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Synthesis of (±)-aculeatins A and B

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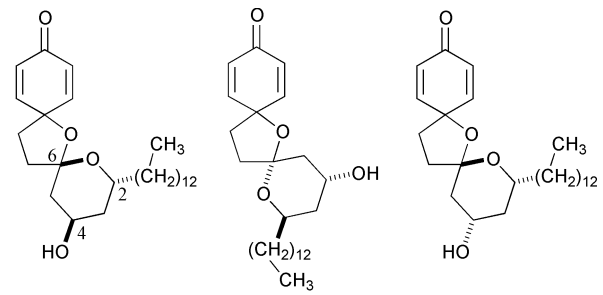
The first synthesis of two new antiprotozoal and natural products was performed using concomitant deprotecting dithiane–phenolic oxidative reactions to form in one-step the 1,7-dioxadispiro[5.1.5.2]pentadecane core.

In 2000 Heilmann and co-workers disclosed the isolation and structures of aculeatins (Fig. 1), a novel biologically active group, from *Amomum Aculeatum* rhizomes.[1,2] Aculeatins A, B, and D appear to be potent antiprotozoal agents. Aculeatin D displays in addition some antibacterial activities. Interestingly, these compounds hold a unique dispiro skeleton including a spiroketal ring system connected with a cyclohexadienone moiety. Spiro or bis-spiro-ketal structures have attracted growing attention with respect to their generation within molecular edifices of biological importance such as polyether ionophores.[3]

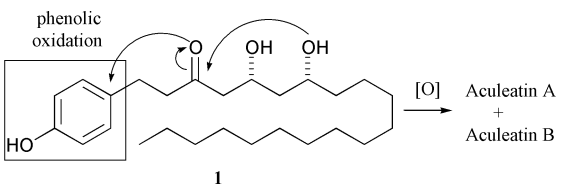


(−)-Aculeatin A [*rel*-(2R,4R,6S)] (+)-Aculeatin B [*rel*-(2R,4R,6R)] (−)-Aculeatin D [*rel*-(2R,4S,6S)]

Fig. 1 Relative configurations of aculeatins A, B, and D.

Considering that aculeatins A and B are spiro epimers, a concise synthetic approach to their 1,7-dioxadispiro-[5.1.5.2]pentadecane skeleton[4] should arise from the biosynthetic proposal (Scheme 1) involving two intramolecular cyclisations initiated by a phenolic oxidation of the plausible bioprecursor **1**. In connection with recent efforts to obtain new cyclohexadienone derivatives,[5] we became aware that phenyliodonium(III) bis(trifluoroacetate) (PIFA) can prove in this case to be the reagent of choice since it has been commonly used to perform phenolic oxidations[6] and also deprotection of dithiane groups[7] among other useful transformations.[8] Uenishi and coworkers have described the use of PIFA for simultaneous activations of ethyl enol ether and deprotection of 1,3-dithiane to form substituted cyclohexenones.[9]

In this context, we wish to report our results on the preparation of the intermediate *rac*-**8** (Scheme 2) and its direct



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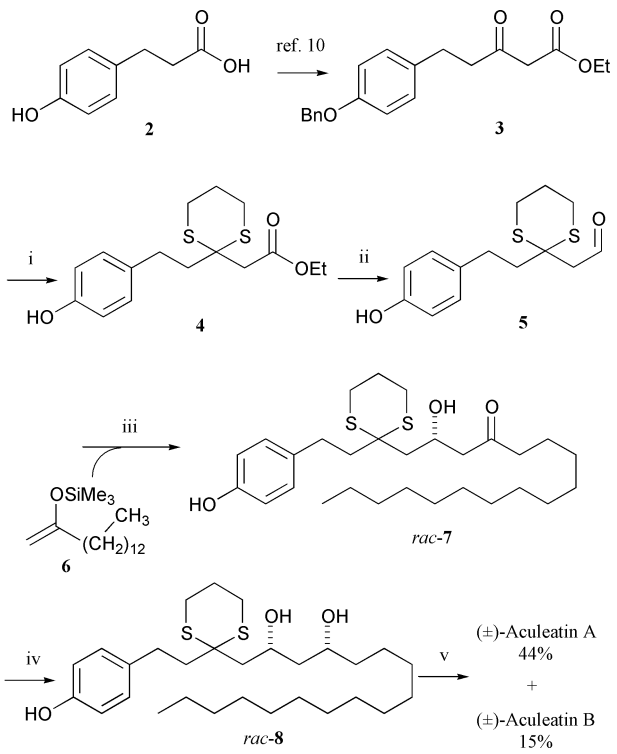
Scheme 1 Plausible synthetic pathway for the formation of aculeatins A and B from precursor **1**.

transformation into (±) aculeatins A and B along two concomitant PIFA reactions. Furthermore, the opportunity to keep a ketone protected by a 1,3-dithiane group until its removal at the final key step simplified the overall synthetic approach.

Starting from commercially available 4-hydroxyphenyl propionic acid **2**, the corresponding β-ketoester **3** was readily obtained according to Doherty's procedure.[10] Deprotection of the phenol followed by protection of the ketone gave the β-1,3-dithiane ester **4** in 88% yield. Selective reduction was carried out using DIBAL-H to form the aldehyde **5** (73%). Concurrently, the synthesis of the silyl enol ether **6** was achieved in three steps from commercially available myristoyl chloride. The aldol reaction between aldehyde **5** and silyl enol ether **6** furnished under $BF_3{\cdot}Et_2O$ catalysis the β-hydroxy ketone *rac*-**7** in 68% yield. Highly diastereoselective reduction using sodium borohydride–triethylborane in THF–MeOH (4:1) at −80 °C[11] provided the *syn* 1,3-diol *rac*-**8** in moderate yield (63%).[12] Finally, as expected, *syn* 1,3-diol *rac*-**8** was readily converted with 2.5 equivalents of PIFA in MeCN–H_2O (6:1) at 0 °C for 5 min into (±)-aculeatins A and B in isolated yields of 44% and 15%, respectively.[13] All our spectroscopical data are in agreement with those reported previously.[1] It is noteworthy that no protection was required for the remaining hydroxy group. During the intramolecular cyclisations, the construction



Scheme 2 *Reagents and conditions*: i, H_2, 10% Pd/C, EtOAc then propane-1,3-dithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 88%; ii, DIBAL-H, toluene, −80 °C, 73%; iii, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 68%; iv, Et_3B, $NaBH_4$, THF–MeOH (4:1), −80 °C, 63%; v, PIFA, MeCN–H_2O (6:1), 0 °C, 5 min.

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of the spiro epimer aculeatin A was favoured in a ratio of 3 : 1 compared to aculeatin B.

Thus, the first and concise total synthesis of (±)-aculeatins A and B have been achieved using a one-step assembling process activated by PIFA. This short synthetic route finds some applications as many racemic analogues should be readily obtained by simply changing the enol ethers during the aldol condensation with the aldehyde **5**. Moreover, the cyclohexadienone moiety also offers the potential to make various transformations. We are currently investigating the synthesis of the *syn* 1,3-diol **8** in optically pure form therefore allowing the assignment of the aculeatins A and B with their absolute configurations. The synthesis of aculeatins C[1] and D are also now under way. All these synthetic results will be reported in due course.

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