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Dipyrone approach toward the synthesis of the cytotoxic natural product auripyrone A

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ABSTRACT

An approach to the synthesis of the cytotoxic natural product auripyrone A **1** via the cyclization of an alcohol onto a γ-pyrone in **3** is described. The bis(pyrone) alcohol **3** was prepared efficiently from the advanced aldolate **4** via silyl ether cleavage, oxidation, pyrone formation, and PMB ether removal. Instead of providing auripyrone A **1**, the attempted cyclization of **3** gave the product of 1,5-acyl migration **8**. Model studies show this to be a general process; therefore, cyclization of an alcohol on such a hindered γ-pyrone under normal conditions is very difficult.

In 1996, Yamada and co-workers reported the isolation and characterization of the two polypropionate natural products, auripyrone A **1** and B **2**, from the Japanese specimens of the sea hare *Dolabella auricularia* (Fig. 1).[1] Extensive NMR investigation of these natural products revealed a complex, fully-substituted spiroketal core, capped at one end by a tetrasubstituted γ-pyrone, residing in an anomerically favored configuration where all the substituents are positioned equatorially except the C-10 methyl and the C-11 acyloxy group. Biological evaluation of auripyrone A **1** and B **2**, which differ only in the nature of their C-11 acyloxy side chains, revealed potent cytotoxicity against HeLa S_3 cells with IC_{50} values of 260 and 480 ng/mL, respectively.

To date, two total syntheses of auripyrone A **1** have been reported, one by Perkins[2] and one by our group,[3] and two total syntheses of auripyrone B **2** by Kigoshi[4] and our group.[5] The synthetic approaches of Perkins and Kigoshi toward the natural products rely on an analogous biomimetic cyclization of acyclic triketone intermediates to generate the common spiroketal moiety of auripyrone A **1** and B **2**, while our strategy utilizes a regioselective hemiketalization of keto diol intermediates followed by spiroketalization onto the stable hemiketal platform. Herein, we wish to report a different spiroketalization approach toward auripyrone A **1**.

Our alternate retrosynthetic analysis toward auripyrone A **1** is presented in Scheme 1. The spiroketal moiety of auripyrone A **1** was envisioned to arise from the acid-catalyzed cyclization of the secondary alcohol of **3** onto the γ-pyrone B under thermodynamic conditions following the protocol developed by Crimmins and Omahony.[6] The γ-pyrone B in **3** was in turn anticipated to originate from the key aldolate **4** through a sequence of deprotection, double oxidation, and cyclization under Yamamura conditions.[7] The key intermediate **4** could be obtained from the optically active epoxy silyl ether **5** as previously described by our group.[3]

Treatment of the optically active aldolate **4**[3] with HF·pyridine provided the diol **6** in 95% yield (Scheme 2). Double oxidation of the diol with Dess–Martin periodinane[8] followed by cyclization of the resulting triketone under Yamamura conditions[7] furnished the dipyrone **7** in 47% yield over two steps. Deprotection of the PMB ether of the dipyrone **7** with DDQ provided the alcohol **3** in 78% yield, which was subjected to Crimmins' conditions[6] for spiroketalization. However, treatment with TFA led to rapid equilibration to afford a 2:1 mixture of the starting material **3** and the product of acyl migration, isomer **8**. Treatment with other acids such as CSA and TsOH also resulted in the formation of a similar mixture. Furthermore, regardless of the acyl migration, no spiroketalization was observed upon prolonged exposure of the mixture of the starting material **3** and its acyl shift isomer **8** to strong acid.

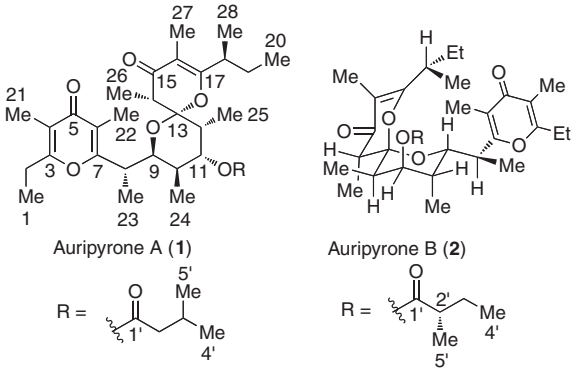

Figure 1. Structures of auripyrones A and B.

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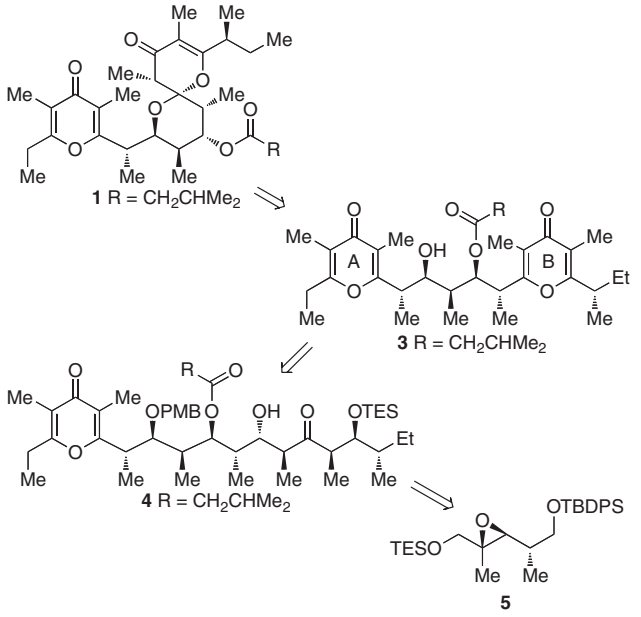
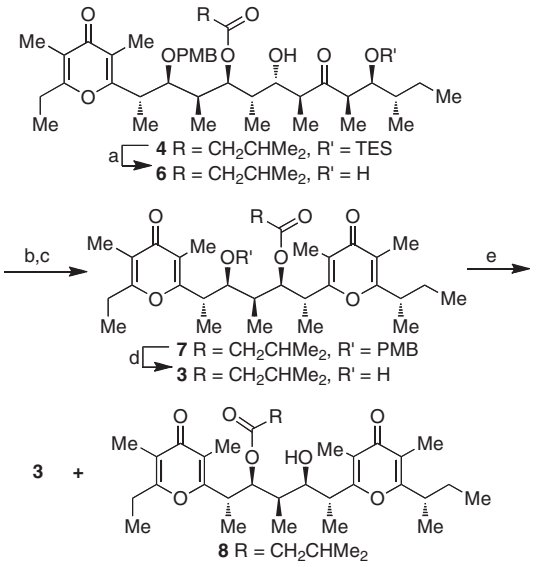
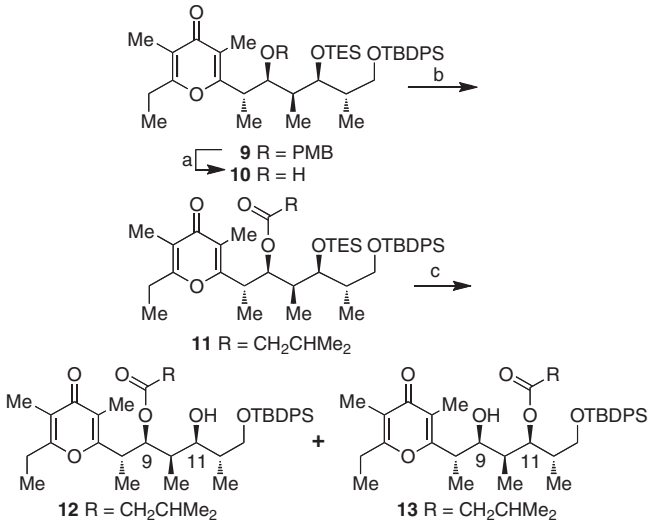


Scheme 1. Retrosynthetic analysis for auripyrone A.



Scheme 2. Reagents and conditions: (a) HF·pyr, CH_3CN, 95%; (b) DMP, CH_2Cl_2, $NaHCO_3$, 3 h; (c) PPh_3, CCl_4, THF, 38 h, 47% over two steps; (d) DDQ, CH_2Cl_2/pH 7 buffer (4:1), 1 h, 78%; (e) TFA, benzene, 1 d.

A simpler control system, bearing similar functionalities to the intermediate **3**, was devised to further study this spiroketalization process (Scheme 3). Oxidative removal of the PMB ether group of the γ-pyrone **9**,[3] obtained in 8 steps from the optically active epoxy silyl ether **5**, with DDQ provided the alcohol **10** in 88% yield, which was acylated under Yamaguchi conditions[9] to afford the ester **11** in 95% yield. Selective acid-catalyzed deprotection of the TES group of the γ-pyrone **11** under mildly acidic conditions afforded the desired alcohol **12** in 68% yield, along with the alcohol **13** in 23% yield.[10] The formation of the alcohol **13** even under mildly acidic conditions illustrates the high propensity of our system for 1,5-acyl migration which presumably arises from the inherent preference of our acyclic polyketide chain[11] to populate the local conformation (**I**) (Fig. 2) where the C-9 and C-11 oxygen moieties reside in



Scheme 3. Reagents and conditions: (a) DDQ, CH_2Cl_2/pH 7 buffer (2:1), 1 h, 88%; (b) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, $Me_2CHCH_2CO_2H$, 95%; (c) PPTS, CH_2Cl_2/MeOH (3:1), 68% **12**, 23% **13**.

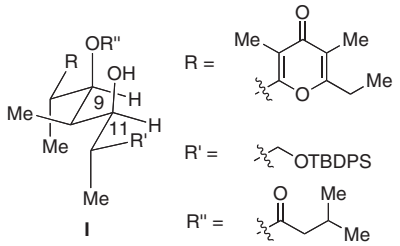
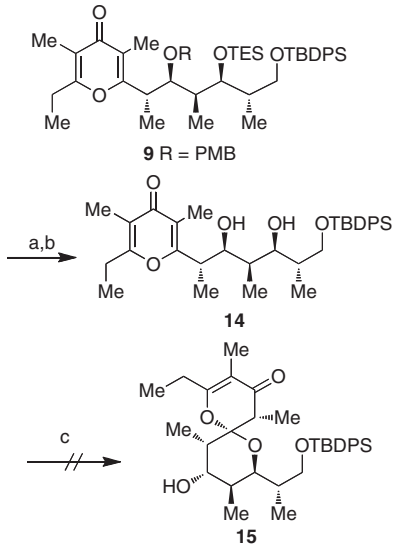


Figure 2. Local conformation of polyketide **12**.



Scheme 4. Reagents and conditions: (a) PPTS, CH_2Cl_2/MeOH (3:1), 96%; (b) DDQ, CH_2Cl_2/pH 7 buffer (2:1), 1 h, 74%; (c) TFA, C_6H_6.

close spatial proximity.[12] In fact, the use of a variety of Brønsted and Lewis acids (*p*-TsOH, $LiBF_4$, $SnCl_4$, $TiCl_4$, and $EtAlCl_2$), including Crimmins conditions (TFA)[6] for the cyclization of the alcohol **12** led to rapid formation of a mixture of the isomers **12** and **13** and no cyclization product was observed.

Finally, we attempted Crimmins cyclization conditions on the diol **14**, synthesized from the pyrone **9** in two steps, but did not observe any cyclized product (Scheme 4). A significant difference between our system and all the reported cyclizations by Crimmins and co-workers is the presence of methyl substituents α to the ketone of the γ-pyrone, presumably increasing the steric congestion of the transition state for cyclization. However, more experiments are necessary to study the variables involved in this reaction.

In conclusion, we have reported an efficient synthesis of the key bis(pyrone) alcohol **3**, a precursor for the Crimmins cyclization, to accomplish a novel synthesis of auripyrone A **1**. This approach failed to provide the desired spiroketal natural product and rather resulted in 1,5-acyl migration to give a mixture of the compounds **3** and **8**. Similar treatment of structurally analogous compounds also gave mostly acyl transfer.

Acknowledgment

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10. The structures of these two products were confirmed by protecting both alcohols separately with the TES group. Only the corresponding silyl ether of the alcohol **12** exhibited identical spectral data with the γ-pyrone **11**, thus confirming the structure of **12**. The minor isomeric alcohol **13** was consequently assigned as the product of the acyl migration of the alcohol **12**.
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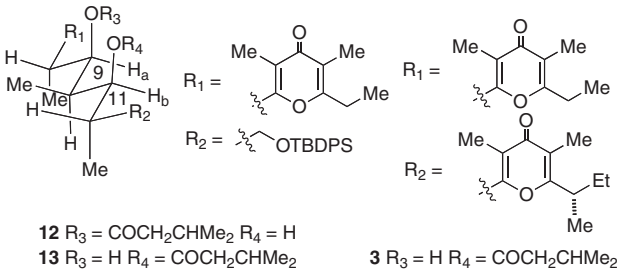
12. Analysis of the relevant coupling constants in these systems indicates that a local conformation such as **I** is likely. For example, in **12**, H_a appears as a dd, J = 9.0, 3.1 Hz while H_b is obscured. In **13**, H_a appears as a dd, J = 8.5, 2.7 Hz and H_b appears as a dd, J = 7.3, 3.5 Hz. Similarly in **3**, H_b appears as a dd, J = 9.0, 3.0 Hz, while H_a is obscured. This pattern of one large and one small coupling constant is consistent with the structures proposed since both H_a and H_b should have one dihedral angle with a vicinal proton of about 180° and a second of about 60°. Other related compounds in this series showed a similar coupling constant pattern.



12 R_3 = $COCH_2CHMe_2$ R_4 = H
13 R_3 = H R_4 = $COCH_2CHMe_2$

3 R_3 = H R_4 = $COCH_2CHMe_2$