions furnished diol **17**, through the intermediacy of compound **16** (two steps, 77% overall yield). Selective monoprotection of **17** at the primary C20 carbon center, followed by oxidation of the C18 secondary alcohol, then gave rise to the desired ketone **13** (two steps, 76% combined yield). This maneuver allowed for the smooth conversion of aldehyde **9** to ketone **13** with a combined yield of about 35%.

The stage was now set for the installation of the C18 tertiary center. This was accomplished by reaction of **13** with 4-butenyllithium, affording a 8:1 mixture of separable alcohols (88% combined yield). Formation of the major diastereomer **20** was predicted to occur via a nonchelated controlled nucleophilic attack, as shown in intermediate **19**.¹³ Nevertheless, additional and unambiguous confirmation of

this stereochemistry had to be postponed until construction of spiroketal **5**, for which the structure was confirmed using the transformations described in Scheme 3. Compound **20** was then treated with TBAF, and the resulting C20 alcohol was oxidized to the aldehyde and transformed to dibromide **22** upon exposure to HMPT and CBr₄ (three steps, 82% overall).¹⁴ After silylation of the tertiary C18 hydroxyl group (TBSOTf, lutidine), the geminal dibromoalkene functionality was converted to alkyne **24** using the modified Corey–Fuchs conditions (two steps, 88% overall).¹⁵ Finally, ozonolysis of the terminal olefin of **24** gave rise to the desired aldehyde **8** in 85% yield.

Assembly of the spiroketal core **5** of reveromycin A proceeded as described in Scheme 2. Lithiation of iodide **7**

Scheme 2. Synthesis of Spiroketal Core Fragment **5**^a



^aReagents and conditions: (a) 1.0 equiv **7**, 2.1 equiv *t*-BuLi, –78 °C, Et₂O, 0.5 h, then 1.4 equiv **8**, 0.5 h, 81%; (b) 1.2 equiv Dess-Martin periodinane, CH₂Cl₂, 25 °C, 1 h, 98%; (c) 3.0 equiv DDQ, 10 equiv H₂O, CH₂Cl₂, 25 °C, 2 h, 81%; (d) 0.1 equiv CSA, CH₂Cl₂/MeOH: 5/1, 25 °C, 1 h, 98% (**26:5** = 1:1.5).

(*t*-BuLi, –78 °C), followed by addition of aldehyde **8** afforded a mixture of secondary alcohols at C15, which upon

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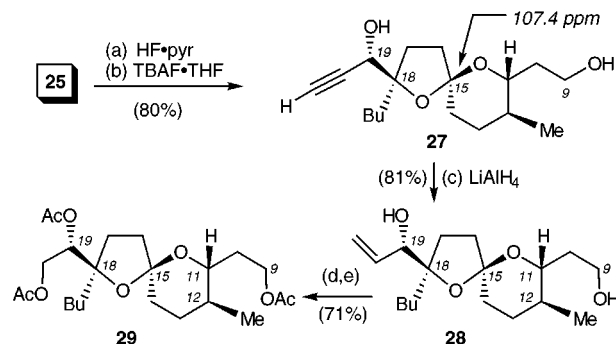
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oxidation with Dess–Martin periodinane¹⁶ furnished ketone **6** (two steps, 79% yield). Selective removal of the C11 and C19 *p*-methoxybenzyl ethers was readily accomplished with DDQ and produced spiroketal **25** as a mixture of diastereomers at the C15 center in 81% combined yield. Our attempts to equilibrate the above mixture toward one of the diastereomers using acid catalysis proved unsuccessful. Nonetheless, upon exposure to acid (CSA, MeOH) we observed selective removal of the C9 silyl group resulting in a 1:1.5 mixture of spiroketals **26** and **5** (91% combined yield) that was readily separated by column chromatography. The stereochemistry at the C15 spiroketal center was assigned on the basis of spectroscopic data. Notably, in spiroketal **26** we observed an NOE cross-peak between the H19 and H11 protons, while in spiroketal **5** such a cross-peak was not detected. Moreover, in compound **26** the C19 hydrogen appears at 5.06 ppm in accordance with the deshielding effect of the axial oxygen, while in spiroketal **5** this hydrogen appears at 4.53 ppm.¹⁷ For the same reason, in spiroketal **5** the C11 hydrogen is deshielded and resonates at 4.11 ppm, while in compound **26** this hydrogen appears at 3.08 ppm (Scheme 2). The remarkable difference in these chemical shifts may also be attributed to the orientation of the C19 acetylene group.¹⁸ In addition, confirmation that compounds **26** and **5** were diastereomers at the C15 spiroketal center was obtained by submitting spiroketal **26** to an acid-catalyzed equilibration, which, as expected, gave rise to a new mixture of spiroketals **26** and **5** in a 1.5:1 ratio and quantitative yield.¹⁹ These results are in good agreement with computational studies that predict a difference of 0.25 kcal/mol between the two spiroketals, in favor of **5**.²⁰

Although the above data confirmed the relative stereochemistry at the C15 and C19 centers, the stereochemistry at the C18 center merited further verification. To address this issue, we sought to convert compound **25** to triacetate **29** and compare its data with those of the known material.^{5,7a} This conversion was executed as shown in Scheme 3. Fluoride-induced removal of all silicon-based protecting groups led to a concomitant trans-spiroketalization, giving rise to spiroketal **27**. The observed trans-spiroketalization was evidenced by the downfield shifting of the C15 carbon center (107.4 ppm in the 5,6 spiroketal system versus 95.9 and 97.2 ppm in the 6,6 spiroketal ring). LiAlH₄-mediated reduction of the terminal acetylene (assisted by the presence of the C19 propargyl alcohol) produced olefin **28**, which

Scheme 3. Conversion of **25** to Triacetate **29**^a



^aReagents and conditions: (a) 5.0 equiv HF·pyr, CH₂Cl₂, 0 to 25 °C, 1 h; (b) 2.1 equiv TBAF·THF, THF, 15 min, 25 °C, (80% over two steps); (c) 5.0 equiv LiAlH₄·Et₂O, Et₂O, 25 °C, 18 h, 81%; (d) O₃, MeOH, -78 °C, 20 min; 4.0 equiv NaBH₄, MeOH, -78 to 25 °C, 2 h, 86%; (e) 5.0 equiv Ac₂O, 8.0 equiv pyr, CH₂Cl₂, 2 h, 25 °C, 83%.

upon exposure to ozonolysis and reduction (NaBH₄) furnished the corresponding triol. Finally, acetylation using acetic anhydride/pyridine gave rise to triacetate **29**. As expected, compound **29** exhibited spectroscopic and analytical data identical with those of the one previously described.^{5,7a} This observation confirmed unambiguously the previous predictions for the formation of the C18 stereocenter and further secured the stereochemical assignment for five out of the seven stereocenters of the reveromycin A framework.

In conclusion, we have presented a concise, enantioselective approach to the [6,6] spiroketal core fragment of reveromycin A (**1**). Fundamental to our strategy was the coupling and subsequent spiroketalization of two suitably functionalized components. Of particular interest is the observation that the desired spiroketal **5** is formed as an equilibrium mixture with its epimer **26**. This result attests to the strain of the core fragment of reveromycin A, in which the C18 hydroxyl group and the C19 side chain reside in axial orientations. Nonetheless, the desired spiroketal **5** can be separated by chromatographic techniques and is amenable to further manipulation. Extension of the above strategy to the synthesis of reveromycin A (**1**) and related compounds is currently underway in our laboratories.

Acknowledgment. Financial support from the Cancer Research Coordinating Committee, the American Cancer Society (RPG CDD-9922901), and the Hellman Foundation is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data (including ¹H and ¹³C NMR spectra) for compounds **5–8**, **13**, **25–27**, and **29**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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