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Total Synthesis of (−)-Reveromycin A

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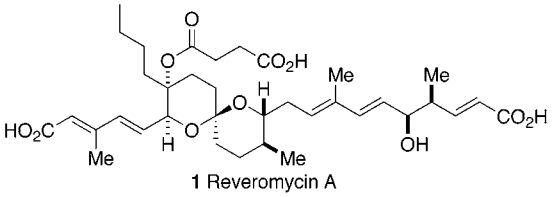
ABSTRACT

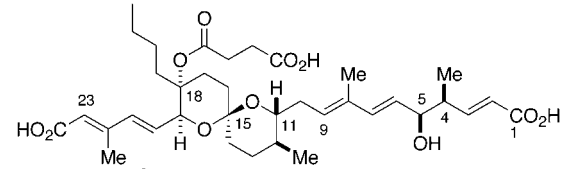


1 Reveromycin A

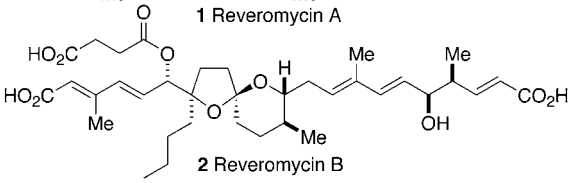
The asymmetric total synthesis of (−)-reveromycin A is described. The key steps involved a Lewis acid catalyzed inverse electron demand hetero-Diels−Alder reaction followed by hydroboration/oxidation to afford the spiroketal core 4 in a highly stereoselective manner and introduction of the C18 hemisuccinate by high-pressure acylation.

The reveromycins A (**1**) and B (**2**) are members of a family of compounds isolated from the soil actinomycete *Streptomyces* sp.[1] Reveromycin A (**1**) is a potent inhibitor (IC_{50} 0.7 μg mL^{-1}) of the mitogenic activity of epidermal growth factor (EGF) in a mouse keratinocyte. In addition, compound **1** exhibits antiproliferative activity against human tumor cell lines (IC_{50} = 1.3−2.0 μg mL^{-1}), as well as antifungal activity (MIC = 2.0 μg mL^{-1}, pH 3).[1b] Recently, reveromycin A (**1**) has been identified as a specific inhibitor of *Saccharomyces cerevisiae* isoleucyl-tRNA synthetase (IleRS) using yeast genetics and biochemical studies.[2]

So far, only one total synthesis of **1** has been reported,[3] and several approaches to the 6,6-spiroketal core have been described,[4−6] while three total syntheses of reveromycin B (**2**) have been completed.[7−9]



1 Reveromycin A



2 Reveromycin B

We now report the total synthesis of (−)-reveromycin A (**1**) using a hetero-Diels−Alder (HDA) strategy to construct the challenging spiroketal moiety of this molecule.[6]

It is known that the reveromycin A (**1**)-type 6,6-spiroketal core **I** can undergo acid-catalyzed isomerization to afford the spiroisomer **II** as the result of an unfavorable steric interaction involving the axial C19 side chain in **I** that is alleviated in **II**, albeit at the cost of an anomeric effect (Figure 1). Thus, the energy difference between the 6,6-

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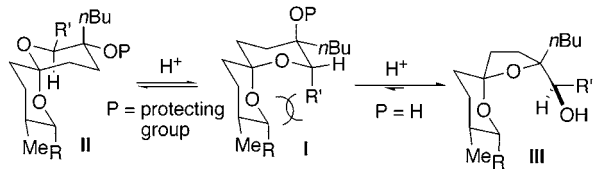
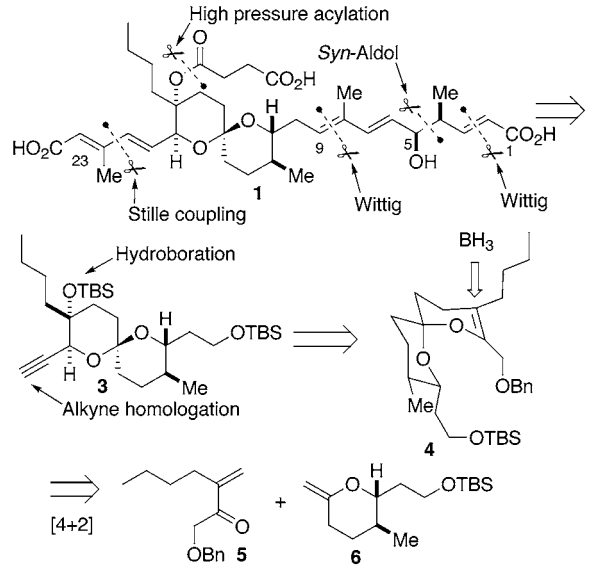


Figure 1.

spiroketals **I** and **II** is small. In addition, when the C18 alcohol is free, acid-induced isomerization provides the more stable reveromycin B (**2**) 5,6-spiroketal core **III** exclusively. This energy profile has been observed in the reported thermodynamic approaches (i.e., cyclization of a "dihydroxyketone" precursor) to the 6,6-spiroketal of **1**, which provided mixtures of spiroisomers,[3−5] and degradative[4,10] and synthetic studies[6,7,9b,11] have demonstrated the strong preference for the reveromycin B-type 5,6-spiroketal **III**.

In light of the above results, we envisioned that a kinetic approach to the reveromycin A spiroketal may circumvent the thermodynamic dilemma cited above. As shown in Scheme 1, the indicated retrosynthetic disconnections of **1**

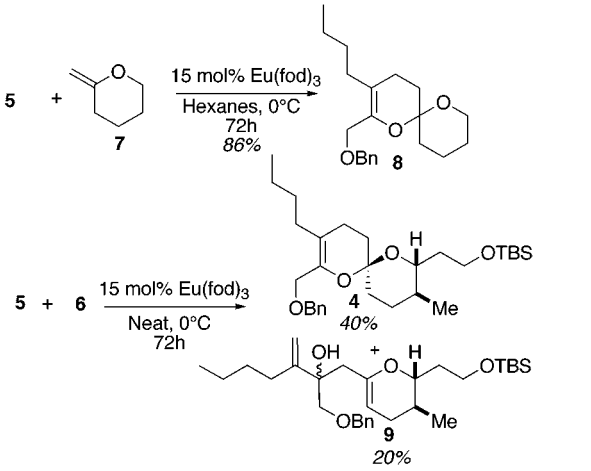
Scheme 1



lead to the intermediate 6,6-spiroketal **3**. This could be obtained from unsaturated spiroketal **4** by regio- and stereoselective hydroboration from the direction shown followed by alkyne homologation. Key spiroketal **4** could be obtained by an inverse electron demand HDA reaction[12] between the diene **5**[6] and the chiral methylene pyran **6**.[9] This critical reaction should set the stereochemistry at the spiro center by an axial approach of the carbonyl oxygen in the HDA transition state.[9] The stereochemistry at C18 and C19 is then set by the hydroboration/oxidation sequence, which circumvents the thermodynamic lability of the reveromycin A type spiroketal **I**. In addition to being stereoselective and convergent, this route would also avoid the need for a large number of different protecting groups.

Earlier, we had found that the HDA reaction of isomerizable methylene pyrans with simple hetero dienes can be achieved thermally in the presence of K_2CO_3, which effectively reduced the amount of the thermodynamically driven *exo* to *endo* isomerization of the dienophile.[9,11] In the case of diene **5**, using this additive gave low yields of spiroketal because of the base lability of the diene.[6] Therefore, Lewis acid promotion of the cycloaddition was surveyed using the diene and model dienophile **7**[9] (Scheme 2). After some experimentation, we found that the HDA

Scheme 2



reaction between **7** and diene **5** was promoted by Eu(fod)$_3$[13] in hexane solvent at 0 °C to give the spiroketal **8** in excellent yield. Unfortunately, in the case of the substituted methylene pyran **6** required for the synthesis of **1**, no HDA reaction was observed in hexane solvent and only slow isomerization occurred to give the *endo* isomer of **6**. Eventually, we found that the cycloaddition proceeded smoothly when a neat mixture[14] of the diene **5** and dienophile **6** was treated with 15 mol % Eu(fod)$_3$ at 0 °C. Although the reaction gave the desired spiroketal **4** as one diastereoisomer in a higher yield than that obtained using K_2CO_3,[6] the byproduct **9**, resulting from an ene reaction, was also isolated as a mixture of diastereoisomers. This was not observed during the studies using the model pyran **7**. The HDA reaction between **5** and **6** was also promoted by $ZnCl_2$ in THF at 0 °C to provide the adduct **4** in a comparable yield.

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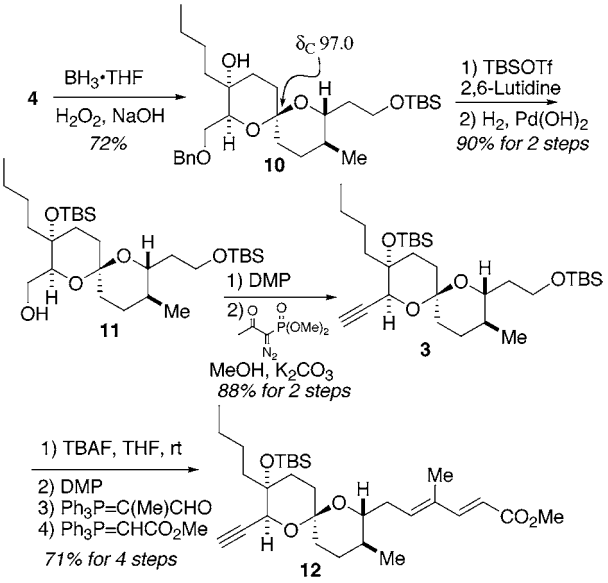
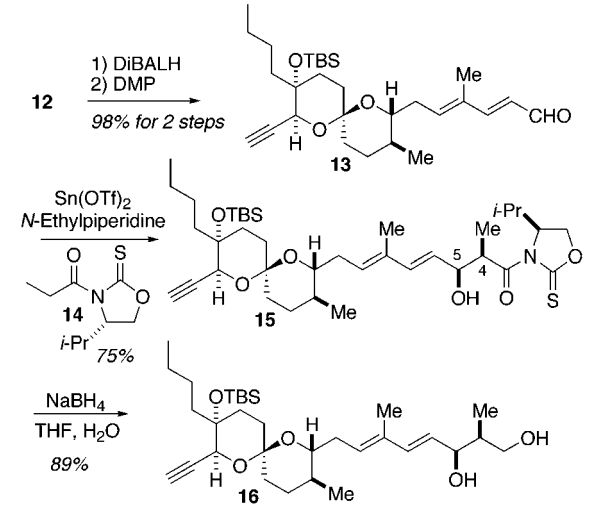
Scheme 3



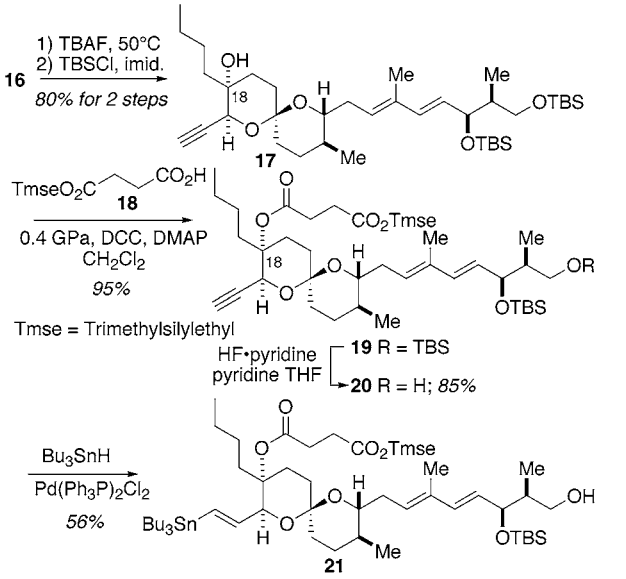
With the desired spiroketal in hand, we next tackled the introduction of the C18 and C19 stereocenters and C5−C10 chain extension as shown in Scheme 3. Hydroboration of spiroketal **4** followed by oxidation proceeded in good yield to afford the tertiary alcohol **10** as the only isomer. The integrity of the 6,6-spiroketal **10** was evidenced by the characteristic ^{13}C NMR chemical shift observed for the spiro carbon,[9,11] and the stereochemistry was confirmed by its conversion into a known reveromycin A degradation product[4] as described previously.[6] Protection of the tertiary alcohol followed by debenzylation afforded alcohol **11** ready for alkyne homologation. Oxidation[15] of **11** and alkyne formation following the Bestmann protocol[16] then gave compound **3**. Selective desilylation of the primary TBS group (TBAF, rt) followed by oxidation and two-stage Wittig extension provided the diene **12** in excellent overall yield for the four steps. Reduction of **12** and subsequent oxidation provided the substrate **13** required for the reagent-controlled aldol reaction (Scheme 4). Treatment of aldehyde **13** with the tin enolate derived from oxazolidine-2-thione **14**[9,17] afforded the desired *syn*-propionate **15**, which when exposed to $NaBH_4$ gave the diol **16** as a result of reductive auxiliary cleavage.

Removal of the C18 TBS ether required warming to 50 °C to proceed at an appreciable rate, and selective primary/secondary alcohol protection yielded bis-TBS ether **17** (Scheme 5). The stage was now set for the somewhat risky late-stage introduction of the C18 hemisuccinate. Several methods for the acylation of hindered alcohols failed,[18] affording mostly the isomerized 5,6-spiroketal as found in **2**, so we turned to the application of high pressure according to the procedure described by Shimizu and Nakata.[3,19] Thus, treatment of a mixture of alcohol **17** and monoprotected succinic acid **18**[9b] with DCC and DMAP at 0.4 GPa in CH_2Cl_2 solvent gave the desired ester **19** in very high yield. Interestingly, we found that the reaction proceeded efficiently at much lower pressures than reported previously (1.5 GPa)[3,19] and required the use of relatively simple high-pressure equipment. Selective deprotection of the primary alcohol in **19** proceeded well using HF·pyridine complex buffered with pyridine[20] to afford the alcohol **20**. Hydrostannylation of the alkyne in **20** proved somewhat difficult under Pd-catalyzed conditions[21] owing to the steric hindrance

Scheme 4



Scheme 5



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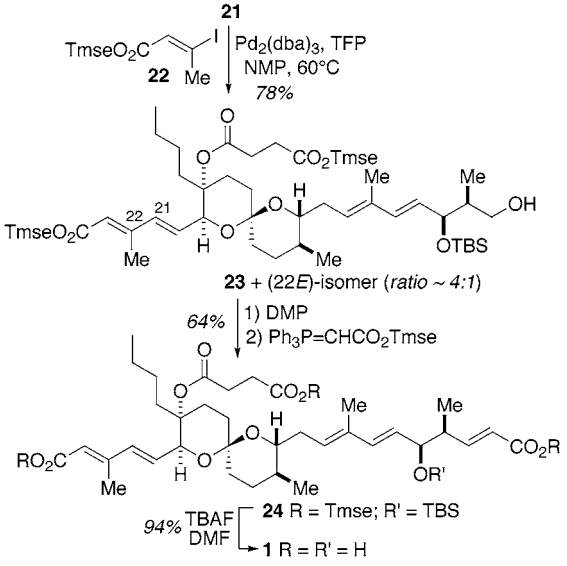
at the axial alkyne functionality, and excessive amounts of protodestannylation occurred during the reaction. We found that slow addition of the catalyst (up to 30 mol % over 5 h) was required to give the vinyl stannane **21** in acceptable yields.

The final steps to the target **1** are outlined in Scheme 6. Stille coupling between stannane **21** and vinyl iodide **22**[9b] afforded the required tetraene **23** along with a small amount of what was tentatively identified as the 22*E*-isomer. This type of isomerization was observed by us during our studies on the total synthesis of reveromycin B (**2**).[9] Oxidation of the free primary alcohol and Wittig extension[22] afforded the fully protected reveromycin A precursor **24**, which upon exposure to TBAF in DMF gave reveromycin A (**1**) in high yield. The synthetic material was purified by reverse-phase chromatography (C18 SPE cartridge, 900 mg, 40−60% MeOH/H_2O) and was identical (NMR, IR, UV, HRMS) to the natural product in all respects {$[\alpha]^{22}_D$ −122.4 (*c*, 0.16, MeOH); lit.[1b] $[\alpha]^{23}_D$ −115 (*c*, 0.1, MeOH)} including retention time on RP-HPLC.

Scheme 6



In conclusion, we have completed the total synthesis of (−)-reveromycin A (**1**), which utilized a HDA reaction hydroboration sequence to construct the spiroketal core in a convergent and stereoselective manner. Application of this methodology to related natural products is underway.[23]

Acknowledgment. We are indebted to Dr. Hiroyuki Osada (RIKEN Institute, Japan) for an authentic sample of reveromycin A (**1**) as well as copies of the NMR spectra. We also thank Professor Rob Capon (University of Queensland) for the HPLC comparisons. This work was financially supported by the Australian Research Council.

Supporting Information Available: Characterization data for compounds **1**, **3**, **4**, **9**−**12**, **15**−**17**, **19**, **20**, **23**, and **24** and copies of the NMR spectra, as well as a comparison of ^{13}C NMR chemical shifts and HPLC traces for natural and synthetic reveromycin A (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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