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Hetero-Diels–Alder synthesis of the spiroketal fragment of reveromycin A

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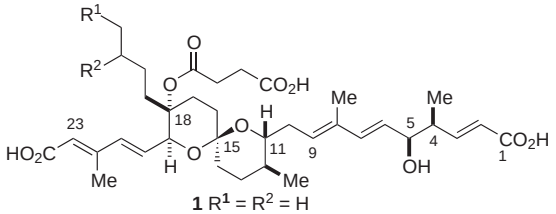
Abstract

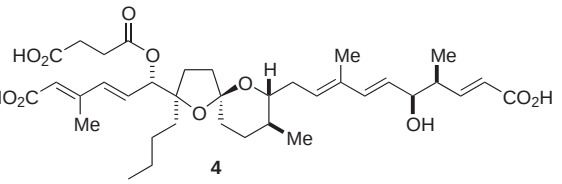
The asymmetric synthesis of the 6,6-spiroketal fragment **15** of the epidermal growth factor inhibitor reveromycin A (**1**) is described. A hetero-Diels–Alder reaction was utilized to construct the 6,6-spiroketal **14** and subsequent stereoselective hydroboration provided reveromycin A spiroketal **15**.

The reveromycins A (**1**), C (**2**), D (**3**) and B (**4**) are recent examples of natural products containing 6,6- and 5,6-spiroketal moieties which were isolated from a soil actinomycete belonging to the *Streptomyces* genus.[1–3] All the reveromycins act as inhibitors of the mitogenic activity of epidermal growth factor (EGF) which has been identified as a possible target for a new type of antitumor drug.

Reveromycin A (**1**) also exhibits antiproliferative activity against human tumor cell lines KB and K562 as well as antifungal activity.[4] The first total synthesis of (–)-reveromycin B (**4**) was reported in 1999[5] and a second total synthesis was communicated soon afterwards.[6] We have also recently reported the asymmetric total synthesis of (–)-reveromycin B (**4**)[7] in which the 5,6-spiroketal segment was synthesized by a hetero-Diels–Alder reaction followed by a novel stereoselective oxidation–rearrangement strategy.[8]



1 $R^1 = R^2 = H$
2 $R^1 = H$; $R^2 = Me$
3 $R^1 = Me$; $R^2 = H$



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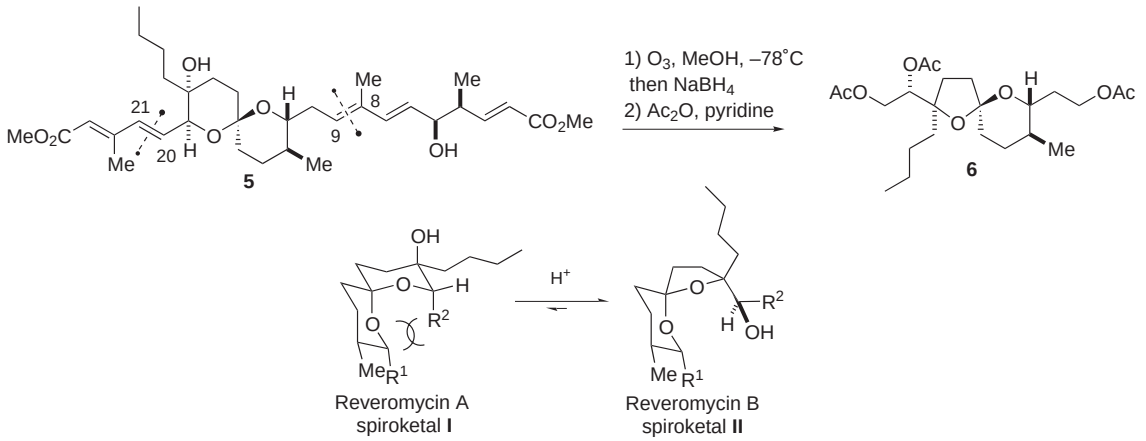
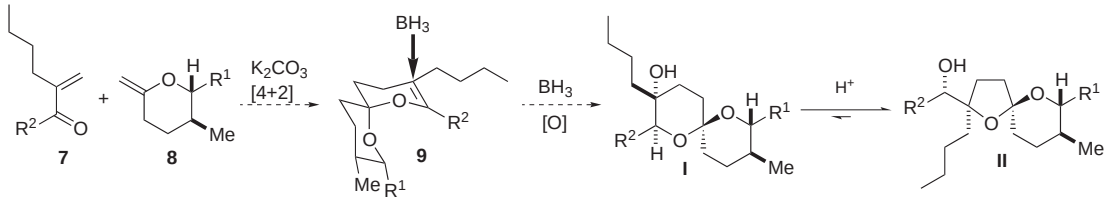
Reveromycin A (**1**) represents a greater synthetic challenge and so far, two independent groups have reported the synthesis of the 6,6-spiroketal fragment found in this compound.[9,10] In both approaches, the 6,6-spiroketal was formed by acid catalysis under *thermodynamic control* which lead to the generation of a mixture of bicylic acetal/6,6-spiroketal[9] or 6,6-spiroketal isomers[10] due to the strain present in the reveromycin A type spiroketal. It has been shown that the spiroketal system in **1** is easily isomerized into the 5,6-spiroketal fragment found in **4**.[9,10] For example, reductive ozonolysis of desucinnoylated reveromycin A dimethyl ester **5**, followed by acetylation gave the 5,6-spiroketal **6** (reveromycin B type) exclusively (Scheme 1).[9] This result can be explained by the presence of a steric interaction in the 6,6-spiroketal system **I** which is alleviated upon acid induced rearrangement to the 5,6-isomer **II**.



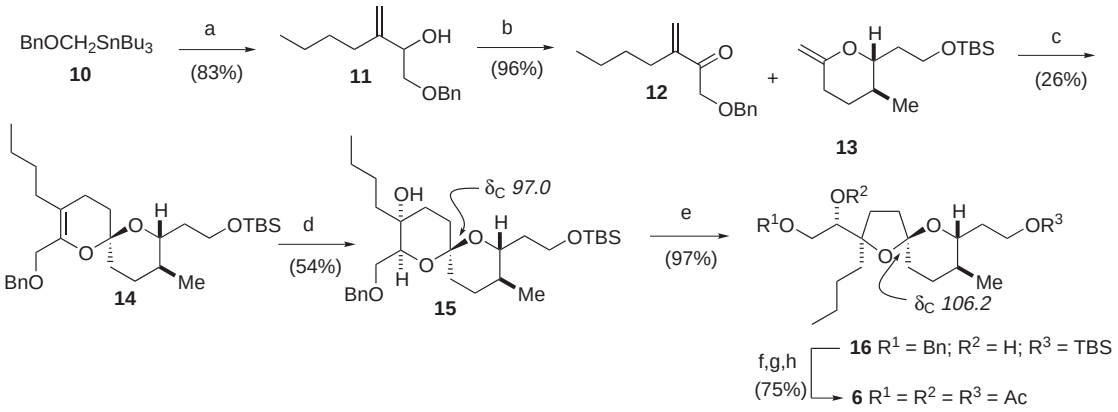
Scheme 1.

We elected to examine an alternative *kinetically controlled* approach to the 6,6-spiroketal system of **1** which utilizes a hetero-Diels–Alder reaction to construct the spiroketal system in a stereoselective manner (Scheme 2).[11] A [4+2] cycloaddition between a heterodiene **7** and a methylene pyran **8** should provide the 6,6-spiroketal **9** as one isomer where the stereochemistry at the spiro centre is controlled in the Diels–Alder reaction by the anomeric effect.[8,12] Stereo- and regioselective hydroboration of the alkene **9** should then occur from the less hindered face as shown to give the reveromycin A type 6,6-spiroketal **I** exclusively. The 6,6-spiroketal **I** should rearrange to the 5,6-isomer **II** upon treatment with a catalytic amount of acid.



Scheme 2.

To test the above proposal, a cycloaddition between the appropriately functionalized diene **12** and the optically pure methylene pyran **13**[8] (available in nine steps from 1,3-propanediol) was investigated (Scheme 3). Lithiation of the stannane **10**[13] and addition of the resultant anion to butylacrolein gave the alcohol **11**.[14] Oxidation with Dess–Martin reagent then provided the sensitive diene **12** which was immediately allowed to react with dienophile **13** in the presence of K_2CO_3[8] at 110°C to give the desired spiroketal **14** as the only detectable isomer. Other products from this reaction included *endo*-isomerized pyran as well as unidentified byproducts from the base induced degradation of diene **12**. Spiroketal **14** was then subjected to hydroboration and oxidation to provide the reveromycin A spiroketal **15**,[15] again as only one diastereoisomer, which exhibited a chemical shift for the spiro carbon (97.0 ppm) that is characteristic for the 6,6-spiroketal.[8–10] As expected, compound **15** completely rearranged to the reveromycin B 5,6-spiroketal **16** upon exposure to a catalytic amount of camphorsulfonic acid in CH_2Cl_2. The spiro carbon atom in 5,6-spiroketal **16** exhibited a signal at 106.2 ppm in the ^{13}C NMR spectrum[8,10] and the structure was further confirmed by its conversion into the known triacetate **6**[16] which was identical to the naturally derived[9] and synthetic compounds[5,9,10] by all the usual criteria.



Scheme 3. Reagents and conditions: (a) *n*BuLi, THF, −78°C, then butylacrolein; (b) Dess–Martin reagent, CH_2Cl_2, rt, 2.5 h; (c) K_2CO_3, 110°C, 22 h; (d) BH_3·THF, 0°C, 2.5 h then $NaOH/H_2O_2$, rt, 2 h (e) cat. CSA, CH_2Cl_2, 2 h, rt; (f) TBAF, THF, 16 h, rt; (g) $Pd(OH)_2$, H_2, MeOH, 2 h, rt; (h) Ac_2O, pyridine, DMAP, rt, 16 h

In conclusion, we have achieved an asymmetric synthesis of the reveromycin A 6,6-spiroketal via a hetero-Diels–Alder strategy. The synthesis is short (11 steps from 1,3-propanediol), convergent and leads to the production of the desired 6,6-spiroketal isomer **15** exclusively. In addition, the methodology could easily be applied to the synthesis of the other reveromycins C (**2**) and D (**3**). Studies towards the total synthesis of this family of compounds are underway.[17]

Acknowledgements

We gratefully acknowledge the Australian Research Council for financial support.

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14. All new compounds were fully charactized by ^{1}H and ^{13}C NMR, IR, $[\alpha]_D$ and HRMS or combustion analysis.
15. Data for spiroketal **15**: colorless oil (62 mg, 54%); R_f 0.32 (10% EtOAc/petrol); $[\alpha]_D^{21}$ +34.7 (*c* 0.75, CH_2Cl_2); IR (film) ν_{max} 3446, 2957, 2861, 1650, 1459, 1253 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.82 (d, $J=6$ Hz, 3H), 0.88 (s, 9H), 0.91 (t, $J=6.6$ Hz, 3H), 1.20–1.88 (m, 17H), 2.30 (m, 1H), 2.78 (s, 1H), 3.56–3.73 (m, 5H), 4.55 (ABq, $J=11.7$ Hz, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.21, −5.23, 14.1, 17.9, 18.3, 23.4, 24.5, 26.0, 27.5, 29.7, 29.8, 31.8, 33.6, 34.8, 36.3, 59.2, 70.1, 71.3, 72.8, 73.6, 76.0, 97.0, 127.8, 127.9 128.5, 137.5; HRMS (ESI) calc. for $C_{30}H_{52}O_5SiNa$ [M+Na^+]: 543.3482. Found: 543.3464.
16. Data for 5,6-spiroketal **6**: colorless solid, m.p. 58–59°C; R_f 0.28 (15% EtOAc/petrol); $[\alpha]_D^{29}$ +45.6 (*c* 1.0, $CHCl_3$); lit.[9] (naturally derived) $[\alpha]_D$ +39.1 (*c* 0.13, CHCl3); lit.[9] (synthetic) $[\alpha]_D$ +44.3 (*c* 0.18, $CHCl_3$); lit.[10] (synthetic) $[\alpha]_D^{25}$ +37.5 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2958, 2934, 2874, 1744, 1459, 1438, 1371, 1243, 1187, 1128, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, $J=6.3$ Hz, 3H),0.90 (t, $J=7.2$ Hz, 3H), 1.20–1.97 (m, 17H), 2.02 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 3.48 (dt, $J=2.7$, 8.4 Hz, 1H), 4.12–4.23 (m, 2H), 4.31 (m, 1H), 4.50 (dd, $J=2.3$, 12 Hz, 1H), 5.17 (dd, $J=2.3$,8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 17.7, 20.9, 21.0, 21.1, 23.2, 25.5, 29.0, 31.4, 32.2, 34.3, 34.5, 34.6, 38.4, 61.7, 63.9, 73.6, 76.5, 86.2, 106.9, 170.3, 171.1. Anal. calc. for $C_{23}H_{38}O_8$: C, 62.42; H, 8.65. Found: C, 62.19; H, 8.36.
17. Note added in proof. The total synthesis of reveromycin A has been reported recently: Shimiza, T.; Masuda, T.; Hiramoto, K.; Nakata, T. *Org. Lett.* **2000**, *2*, 2153–2156.