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Total Synthesis of Auripyrone B Using a Non-Aldol Aldol−Cuprate Opening Process

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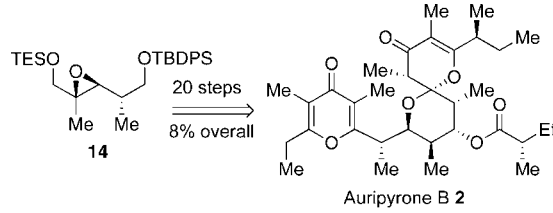
ABSTRACT



A non-aldol aldol−cuprate opening generates the polypropionate 11 from the epoxy ether 14 in eight steps as a single diastereomer. A highly stereoselective aldol reaction of 8 with 9 gives the aldol product 7 in high yield and excellent diastereoselectivity, due to double stereodifferentiation. This compound was used for an efficient synthesis of the natural product auripyrone B 2 in only 20 steps and 8% overall yield from 14 using a late-stage spiroketalization onto a stable hemiketal as the final key step.

Auripyrones A (**1**) and B (**2**), two polypropionate natural products from the Japanese species of sea hare *Dolabella auricularia* (Aplysiidae) (Figure 1), were isolated and characterized by Yamada and co-workers in 1996.[1]

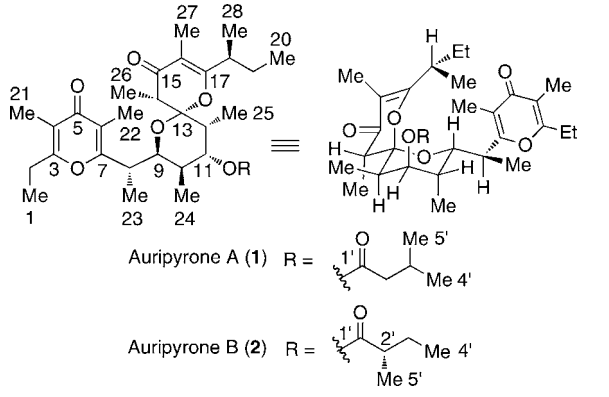


Figure 1

Extensive NMR investigation of these compounds revealed a complex, fully substituted spiroketal core in a double anomerically favored configuration in which all of the the substituents are positioned equatorially except for the C10 methyl and the C11 acyloxy groups. Differing only in the nature of their C11 acyloxy side chains, auripyrones A (**1**) and B (**2**) also possess a common tetrasubstituted γ-pyrone moiety and exhibited potent cytotoxicity against HeLa S_3 cells with IC_{50} values of 260 and 480 ng/mL, respectively.

In the past few years, two total syntheses of auripyrone A (**1**) have been reported: one by Perkins[2] which uses the Evans dipropionate methodology[3] for the synthesis of the polypropionate backbone and a biomimetic cyclization of an acyclic triketone intermediate to generate the spiroketal moiety and

(1) Suenaga, K.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett.* **1996**, *37*, 5151–5154.

(2) Lister, T.; Perkins, M. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 2560–2564.

(3) (a) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 77–91. (b) Evans, D. A.; Ennis, M. D.; Le, J. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156. (c) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142.

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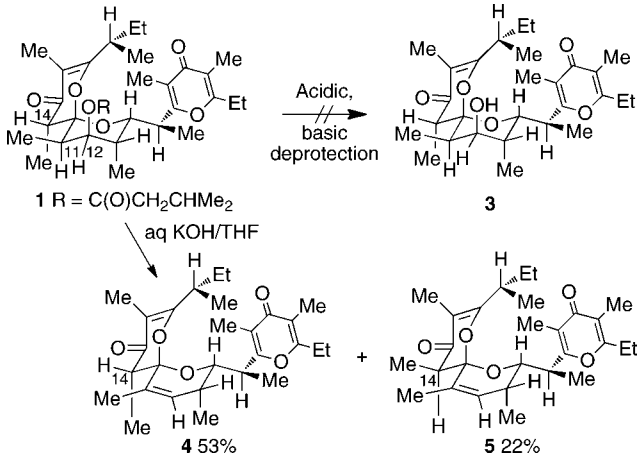
the other by our group[4] employing a tandem non-aldol aldol[5]/Paterson lactate-derived aldol[6] process to generate the stereopentad core and a regioselective hemiketalization of a keto diol followed by cyclization onto the stable hemiketal to afford the spiroketal moiety. Recently, Kigoshi and co-workers published[7] a synthesis of auripyrone A **1** and the first total synthesis of auripyrone B **2**, establishing the absolute configuration of the C2′ carbon of the natural product. The key steps of their synthesis are a diastereoselective aldol reaction between a γ-pyrone and an optically active aldehyde for the preparation of the stereopentad backbone, and a late stage spiroketalization of a triketone intermediate analogous to the Perkins' approach. This very recent report prompts us to present our total synthesis of auripyrone B **2**.

It might be assumed that the most direct approach toward the synthesis of auripyrone B **2** would involve the deprotection of the acyl moiety of auripyrone A **1** followed by coupling of the appropriate acyl side chain. However, attempts to remove the acyl substituent of auripyrone A **1**[4] under acidic or basic conditions were generally unsuccessful in providing the desired alcohol **3** (Scheme 1). Deprotection

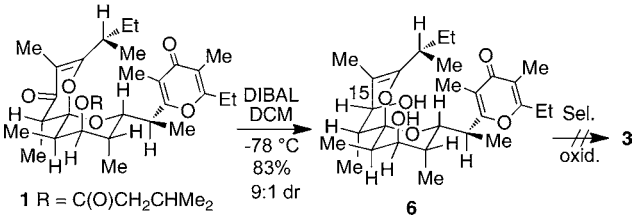
Scheme 1



with a variety of acidic conditions led to the decomposition of the natural product, while basic conditions afforded a separable mixture of two eliminated products **4** and **5** rather than the desired alcohol **3**. The high propensity of auripyrone A (**1**) to undergo E2-elimination under basic conditions presumably originates from the antiperiplanar relationship of the C-11 hydrogen and the C-12 acyloxy moieties. Although no crystal structures were obtained, based on NMR studies, we tentatively propose the structures of **4** and **5** as the C-14 epimers of the elimination product of auripyrone A (**1**). In the natural product, the C-14 methyl moiety resides exclusively in the equatorial position to presumably prevent an undesired *syn*-pentane interaction with the C-11 methyl substituent.[8] However, elimination of the C-12 acyloxy group along with the C-11 hydrogen moiety generates the alkene and thereby creates a conformational change, displacing the C-11 methyl substituent away from its original equatorial position. This conformational change would in turn diminish the *syn*-pentane effect and could lead to epimerization at the C-14 position under basic conditions to give the epimer **5** as a minor product.

We next set about synthesizing the key alcohol intermediate **3** via a two-step approach (Scheme 2). Reduction of

Scheme 2



auripyrone A (**1**) with DIBAL-H afforded the diol **6** in 83% yield and 9:1 diastereomeric ratio, the major diastereomer being the axial alcohol due to the approach of the hydride from the less hindered β-face of the enoate.[9,10] Despite numerous efforts to selectively oxidize the allylic alcohol of **6**, we were unable to generate the desired intermediate **3**. Consequently, we decided to introduce the appropriate acyl moiety earlier in our synthesis of auripyrone B (**2**).

According to our retrosynthetic analysis (Scheme 3), auripyrone B (**2**) was envisioned to arise from the key intermediate **7** through regioselective hemiketalization of the keto diol followed by spiroketalization onto the stable hemiketal.[4] The key aldolate **7** could be obtained from a fully matched[11] double stereodifferentiating[12] *anti* aldol reaction of the boron enolate of the ketone **8** with the aldehyde **9**. The aldehyde **9** would in turn originate through a sequence of acylation, desilylation, and oxidation from the γ-pyrone **10** which could result from the key aldehyde **11** as described previously.[4] The stereopentad **11** would arise from the *anti*-cuprate[13] opening of the epoxide **12** followed by selective protection of the secondary alcohol via the *p*-methoxyben-

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(5) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208–12209. (b) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J. M. *Org. Lett.* **2003**, *5*, 3159–3161.

(6) (a) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083–9086. (b) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087–9090. (c) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652.

(7) Hayakawa, I.; Takemura, T.; Fukasawa, E.; Ebihara, Y.; Sato, N.; Nakamura, T.; Suenaga, K.; Kigoshi, H. *Angew. Chem., Int. Ed.* **2010**, 2401–2404.

(8) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070.

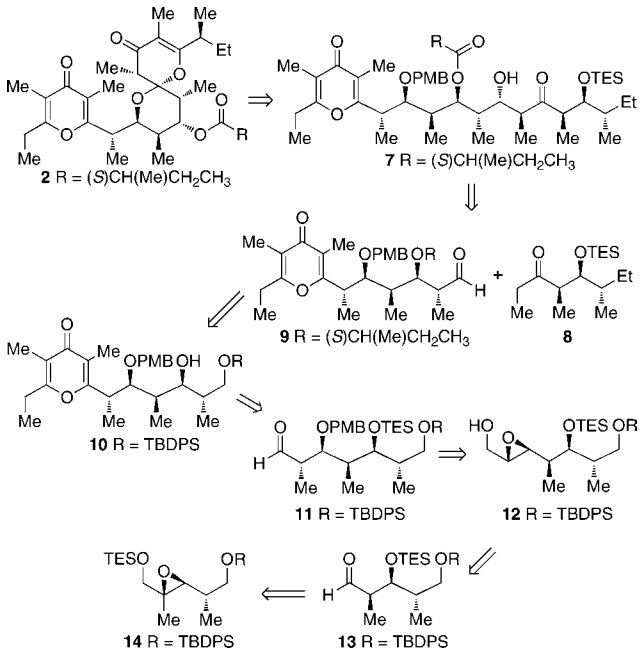
(9) Lopez, R.; Poupon, J.-C.; Prunet, J.; Ferezou, J.-P.; Ricard, L. *Synthesis* **2005**, *64*, 4–661.

(10) The stereochemistry at the new allylic alcohol center C-15 was assigned on the basis of the coupling constant between H-15 and H-14 (2.4 Hz) indicating that they were cis and not trans-diaxial.

(11) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073–9074.

(12) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.

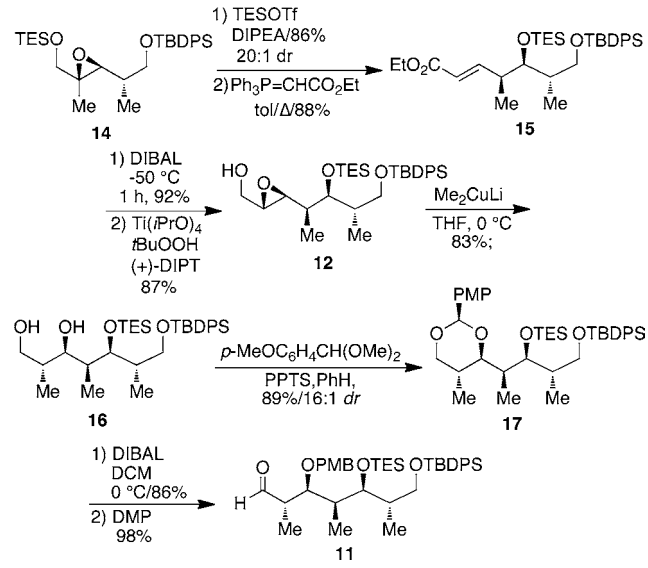
Scheme 3



zylidene acetal and oxidation of the primary alcohol to the aldehyde. The epoxide **12** could be obtained from the aldolate **13** through a sequence of Wittig olefination, reduction, and Sharpless epoxidation.[14] The *syn*-aldolate **13** was proposed to arise from the non-aldol aldol rearrangement[5] of the optically active epoxy silyl ether **14**.[4]

The synthesis commenced with the assembly of the stereopentad **11** (Scheme 4). Treatment of the known epoxy silyl ether **14**[4] with TESOTf and Hunig's base at −45 °C provided the desired *syn* non-aldol aldol product in 86% yield and 20:1 diastereomeric ratio which was subjected to Wittig olefination conditions with ethyl 2-triphenylphosphoranylidene acetate to afford in 88% yield the *E*-enoate **15**. Reduction of the *E*-enoate **15** with DIBAL-H (92% yield) followed by stereoselective epoxidation of the *E*-allylic alcohol under Sharpless conditions[13] furnished the epoxide **12** in 87% yield as a single diastereomer. Treatment of the epoxy alcohol **12** with lithium dimethylcuprate provided the desired diol **16** in 83% yield, setting the desired *anti* stereochemistry. To conclude the synthesis of the stereopentad **11**, the diol **16** was subsequently reacted with *p*-methoxybenzaldehyde dimethyl acetal and catalytic PPTS[15] to afford the *p*-methoxybenzylidene acetal **17** in 89% yield and 16:1 diastereomeric ratio. Selective reduction of the acetal **17** with DIBAL-H in dichloromethane provided exclusively, in 86% yield, the primary alcohol which was oxidized with Dess−Martin periodinane[16] to provide the

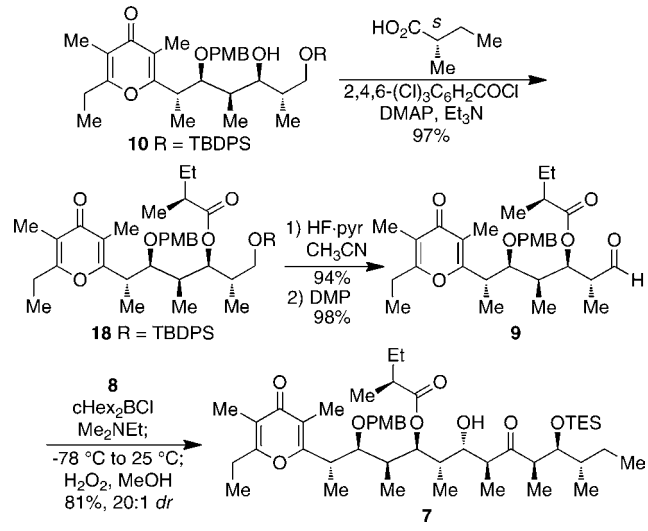
Scheme 4



desired stereopentad **11** in 98% yield. Although this *syn* non-aldol aldol[5]/*anti* cuprate opening[13] strategy is less convergent than our previously reported[4] tandem non-aldol aldol/Paterson lactate-derived aldol approach, it nonetheless provides an alternate, highly reliable route for multigram synthesis of the stereopentad **11** as a single diastereomer.

We next turned our attention to the synthesis of the key intermediate **7** (Scheme 5). There was no way of knowing

Scheme 5



the absolute configuration of the C2′ ester stereocenter in auripyrone B (**2**), but since the C17−20 and C28 portions of the auripyrones had the (*S*) configuration, we concluded that the ester stereocenter would likely have the (*S*) configuration as well, a decision that was shown to be correct. Thus, the alcohol **10**, obtained from the key stereopentad **11** in

(13) (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888. (b) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307–310.

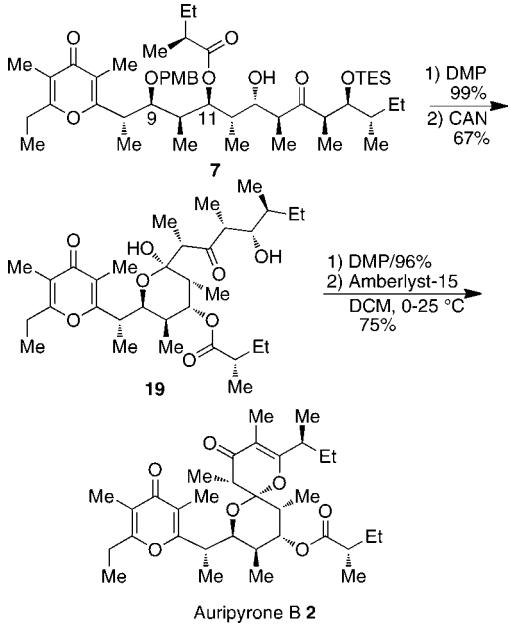
(14) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(15) PPTS was the catalyst of choice for this reaction since more acidic catalysts such as CSA led to the deprotection of the triethylsilyl (TES) ether group and the formation of multiple products.

four steps as previously reported,[4] was subjected to Yamaguchi esterification conditions[17] with (*S*)-2-methylbutanoic acid[18] to give the polypropionate **18** in 97% yield. Treatment of the silyl ether **18** with HF·pyridine furnished the primary alcohol, which was oxidized with Dess−Martin periodinane to afford the aldol precursor **9** in 92% yield over two steps. A fully matched[11] double stereodifferentiating[12] *anti*-aldol reaction of the boron enolate of the ketone **8** with the aldehyde **9** provided the aldolate **7** in 81% yield and 20:1 diastereomeric ratio.[19]

To conclude the synthesis of auripyrone B (**2**) (Scheme 6), the alcohol **7** was oxidized to the corresponding diketone

Scheme 6



with Dess−Martin periodinane, followed by concurrent removal of the PMB and TES ethers with ceric ammonium nitrate, resulting exclusively in the stable hemiketal **19** as a single diastereomer in 66% yield over two steps. Oxidation of the hemiketal **19** with Dess−Martin periodinane[16] afforded the diketone which was treated with Amberlyst-15 to furnish auripyrone B (**2**) as a single diastereomer in 72% yield over two steps. The NMR data for the synthetic material matched that of the natural product.[20] This cyclization approach onto a stable hemiketal provides a highly efficient method for the synthesis of auripyrone B (**2**) from the key aldolate intermediate **7** in four steps and 48% overall yield. In contrast, our attempts to generate the spiroketal moiety of auripyrone through acidic cyclization of an acyclic triketone intermediate, obtained from the key intermediate **7** through a three-step sequence of desilylation, double oxidation, and PMB deprotection afforded the natural product in less than 10% yield. The poor yield in the spiroketalization of this particular acyclic triketone intermediate, which was also observed by Kigoshi and co-workers in their total synthesis of auripyrone B (**2**) (17%),[7] arises from a rapid acid-catalyzed 1,5-acyl migration[21] between the C-9 and C-11 hydroxy moieties leading to the formation of multiple byproduct. This problem is circumvented in our spiroketalization approach where the stable hemiketal platform serves as a pseudoprotecting group for the C-9 hydroxy substituent to prevent 1,5-acyl migration, providing a highly efficient route for the synthesis of the spiroketal moiety of the natural product.

In summary, we have reported the total synthesis of auripyrone B (**2**) in 20 steps and 8% yield from the known epoxide **14**, utilizing a *syn* non-aldol aldol/*anti* cuprate opening strategy to generate the polyketide backbone and a highly efficient late-stage cyclization onto a stable hemiketal platform for the synthesis of the spiroketal moiety.

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Supporting Information Available: Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(18) (*S*)-2-Methylbutanoic acid was obtained via Jones oxidation of commercially available (*S*)-2-methyl-1-butanol.

(19) Careful aqueous workup of the reaction is crucial. Quenching with pH 7 buffered solution at 0 °C is necessary to prevent acyl migration.

(20) We thank Professors Kiyoyuki Yamada (Nagoya) and Kiyotake Suenaga (Keio) for providing the spectroscopic data.

(21) Unpublished results. Salehi-Rad, R. Ph.D. Thesis, UCLA, 2009.