Natural Product Synthesis

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Total Synthesis of Auripyrones A and B and Determination of the Absolute Configuration of Auripyrone B**

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Compounds containing the γ-pyrone functional group have been isolated from marine animals (Figure 1).[1] These compounds show valuable biological activities: for example, peroniatriols I (**1**) and II (**2**) exhibited significant cytotoxicity against L1210 cells.[2] Also, vallartanone B (**3**)[3] and onchidione (**4**)[4] are chemical defense compounds of mollusks. Therefore, the development of a method to synthesize γ-pyrone-containing compounds is an important topic in natural product synthesis.

In 1996, auripyrones A (**5**) and B (**6**) were isolated from the sea hare *Dolabella auricularia* (Aplysiidae) by Yamada and co-workers (Figure 2).[5] Auripyrones A (**5**) and B (**6**) exhibited cytotoxicity against HeLa S_3 cells with IC_{50} values of 0.26 and 0.48 μg mL^{-1}, respectively. The relative stereochemistry of the two compounds, except for the configuration of C2′ in auripyrone B (**6**), were deduced using detailed spectroscopic analysis to be structures **5** and **6**. The main structural features of auripyrones are a γ-pyrone ring and a spiroacetal moiety.

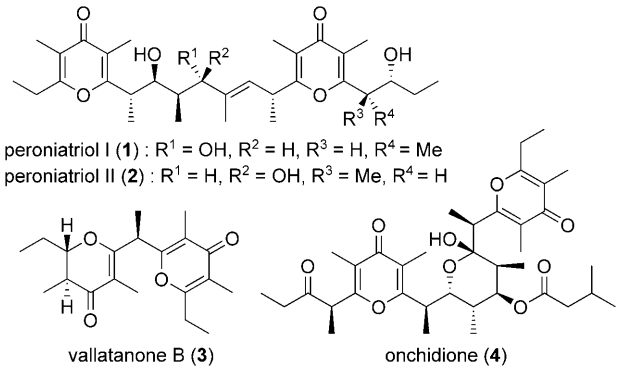

Figure 1. Marine natural products that contain the γ-pyrone framework.

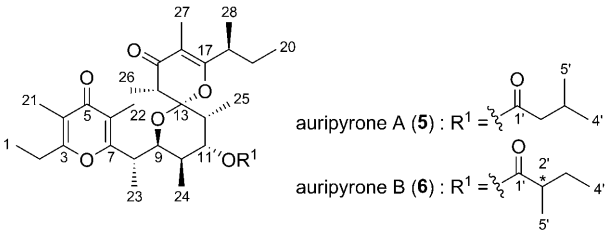

Figure 2. Structures of auripyrone A and B.

In 2006, Perkins and Lister achieved the first total synthesis of auripyrone A (**5**), the key reaction of which was spiroacetalization.[6] This synthesis determined the absolute configuration of auripyrone A (**5**). Very recently, Jung and Salehi-Rad reported the total synthesis of auripyrone A (**5**) using a tandem non-aldol aldol/Paterson aldol process as a key step.[7] However, the configuration of auripyrone B (**6**) at the C2′ position remained unknown. Therefore, we decided to complete the syntheses of auripyrones A (**5**) and B (**6**) and to determine the absolute configuration of auripyrone B (**6**).

Our retrosynthetic analyses of auripyrones A (**5**) and B (**6**) are shown in Scheme 1. We expected that a spiroacetalization of triketone **7**, as was utilized in the total synthesis by Perkins and Lister,[6] would provide auripyrones A and B. Triketone **7** might be obtained from an aldol reaction between C1–C13 segment **8** and C14–C20 segment **9**. The five contiguous chiral centers in C1-C13 segment **8** could be prepared by a crotylboration and diastereoselective aldol-type reaction[8] between 2,6-diethyl-3,5-dimethyl-4-pyrone (**12**) and the optically active aldehyde **13** as the key steps.

Recently, we reported the diastereoselective aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**12**) and different aldehydes (Scheme 2).[8] This reaction has the advantages of affording straightforward access even to complex molecules and the construction of two stereogenic centers at once.

The starting point for this work was the construction of C1-C13 segment **20** (Scheme 3). The diastereoselective aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**12**)[9] and the known compound, optically active aldehyde **14**,[10] afforded the desired compound **15** in 47% yield along with other diastereomers (21% yield).[8] The stereochemistry of **15** was determined using ^{1}H–^{1}H coupling constants and

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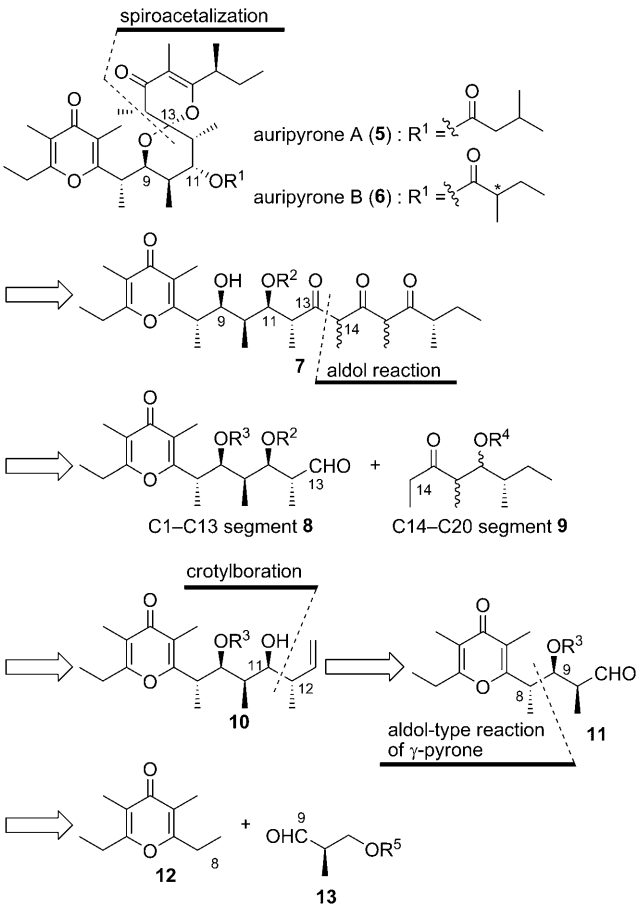
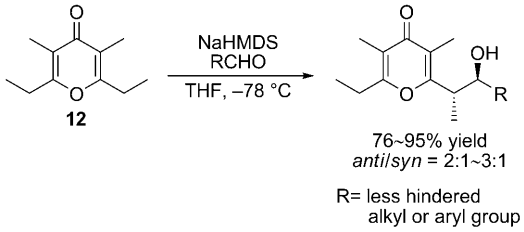
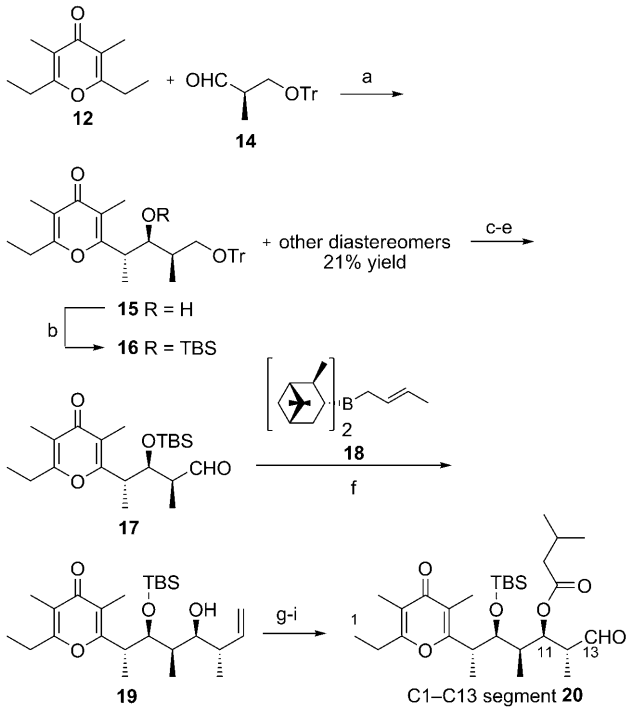


Scheme 1. Retrosynthetic analyses of auripyrones A (**5**) and B (**6**).



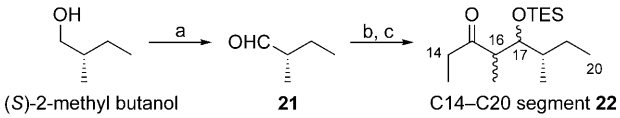
Scheme 2. Aldol-type reaction of 2,6-diethyl-3,5-dimethyl-4-pyrone (**12**) NaHMDS = sodium hexamethyldisilazide, THF = tetrahydrofuran.

NOESY correlations of the corresponding acetonide derivative.[8] The secondary hydroxy group in compound **15** was protected as a TBS ether to afford compound **16**. The trityl group was removed, and the primary hydroxy group was oxidized by Swern oxidation to give aldehyde **17**. The Brown crotylboration reaction[11] between aldehyde **17** and boronate **18** afforded homoallylic alcohol **19** as a single diastereomer.[12] Acylation of the secondary hydroxy group in **19** and subsequent dihydroxylation of the terminal olefin gave a diol in 90% yield. Oxidative cleavage of the resulting dihydroxy group with $NaIO_4$ afforded aldehyde **20** as a C1–C13 segment. This two-step procedure was superior to the direct Lemieux-Johnson conditions[13] in both yield and reproducibility because of the instability of aldehyde **20**.



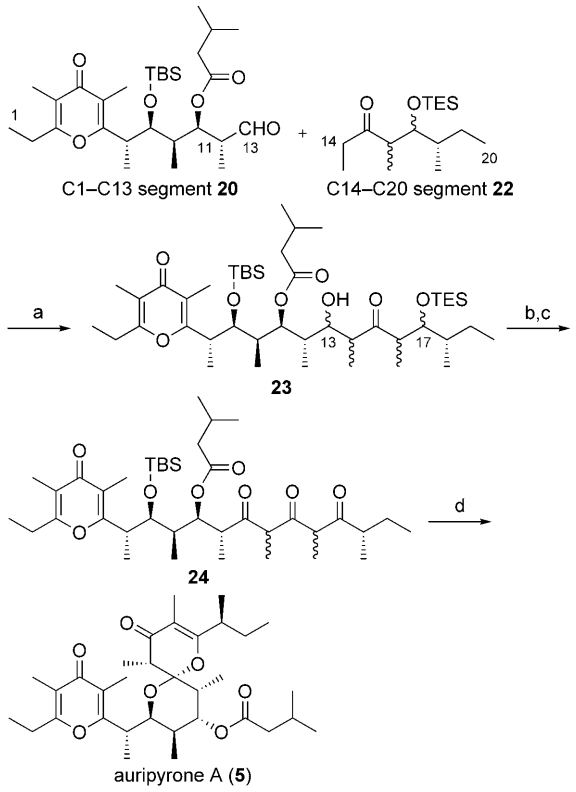
Scheme 3. Synthesis of the C1-C13 segment (**20**). Reagents and conditions: a) NaHMDS, THF, −78 °C, 47% yield; b) TBSCl, imidazole, DMF, 99% yield; c) HCO_2H, Et_2O, RT; d) 25% NH_3 aq., MeOH, RT, 92% yield over 2 steps; e) $(COCl)_2$, DMSO, iPr_2NEt, CH_2Cl_2, −78 °C then 0 °C, 99% yield; f) **18**, $BF_3{\cdot}OEt_2$, THF, −40 °C then NaOH, H_2O_2, 71% yield; g) isovaleryl chloride, DMAP, pyr, RT, quantitative yield; h) OsO_4, NMO, acetone/H_2O (1:1), RT, 90% yield; i) $NaIO_4$, acetone/H_2O (1:1), RT, 72%. Tr = triphenylmethyl, NaHMDS = sodium hexamethyldisilazide, THF = tetrahydrofuran, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, DMAP = 4-dimethylaminopyridine, pyr = pyridine, NMO = *N*-methylmorpholine oxide.

C14–C20 segment **22** was prepared as follows. Aldehyde **21** was synthesized from commercially available (*S*)-2-methy-1-butanol using a previously reported method.[14] The aldol reaction between aldehyde **21** and 3-pentanone, and protection of the resulting secondary hydroxy group afforded C14–C20 segment **22** as a diastereomeric mixture (Scheme 4). This segment **22** was used for the next reaction without separation because the configurations of these newly generated stereocenters were either lost by oxidation or epimerization in the subsequent steps.



Scheme 4. Synthesis of the C14-C20 segment (**22**). Reagents and conditions: a) $(COCl)_2$, DMSO, iPr_2NEt, CH_2Cl_2, −78 °C then 0 °C, 30% yield; b) LDA, 3-pentanone, THF, −78 °C, 89% yield; c) TESCl, imidazole, DMF, RT, 95% yield. DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, THF = tetrahydrofuran, TES = triethylsilyl, DMF = *N*,*N*-dimethylformamide.

With both C1–C13 segment **20** and C14–C20 segment **22** in hand, we attempted the coupling reaction between **20** and **22**. Although γ-pyrone compounds are readily deprotonated at the α-alkyl group by LDA, LHMDS, NaHMDS, and KHMDS, which often results in the formation of by-products, the Paterson aldol reaction[15] by $Sn(OTf)_2$ and Et_3N gave coupling compound **23** as a diastereomeric mixture in good yield (Scheme 5). Selective removal of the TES group in **23**



Scheme 5. Completion of the synthesis of auripyrone A (**5**). Reagents and conditions: a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C, 99% yield; b) AcOH/THF/H_2O (4:1:4), RT, 73% yield; c) Dess–Martin periodinane, CH_2Cl_2, RT, 83% yield; d) HF·pyr/THF/pyr (5:7:3), 60 °C, 22% yield. OTf = trifluoromethanesulfonate, Ac = acetyl, THF = tetrahydrofuran, pyr = pyridine.

gave a diol that was converted into triketone **24** using Dess–Martin periodinane; triketone **24** was an equilibrium mixture of the keto and enol forms. Cleavage of the TBS ether group in triketone **24** by HF·pyr and a spontaneous spiroacetalization reaction afforded auripyrone A (**5**). Synthetic auripyrone A (**5**) gave spectral data (^{1}H NMR and ^{13}C NMR spectroscopy, HRMS, and optical rotation) that were in full agreement with those of the natural compound,[5] thus completing the total synthesis.

Stereocontrol of the C14 methyl group in the spiroacetalization to afford auripyrone A (**5**) can be explained as follows (Figure 3). Triketone **24** was transformed into hemiacetals **24a** and **24b**. The stereochemistry of C13 in hemiacetals **24a** and **24b** was controlled by the double anomeric effect. The C14 methyl group in hemiacetal **24a** was epimerized into the

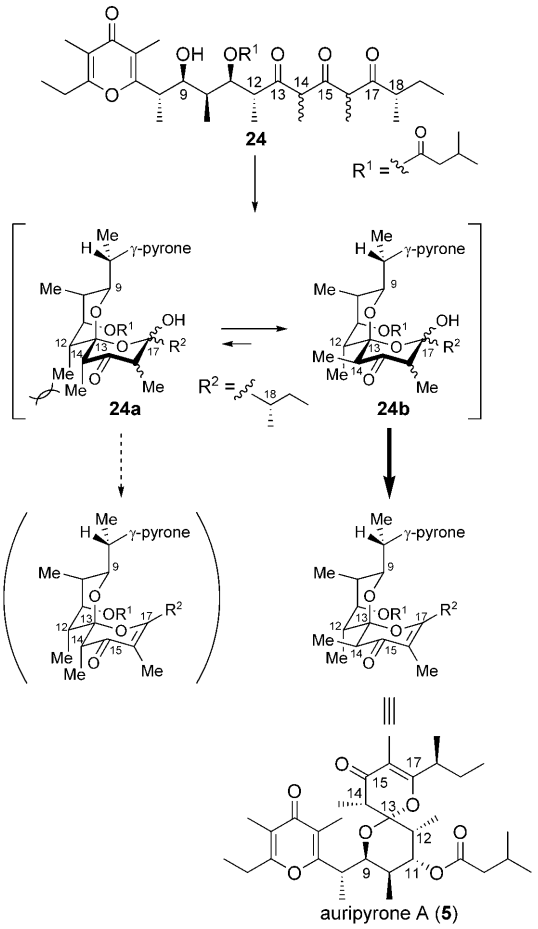
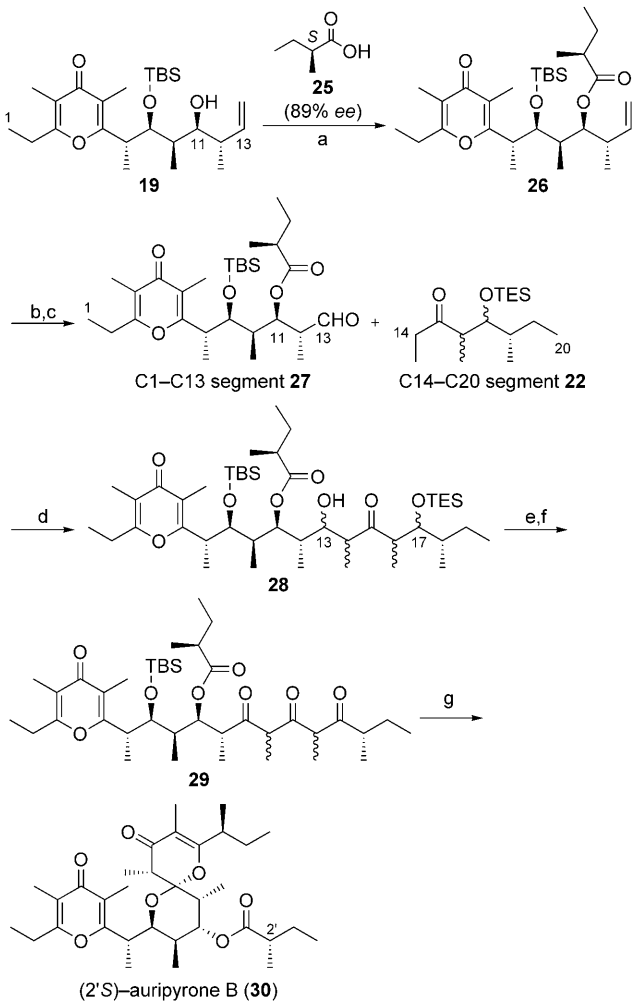


Figure 3. Spiroacetalization of triketone **24**.

equatorial position (hemiacetal **24b**) so as to avoid a 1,3-diaxial interaction between the C12 and C14 methyl groups of **24a**.

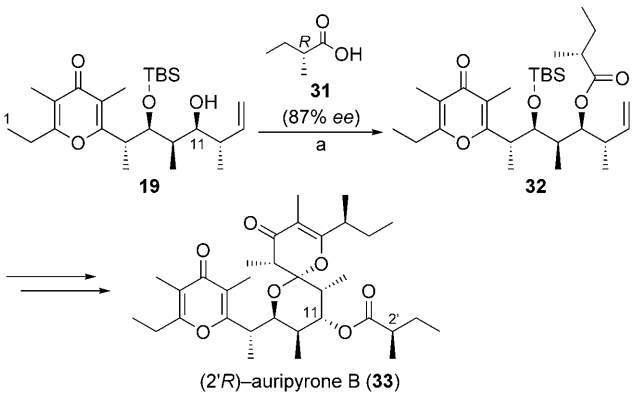
Next, we attempted the synthesis of (2′*S*)- and (2′*R*)-auripyrone B. First, we tried to remove the acyl group in auripyrone A (**5**). However, whilst we could not obtain a deacylated derivative, we did obtain a bis(pyrone) compound. Then, we attempted to convert homoallylic alcohol **19** into auripyrone B using our synthetic strategy for auripyrone A (**5**; Scheme 6). An esterification reaction between compound **19** and (*S*)-2-methylbutyric acid (**25**)[16] under the conditions described by Yamaguchi et al.[17] afforded compound **26**. Dihydroxylation of the terminal olefin in **26** gave a diol, and the resulting dihydroxy group was oxidatively cleaved to afford aldehyde **27**. The Paterson aldol reaction[15] of aldehyde **27** and C14-C20 segment **22** afforded the coupling product **28** as a diastereomeric mixture. The TES group in **28** was removed, and oxidation of the dihydroxy group afforded triketone **29** as a mixture of the keto and enol forms, a precursor for the spiroacetalization reaction. Removal of the TBS group in triketone **29** by HF·pyr and a spontaneous spiroacetalization afforded (2′*S*)-auripyrone B (**30**).

The (2′*R*)-auripyrone B (**33**) was also prepared from **19** in the same manner with (*R*)-2-methylbutyric acid (**31**)[16] (Scheme 7).



Scheme 6. Completion of the synthesis of (2′*S*)-auripyrone B (**30**). Reagents and conditions: a) **21**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, −78 °C to 0 °C, 93% yield; b) OsO_4, NMO, acetone/H_2O (1:1), RT, 94% yield; c) $NaIO_4$, acetone/H_2O (1:1), RT, 82% yield; d) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C, 99% yield; e) AcOH/THF/H_2O (4:1:4), RT, 90% yield; f) Dess–Martin periodinane, CH_2Cl_2, RT, 95% yield; g) HF·pyr/THF/pyr (5:7:3), 60 °C, 17% yield. DMAP = 4-dimethylaminopyridine, NMO = *N*-methylmorpholine oxide, OTf = trifluoromethanesulfonate, Ac = acetyl, THF = tetrahydrofuran, pyr = pyridine.

With both diastereomers (2′*S*)-auripyrone B (**30**) and (2′*R*)-auripyrone B (**33**) in hand, we compared the ^1H NMR spectra of their synthetic samples with those reported for the natural sample of auripyrone B (**6**).[18] Although the chemical shifts of the acyl group protons (H4′, H5′) in (2′*R*)-auripyrone B (**33**) were clearly different from those of the natural auripyrone B (**6**), the data for (2′*S*)-auripyrone B (**30**) were in good agreement with those of the natural product. Comparison of the optical rotation of synthetic (2′*S*)-auripyrone B (**30**) with that of natural samples identified the absolute configuration: the optical rotation of synthetic (2′*S*)-auripyrone B (**30**) $\{[\alpha]_D^{25} = +43$ ($c = 0.29$, $CHCl_3$)$\}$ corresponded to the reported values $\{[\alpha]_D^{26} = +39$ ($c = 0.14$, $CHCl_3$)$\}$. Therefore, this synthesis established the stereochemistry and absolute configuration at C2′ of auripyrone B (**6**; Figure 4).



Scheme 7. Completion of the synthesis of (2′*R*)-auripyrone B (**33**). Reagents and conditions: a) **31**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, −78 °C to 0 °C, 94% yield. DMAP = 4-dimethylaminopyridine.

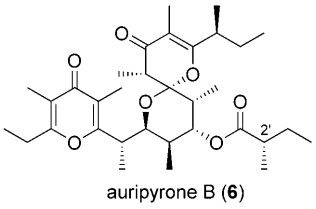


Figure 4. Absolute stereochemistry of auripyrone B (**6**).

In conclusion, we have achieved the total synthesis of auripyrones A (**5**; 2.6% overall yield in 13 steps) and B (**6**; 2.8% overall yield in 13 steps) by using a diastereoselective aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone (**12**) as a key step. From this synthetic work, we determined the stereostructure and absolute configuration of auripyrone B (**6**). Further application of the diastereoselective aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone (**12**) is currently underway in our group.

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[18] ^{1}H NMR spectra of synthetic and natural samples of auripyrone B are shown in the Supporting Information.

