Natural Products

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

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In 1996 Yamada and co-workers reported the isolation of auripyrones A (**1**) and B (**2**) from the methanol extracts of the sea hare *Dolabella auricularia* (Aplysiidae; Figure 1).[1]

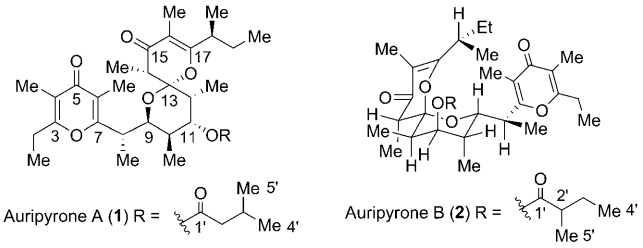
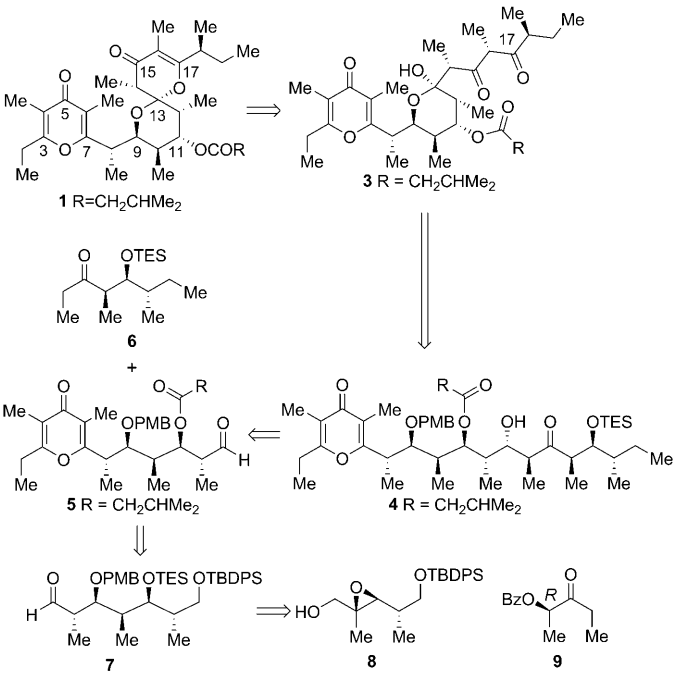


Figure 1.

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 wherein all but the substituents are positioned equatorially except for the C10 methyl and the C11 acyloxy groups. Auripyrones A (**1**) and B (**2**) showed cytotoxicity against HeLa S_3 cells with IC_{50} values of 260 and 480 ng mL^{-1}, respectively. To date one total synthesis[2] of **1** has been reported by Perkins et al., which utilizes 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% based on recovered starting material). Nonetheless, Perkins' convergent total synthesis of **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 auripyrone A (**1**) as a single diastereomer in high chemical yield.

In our retrosynthetic analysis (Scheme 1), the sensitive spiroketal moiety of **1** could be derived from a late-stage



Scheme 1. Retrosynthetic analysis.

cyclization of the C17 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** with the aldehyde **5**. The γ-pyrone moiety of **5** would result from the aldehyde **7** by using the protocol of Gillingham and Hoveyda.[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 five steps from (*S*)-Roche ester),[10] under either reagent controlled Sharpless conditions[11] or substrate controlled reaction conditions with *m*CPBA,[12] furnished the epoxide **8** in 85% yield and 20:1 diastereomeric ratio (d.r.), or 90% yield and 16:1 d.r., respectively. Protection of **8** with TESCl provided the corresponding silyl ether which was then treated with TESOTf at −45 °C to give, by the non-aldol aldol reaction, the *syn*-aldol adduct **11** in 86% yield and 20:1 d.r. Unlike conventional auxiliary-based aldol methods which require a protection step and subsequent removal of the chiral auxiliary to generate the protected aldehyde, the

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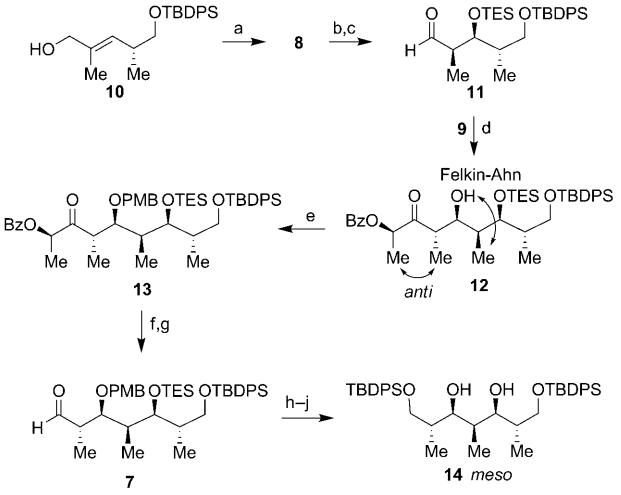
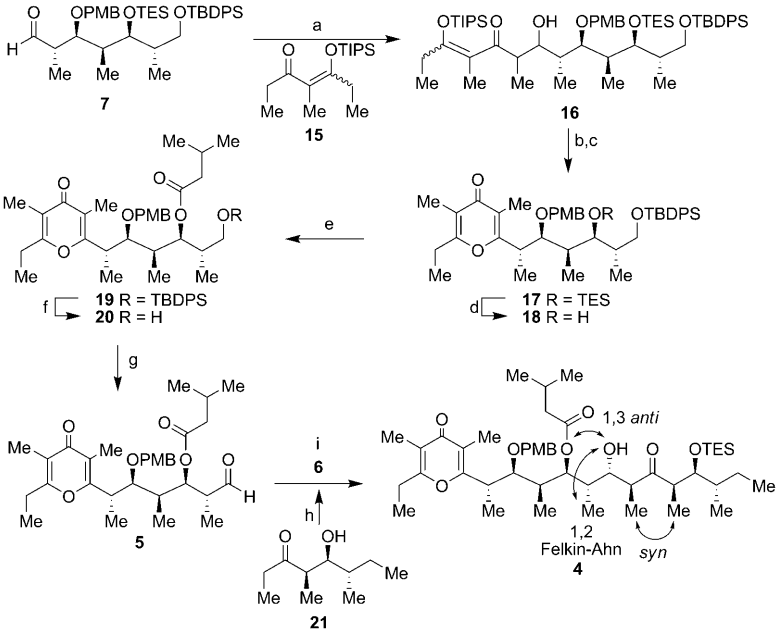


Scheme 2. Reagents and conditions: a) $Ti(OiPr)_4$, *t*BuOOH, (+)-DIPT, CH_2Cl_2, −10 °C, 85 %, 20:1 d.r. or *m*CPBA, K_2HPO_4, CH_2Cl_2, −10 °C, 90 %, 16:1 d.r.; b) TESCl, imidazole, CH_2Cl_2, 98 %; c) TESOTf, DIPEA, CH_2Cl_2, −45 °C, 86 %, 20:1 d.r.; d) **9**, $cHex_2BCl$, Me_2NEt, Et_2O, −78 °C→0 °C, 2 h; 0 °C→−78 °C; **11**, −78 °C→−25 °C, 15 h; H_2O_2, MeOH, pH 7 buffer, 0 °C, 1 h, 86 %, one isomer; e) PMBOC(=NH)-CCl_3, $Sc(OTf)_3$, toluene 93 %; f) $LiBH_4$, THF, 97 %, 8:1 d.r.; g) $NaIO_4$, MeOH/pH 7 buffer (2:1), 86 %. h) $NaBH_4$, EtOH, 0 °C, 81 %; i) TBDPSCl, imidazole, CH_2Cl_2; j) CAN, CH_3CN/H_2O (9:1), 78 % over two steps. DIPT = diisopropyltartrate, *m*CPBA = *meta*-chloroperbenzoic acid, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, DIPEA = diisopropylethylamine, Bz = benzoyl, PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, CAN = ceric ammoinuim nitrate.

non-aldol aldol reaction provides direct access to pure silyl-protected aldehydes without the flash column chromatography 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 a result of double stereodifferentiation,[5] where the stereoinduction 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 removal 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 $LiBH_4$ and periodate cleavage of the resulting diol[16] afforded the desired aldehyde **7** in 83 % yield over two 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 into the *meso*-polypropionate **14**, which possessed no optical rotation and displayed only twelve ^{13}C NMR resonances indicating a symmetrical structure, confirmed the assigned stereochemistry of **7**.

Next, we turned to the synthesis of the γ-pyrone moiety[2a,17] (Scheme 3). By using the protocol of Gillingham and Hoveyda,[6] we obtained, through the aldol reaction of the lithium enolate of the silyloxy enone **15**[16] with the aldehyde **7**, the aldolate **16** in 94 % yield as a mixture of isomers.[18] Oxidation of the isomeric mixture of **16** with 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 removal 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 then oxidized with DMP to afford the aldol precursor **5**. The other component of the aldol reaction, the α-methyl-β-hydroxy ketone **6**, was also readily available from protecting the known ketone **21**[2a] as the TES ether (96 % yield). The *E*-boron enolate of the ketone **6** underwent a highly diastereoselective *anti*-aldol reaction with **5** to provide the Felkin–Ahn 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 stereoinduction from both the β-hydroxy[23] and the α-methyl[14] substituent of the aldehyde, and the α-methyl stereocenter of the ketone[24] are reinforcing.



Scheme 3. Reagents and conditions: a) **15**, LDA, −78 °C, **7**, 94 %; b) DMP, CH_2Cl_2, $NaHCO_3$; c) DMF, 55 °C μw, 6 h, 68 % over two steps; d) PPTS, CH_2Cl_2/MeOH (3:1), 96 %; e) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, isovaleric acid, 98 %; f) HF·py, CH_3CN/py (7:1), 94 %; g) DMP, CH_2Cl_2, $NaHCO_3$, 98 %; h) TESCl, imidazole, CH_2Cl_2, 96 %; i) **6**, $cHex_2BCl$, Me_2NEt, Et_2O, −78 °C→0 °C, 2 h, 0 °C→−78 °C, **5**, −78 °C→−25 °C, 15 h, H_2O_2, MeOH, pH 7 buffer, 0 °C, 1 h, 94 %, 21:1 d.r. TIPS = triisopropylsilyl, LDA = lithium diisopropylamide, DMP = Dess–Martin periodinane, DMF = *N*,*N*-dimethylformamide, PPTS = pyridinium *para*-toluenesulfonate, DMAP = 4-dimethylaminopyridine, py = pyridine.

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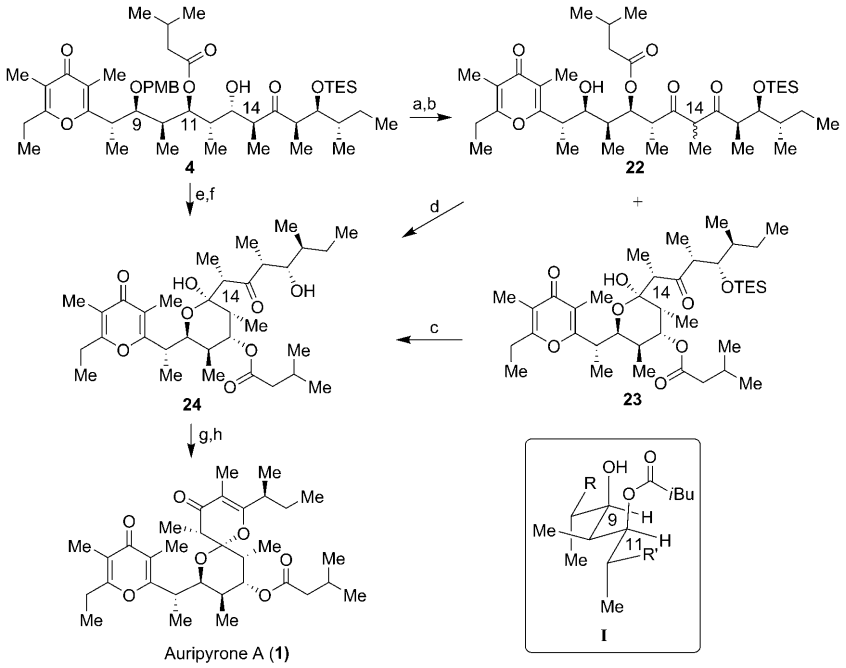
With the key intermediate **4** in hand, we set out to investigate the formation of the spiroketal moiety of **1** (Scheme 4). Our initial attempts at generating the desired



Scheme 4. Reagents and conditions: a) DMP, CH_2Cl_2, $NaHCO_3$, 94%; b) DDQ, CH_2Cl_2/pH 7 buffer (9:1), 66% **23**, 21% **22**; c) HF·py, CH_3CN/py (5:1), 86%; d) HF·py, CH_3CN/py (5:1), 78%; e) DMP, CH_2Cl_2, $NaHCO_3$; f) CAN, CH_3CN:H_2O (9:1), 74% over two steps; g) DMP, CH_2Cl_2, $NaHCO_3$; h) Amberlyst-15, CH_2Cl_2, 0°C→25°C, 80% over two steps. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

spiroketal by acid-catalyzed cyclization of the C9 hydroxy group onto either an 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 C9 and C11 oxygen moieties are in close spatial proximity. To circumvent this problem, we decided to mask the C9 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 then deprotected with DDQ to furnish the hemiketal **23** as the major product (determined by ^1H and ^{13}C NMR analyses of the crude reaction mixture). 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 C14 methyl epimers.[29] Removal 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 removal of the TES group on the acyclic diketone **22** also afforded the hemiketal **24** exclusively, as a mixture of C14 epimers, in 78% yield. The mixed configuration of the C14 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 removal of the ethers. Gratifyingly, oxidation of the aldolate **4** and then treatment with CAN in acetonitrile/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 removal of the PMB and TES ethers unveils two alcohols which could potentially cyclize onto the C13 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 two 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 auripyrone 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 C14 stereocenter of the isomerically pure starting material **24** matches the desired configuration in the natural product.

The chemistry described herein constitutes a highly convergent approach for the synthesis of auripyrone 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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[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 to that of 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.

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