Synthetic Studies toward the Reveromycins: Asymmetric Synthesis of the Spiroketal Segment of Reveromycin B

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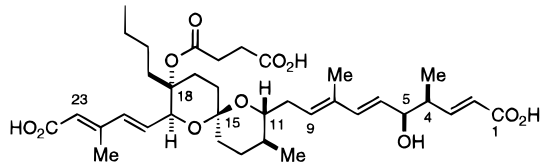
The reveromycins A (**1**) and B (**2**)[1,2] are recent examples of spiroketal-containing natural products[3] isolated from a soil actinomycete belonging to the *Streptomyces* genus. Both **1** and **2** act as inhibitors of the mitogenic activity of epidermal growth factor (EGF), while **1** also exhibits antiproliferative activity against human tumor cell lines KB and K562 as well as antifungal activity.[4] The gross structures of **1** and **2** were deduced by spectroscopic analysis, while the absolute configuration of **1** depicted followed from chiroptical and spectroscopic analysis of various degradation products.[5] The absolute configuration depicted for reveromycin B (**2**) is proposed by analogy with **1** and remains to be confirmed. Structural features of these compounds include the highly substituted 1,7-dioxaspiro[5.5]undecane (6,6-spiroketal) or 1,6-dioxaspiro-[4.5]decane (5,6-spiroketal) moieties as well the common succinate half ester and C-1−9 triene acid segment.



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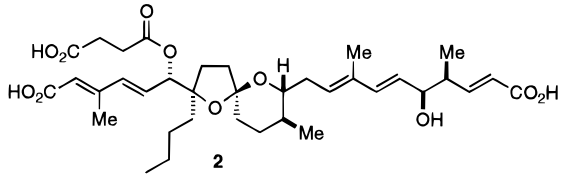
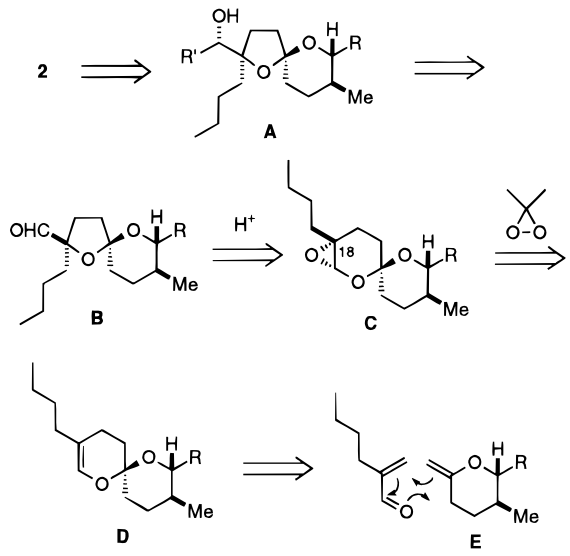


2

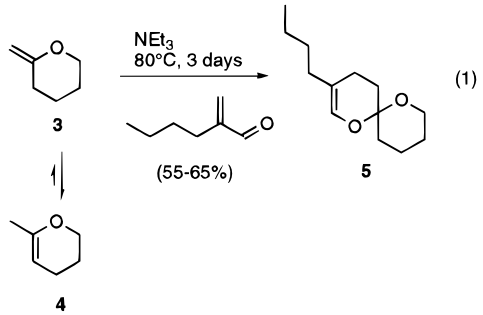
For the synthesis of reveromycin B (**2**),[6] we envisaged that a desuccinylated derivative **A** could arise from an anion addition to aldehyde **B**, which in turn could be obtained in a highly convergent manner via a hetero-Diels−Alder/oxidation/acid rearrangement sequence as depicted in Scheme 1. This sequence initially involves the construction of 6,6-spiroketal **D** by an inverse-electron-demand hetero-Diels−Alder reaction[7−9] between

Scheme 1



butylacrolein and the enol ether **E**. Stereoselective epoxidation[10] of enol ether **D** from the face opposite the axial spiroketal oxygen would set the C-18 stereochemistry, and acid-catalyzed rearrangement[10] of the intermediate epoxide **C** then provides aldehyde **B**.

A major problem with the hetero-Diels−Alder approach to spiroketals arises due to the propensity of the double bond in exo enol ethers such as **E** to undergo facile isomerization to the endo position.[11] Therefore, we first investigated the inverse-electron-demand hetero-Diels−Alder reaction between butyl acrolein and the model dienophile **3**[9,12] (eq 1). Initial attempts to induce cycload-



(1)

dition by mixing together excess enol ether **3** and freshly distilled butylacrolein in base-washed glassware at room temperature gave no spiroketal product **5**, while at higher temperatures, only rapid isomerization of **3** to exo isomer **4** occurred. This is in contrast to the cycloadditon between **3** and acrolein that occurs at room temperature over 5 days.[8] To retard this undesired isomerization various bases were added to the reaction mixture, and it was found that cycloaddition occurred at 80 °C in the presence of NEt_3 while isomerization was suppressed. Using this procedure, spiroketal **5** was obtained in good yield on a multigram scale after distillation.

Encouraged by these results, we next embarked on the asymmetric synthesis of the fully substituted spiroketal

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(2) Koshino, H.; Takahashi, H.; Osada, H.; Kiyoshi, I. *J. Antibiot.* **1992**, *45*, 1420−1427.

(3) For a review on spiroketals see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661.

(4) Takahashi, T.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414−1419.

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(6) A synthesis of the 6,6-spiroketal segment of reveromycin A (**1**) has been reported recently: Shimizu, T.; Kobayashi, R.; Osako, K.; Osada, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6755−6758.

(7) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1954**, 672−678.

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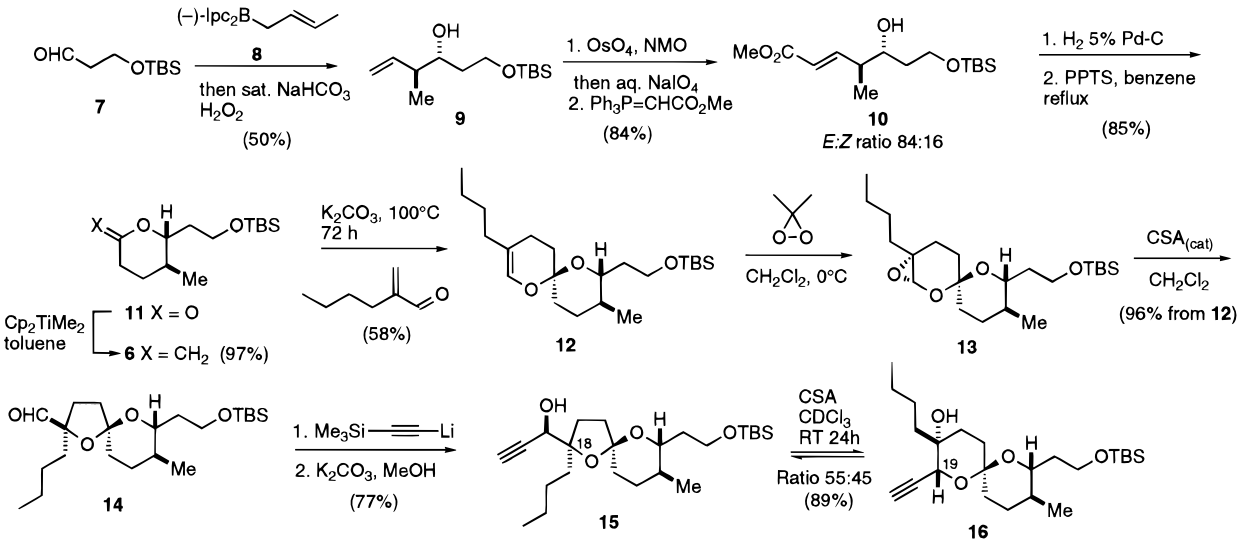
(10) Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152−7165.

(11) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303−1312. Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271−3278.

(12) Taskinen, E. *Ann. Acad. Sci. Fenn. Ser. A* **1972**, *163*, 3. A modified procedure for the synthesis of enol ether **3** can be found in the Supporting Information.

S0022-3263(96)02316-X CCC: $14.00

Scheme 2



system (Scheme 2). The approach to the enol ether **6**, required for the hetero-Diels−Alder reaction, began with the Brown crotylmetalation[13] of aldehyde **7** with crotylborane **8** (derived from (+)-pinene) to give alkene **9**.[14] Oxidative cleavage and Wittig extension provided ester **10** as a mixture of *E*/*Z* isomers that were hydrogenated and cyclized to give lactone **11** in high yield. Methylenation of **11** with dimethyltitanocene[15] then afforded the acid-sensitive enol ether **6**, which was readily purified by chromatography on basic alumina.[16] In contrast to the model system, heating a mixture of **6** and butylacrolein in the presence of NEt_3 at 80 °C resulted only in the rapid production of endo-isomerized alkene. Eventually, it was found that isomerization was sufficiently suppressed by anhydrous K_2CO_3, and the hetero-Diels−Alder reaction proceeded at 100 °C to provide desired spiroketal **12**[17] along with some isomerized alkene. Treatment of **12** with cold anhydrous dimethyldioxirane[18] gave the labile epoxide **13** as one diastereoisomer, as deduced by ^1H and ^{13}C NMR analysis, and subsequent acid-induced rearrangement with CSA afforded aldehyde **14**. Addition of lithium (trimethylsilyl)acetylide to **14** proceeded stereoselectively, and desilylation gave the acetylene **15** in excellent overall yield with the correct configuration at C-18 as determined by NOE analysis (Figure 1). Acid-induced equilibration then afforded **15** (49%) and the 19-*epi*-reveromycin A-type 6,6-spiroketal **16** (40%), the structure of which was deduced by 1D and 2D NMR spectroscopy (Figure 1). Attempts at Mitsunobu inversion[19] of alcohol **15** gave low yields, so an oxidation[20]/reduction[21] protocol was utilized to provide an inseparable mixture of the reveromycin B (**2**) 5,6-spiroketal

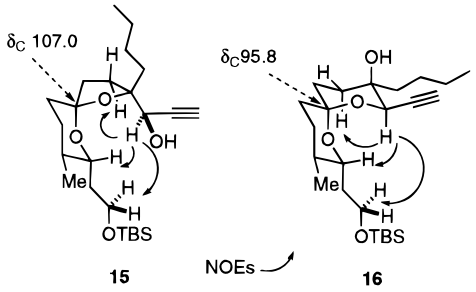
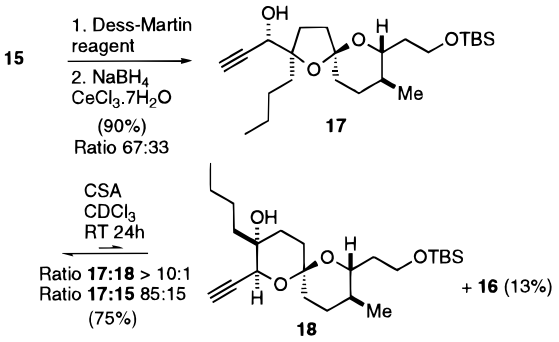


Figure 1. NOE data for compounds **15** and **16**.

Scheme 3



segment **17** and **15** in a ratio of 67:33 (Scheme 3). Unfortunately, acid-catalyzed equilibration of this mixture in $CDCl_3$ strongly favors the 5,6-spiroketal **17** over the corresponding reveromycin A-type 6,6-spiroketal **18**, in which the C-19 substituent is axially oriented. However, since the 19-*epi* isomer **15** equilibrates to the corresponding 6,6-spiroketal **16**, one cycle of the acid equilibrium process followed by chromatography provides an 85:15 mixture of the reveromycin B segment **17** and **15**, respectively, in 75% yield.

Application of this methodology to the total synthesis of the reveromycins is underway and will be reported in due course.

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

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **3**, **5**, **6**, and **9**−**17** (8 pages).

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(16) Less than 5% isomerization was detected after purification by this method.

(17) The stereochemistry at the spirocenter in **12** is controlled in the Diels−Alder reaction by the anomeric effect.

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