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Total Synthesis of Auripyrrone A Using a Tandem Non-Aldol Aldol-Paterson Aldol Process as a Key Step**

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Abstract

A tandem non-aldol aldol-Paterson aldol generates the polypropionate **12** from the epoxy alcohol **8** and the ketone **9** in only two steps and 74% overall yield as a single diastereomer, due to double stereodifferentiation, where the stereoiduction from the enolate and the α -methyl substituent of the aldehyde are reinforcing. This compound was used for an efficient synthesis of the natural product auripyrrone A, **1**, in only 18 steps and 17% overall yield, using a highly regioselective hemiketalization of a keto diol and a late stage spiroketalization onto a stable hemiketal as the final key steps.

Keywords

Aldol react; Synthesis (org.); Epoxides; Rearrangements; Natural prod

In 1996, Yamada, et al., reported the isolation of auripyrrones A **1** and B **2** from the methanol extracts of the sea hare *Dolabella auricularia* (Aplysiidae) (Figure 1).^[1] Extensive NMR investigation of the compounds revealed a complex 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 C10 methyl and the C11 acyloxy groups. Auripyrrones A **1** and B **2** showed cytotoxicity against HeLa S₃ cells with IC₅₀ values of 260 and 480 ng/mL, respectively. To date one total synthesis^[2] of auripyrrone A **1** has been reported by Perkins and coworkers, utilizing an elegant biomimetic cyclization of an acyclic triketone intermediate to generate the spiroketal moiety.^[3] The major drawback of this approach, however, is the late stage formation of the γ -pyrone in the presence of the sensitive spiroketal moiety which proceeded with poor yield (39% BRSM). Nonetheless, Perkins' convergent total synthesis of auripyrrone A **1** constitutes the only established synthetic route, and led to the determination of the absolute stereochemistry of the natural product. Herein, we report our convergent approach for the total synthesis of auripyrrone A **1** as a single diastereomer in high chemical yield.

In our retrosynthetic analysis (Scheme 1), the sensitive spiroketal moiety of auripyrrone A **1** could be derived from a late stage cyclization of the C-17 ketone onto the hemiketal **3**, which should be available from the aldolate **4**. The key intermediate **4** could be obtained from a fully matched^[4] double stereodifferentiating^[5] *anti* aldol reaction of the boron enolate of the ketone **6** and the aldehyde **5**. The γ -pyrone moiety of **5** would result from the

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aldehyde **7** following the protocol of Hoveyda and coworkers.^[6] Finally, the stereopentad **7** was envisioned to arise from the known epoxide **8**^[7] by a novel tandem non-aldol aldol^[8]/Paterson lactate-derived aldol^[9] reaction with the ketone **9**.

The synthesis commenced with the assembly of **7**, using a highly convergent tandem non-aldol aldol/Paterson lactate-derived aldol reaction (Scheme 2). Epoxidation of the allylic alcohol **10** (synthesized in 5 steps from (*S*)-Roche ester)^[10] under reagent-controlled Sharpless conditions,^[11] or substrate controlled conditions with *m*CPBA,^[12] furnished the epoxide **8** in 85% yield and 20:1 diastereomeric ratio (dr), or 90% yield and 16:1 dr, respectively. Protection of **8** with TESCl provided the corresponding silyl ether which was treated with TESOTf at –45 °C to give, via the non-aldol aldol rearrangement, the *syn*-aldol adduct **11** in 86% yield and 20:1 dr. Unlike conventional auxiliary based aldol methods which require a protection step followed by removal of the chiral auxiliary to generate the protected aldehyde, the non-aldol aldol reaction provides direct access to pure silyl protected aldehydes without flash column purification^[13] for an iterative aldol process. To that end, the subsequent *anti* aldol reaction of the aldehyde **11** with the *E*-boron enolate of Paterson's lactate-derived ketone **9**^[9c] furnished the desired *anti*-aldolate **12** in 86% yield as a single diastereomer. The remarkable stereoselectivity of this reaction is due to double stereodifferentiation,^[5] where the stereoiduction from the enolate^[9c] and the α -methyl substituent of the aldehyde^[14] are reinforcing. Mild Lewis acid catalyzed^[15] protection of the alcohol **12** as the PMB ether proceeded smoothly without deprotection of the acid sensitive TES group to afford the ketone **13** in 93% yield. Reduction of **13** and concomitant removal of the α' -benzoate with LiBH₄ followed by periodate cleavage of the resulting diol^[16] afforded the desired aldehyde **7** in 83% yield over 2 steps. This novel tandem non-aldol aldol/Paterson lactate-derived aldol protocol constitutes a highly efficient, convergent approach for the synthesis of the desired stereopentad **7**, generating four aldol stereocenters in two steps. Conversion of the aldehyde **7** in three steps to the *meso*-polypropionate **14**, which possessed no optical rotation and displayed only twelve ¹³C NMR resonances indicating a symmetrical structure, confirmed the assigned stereochemistry of **7**.

Next, we turned to the synthesis of the γ -pyrone moiety^[17] (Scheme 3). Following the protocol of Hoveyda,^[6] we obtained, via the aldol reaction of the lithium enolate of the silyloxy enone **15**^[6] with the aldehyde **7**, the aldolate **16** in 94% yield as a mixture of isomers.^[18] Oxidation of the isomeric mixture of **16** with Dess-Martin periodinane (DMP)^[19] and subsequent heating of the resulting diketone in DMF^[20] provided the desired γ -pyrone **17** in 68% yield over two steps. Acid promoted deprotection of the TES ether furnished the alcohol **18** which was subjected to Yamaguchi esterification^[21] with isovaleric acid to give the ester **19** in 98% yield. Treatment of the silyl ether **19** with HF-pyridine provided the primary alcohol **20**^[22] which was oxidized with DMP to afford the aldol precursor, the aldehyde **5**. The other component of the aldol reaction, the α -methyl- β -hydroxy ketone **6**, was also readily available from TES protection of the known ketone **21**^[2a] in 96% yield. The *E*-boron enolate of the ketone **6** underwent a highly diastereoselective *anti* aldol reaction with **5** to provide the Felkin product **4** in 94% yield and 21:1 diastereomeric ratio. The excellent diastereoselectivity of this double stereodifferentiating^[5] aldol reaction could be attributed to a fully matched^[4] reactant pair, where the stereoiduction from the β -hydroxy^[23] and the α -methyl^[14] substituent of the aldehyde and the α -methyl stereocenter of the ketone^[24] are reinforcing.

With the key intermediate **4** in hand, we set out to investigate the formation of the spiroketal moiety of auripyron A **1** (Scheme 4). Our initial attempts at generating the desired spiroketal by acid-catalyzed cyclization of the C-9 hydroxyl group onto either a γ -pyrone^[25] or an acyclic triketone^[2a] failed and led to rapid 1,5-acyl migration. The high propensity of our system for acyl migration presumably arises from the inherent preference of the acyclic

polyketide^[26] to populate the local conformation **I** where the C-9 and C-11 oxygen moieties are in close spatial proximity. To circumvent this problem, we decided to mask the C-9 hydroxy substituent and attempt spiroketalization from a hemiketal platform.^[27] Oxidation of the alcohol **4** afforded the corresponding diketone as a single isomer^[28] which was deprotected with DDQ to furnish the hemiketal **23** as the major product by crude ¹H and ¹³C NMR. However, purification on silica gel gave the desired cyclic isomer **23** only in 66% yield as a single isomer, along with the open chain isomer **22** in 21% yield as a mixture of two C-14 methyl epimers.^[29] Deprotection of the TES ether of the hemiketal **23** with HF·pyridine provided the hemiketal **24** in 86% yield as a single isomer^[30] which was stable to column chromatography. Interestingly, the TES deprotection of the acyclic diketone **22** also afforded the hemiketal **24** exclusively, as a mixture of C-14 epimers, in 78% yield. The mixed configuration of the C-14 stereocenter in the hemiketal **24** is not critical since both diastereomers could equilibrate under thermodynamic cyclization conditions to the natural product. Nonetheless, to circumvent having to purify the unstable hemiketal **23** and recycle the acyclic diketone **22**, a variety of conditions were screened for the deprotection of the ethers. We were gratified to find that oxidation of the aldolate **4** followed by treatment with CAN in acetonitrile and water (9:1) for 15 minutes led to concurrent removal of the PMB and TES ethers, providing exclusively the stable hemiketal **24** as a single diastereomer in 74% yield over two steps.^[31] The selectivity of this reaction is remarkable and yet difficult to explain since the deprotection of the PMB and TES ethers unveils two alcohols which could potentially cyclize on the C-13 ketone to form a hemiketal. Simple thermodynamic MM2 calculations proved ineffective and higher level calculations will be necessary to elucidate the remarkable selectivity of this reaction for exclusive formation of the hemiketal **24**.

Having successfully prepared the hemiketal **24** as a single diastereomer from the aldolate **4** in 2 steps in excellent yield, we next oxidized the alcohol of **24**, and the resulting diketone^[32] was treated with Amberlyst-15 to afford the natural product auripyronone **A 1** as a single diastereomer in 80% yield over two steps. The remarkably high chemical yield of this spiroketalization could presumably be attributed to the lower entropic cost of cyclization onto a conformationally limited hemiketal platform, or the increase in the rate of the acid-catalyzed cyclization, since the configuration of the C-14 stereocenter of the isomerically pure starting material **24** matches the desired configuration in the natural product.

The chemistry described here constitutes a highly convergent approach for the synthesis of auripyronone **A 1** from the known epoxide **8** in 18 steps and 17% overall yield. Our strategy employs a novel tandem non-aldol aldol/Paterson lactate-derived aldol to generate the stereopentad backbone, a highly regioselective hemiketalization of a keto diol, and a late stage spiroketalization onto the stable hemiketal.

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29. The rate of the column chromatography changed the ratio of **22/23** from 3:1 to 1:1.
30. The structure of this hemiketal was tentatively assigned since reprotecting the alcohol group of the hemiketal **24** as the TES ether afforded a compound that exhibited identical spectral data with the hemiketal **23**.
31. The short reaction time is critical, since prolonged exposure led to the formation of the ketal.
32. This diketone was also stable to column chromatography and existed as a single isomer.

Figure 1.

Scheme 1.

Scheme 2.

Reagents and conditions: a) $\text{Ti}(\text{OiPr})_4$, $t\text{BuOOH}$, (+)-DIPT, DCM, -10°C , 85%, 20:1 *dr* or *mCPBA*, K_2HPO_4 , DCM, -10°C , 90%, 16:1 *dr*; b) TESCl , Imidazole, DCM, 98%; c) TESOTf , DIPEA, DCM, -45°C , 86%, 20:1 *dr*; d) **9**, cHex_2BCl , Me_2NEt , Et_2O , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 2 h; $0^\circ\text{C} \rightarrow -78^\circ\text{C}$; **11**, $-78^\circ\text{C} \rightarrow -25^\circ\text{C}$, 15 h; H_2O_2 , MeOH, pH 7 buffer, 0°C , 1 h, 86%, one isomer; e) $\text{PMBOC}(=\text{NH})\text{CCl}_3$, $\text{Sc}(\text{OTf})_3$, toluene 93%; f) LiBH_4 , THF, 97%, 8:1 *dr*; g) NaIO_4 , MeOH:pH 7 buffer (2:1), 86%. h) NaBH_4 , EtOH, 0°C , 81%; i) TBDPSCl , Imidazole, DCM; j) CAN, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (9:1), 78% two steps.

Scheme 3.

Reagents and conditions: a) **15**, LDA, $-78\text{ }^{\circ}\text{C}$, **7**, 94%; b) DMP, DCM, NaHCO_3 ; c) DMF, $55\text{ }^{\circ}\text{C}$ μw , 6 h, 68% two steps; d) PPTS, DCM:MeOH (3:1), 96%; e) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N , isovaleric acid, 98%; f) HF $\cdot$ pyr, CH_3CN /pyr, 94%; g) DMP, DCM, NaHCO_3 , 98%; h) TESCl, imidazole, DCM, 96%; i) **6**, cHex_2BCl , Me_2NEt , Et_2O , $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 2 h, $0\text{ }^{\circ}\text{C} \rightarrow -78\text{ }^{\circ}\text{C}$, **5**, $-78\text{ }^{\circ}\text{C} \rightarrow -25\text{ }^{\circ}\text{C}$, 15 h, H_2O_2 , MeOH, pH 7 buffer, $0\text{ }^{\circ}\text{C}$, 1 h, 94%, 21:1 *dr*.

Scheme 4.

Reagents and conditions: a) DMP, DCM, NaHCO_3 , 94%; b) DDQ, DCM:pH 7 buffer (9:1), 66% **23**, 21% **22**; c) HF-pyr, CH_3CN /pyr, 86%; d) HF-pyr, CH_3CN /pyr, 78%; e) DMP, DCM, NaHCO_3 ; f) CAN, CH_3CN : H_2O (9:1), 74% two steps; g) DMP, DCM, NaHCO_3 ; h) Amberlyst-15, DCM, $0\text{ }^\circ\text{C} \rightarrow 25\text{ }^\circ\text{C}$, 80% two steps.