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Synthetic Studies on Fully Substituted γ-Pyrone-Containing Natural Products: The Absolute Configurations of Ilikonapyrone and Peroniatriols I and II

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Summary: Mild cyclization method [DMSO - $(COCl)_2$ or Ph_3P - CCl_4] of triketides bearing optically active functional groups to the corresponding γ-pyrones provided determination of the absolute configurations of ilikonapyrone and peroniatriols I and II isolated from the marine molluscs *Onchidium verruculatum* and *Peronia peronii*.

The family of ilikonapyrone (**1**)[1] and peroniatriols I and II (**2** and **3**),[2] metabolites of the marine molluscs is one of the intriguing targets for synthetic chemists for the propionate-derived bispyrone structures bearing the continuous stereogenic centers along with their interesting biological activities. The relative stereochemistries of **2** and **3** were spectroscopically deduced by comparison with that of **1** which had been established by an X-ray crystallographic analysis. However difficulties to construct such pyrone-containing linear system by conventional manners prevented synthetic studies toward these natural products, even determination of their absolute configurations. In this context, we reported the effective cyclization of triketides under DMSO - $(COCl)_2$ or Ph_3P - CCl_4 conditions to the corresponding γ-pyrones without any serious epimerization and/or elimination of adjacent stereogenic centers.[3] Availability of this methodology could realize determination of the absolute configurations at the C_3 and C_4 positions of **2** and **3**.[4] After our publication, closely related onchitriols

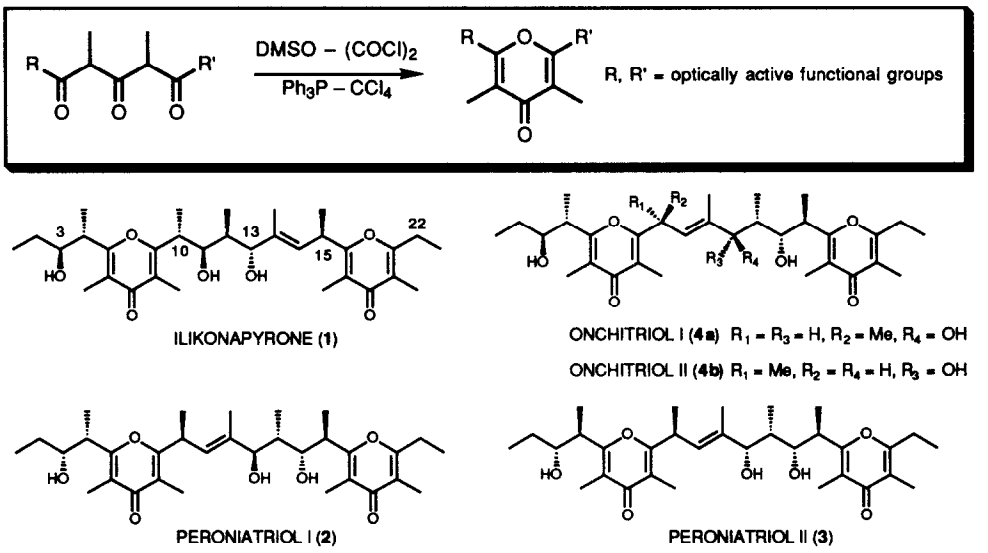
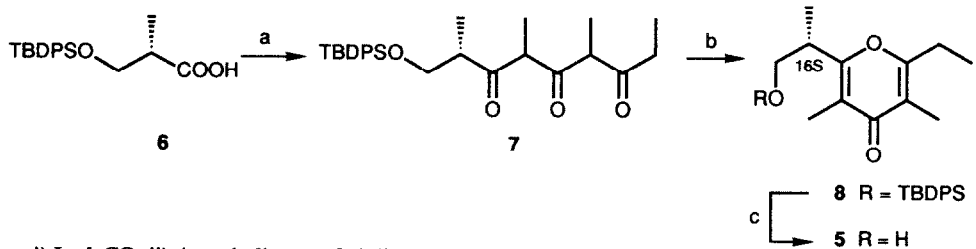


Figure 1.

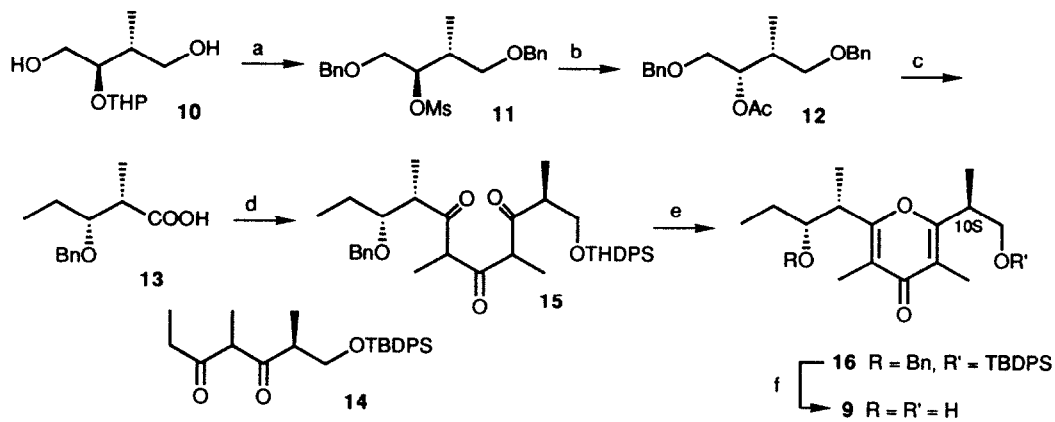
(**4a** and **4b**) were isolated from the mollusc *Onchidium* sp., and their stereostructures including absolute configuration were determined by comparison of the NMR data with those of **1**, **2** and **3**, and by Mosher - Trost's method.[5] This work prompted us to develop our synthetic investigation related to these natural products. We disclose herein our recent findings.

Absolute configuration of ilikonapyrone (1). Since the relative stereochemistry of **1** was proved as mentioned above, stereospecific synthesis of the degradation product (**5**) corresponding to the C_{15} - C_{23} segment[1] would fix all of the absolute configuration, and our cyclization methodology would be available for an access to **5**. Accordingly synthesis of **5** was undertaken as depicted in Scheme 1: the carboxylic acid (**6**) prepared from commercially available methyl (S)-3-hydroxy-2-methylpropionate [1. TBDPSCl, Imd (100%); 2. LiOH (100%)] was converted to the triketide (**7**) in two steps, which was submitted to the Ph_3P - CCl_4 conditions,[3] leading to the desired γ-pyrone (**8**) as a single isomer in 65% yield. Upon treatment with TBAF, **8** provided **5**[6] carrying the 16S-configuration. Although the ^1H NMR data of synthetic **5** were identical with that of **5** derived from **1**, the optical rotations showed opposite signs {$[\alpha]_D$ +32.8° (synthetic); -16.7° (natural)}. This result indicated the absolute configuration of ilikonapyrone (**1**) as depicted in Figure 1.



a. i) Imd_2CO; ii) 4-methylheptan-3,5-dione, LDA-DMPU, -70°C (75% in two steps). b. Ph_3P-CCl_4 / THF (65%). c. TBAF / THF (92%).

Scheme 1.

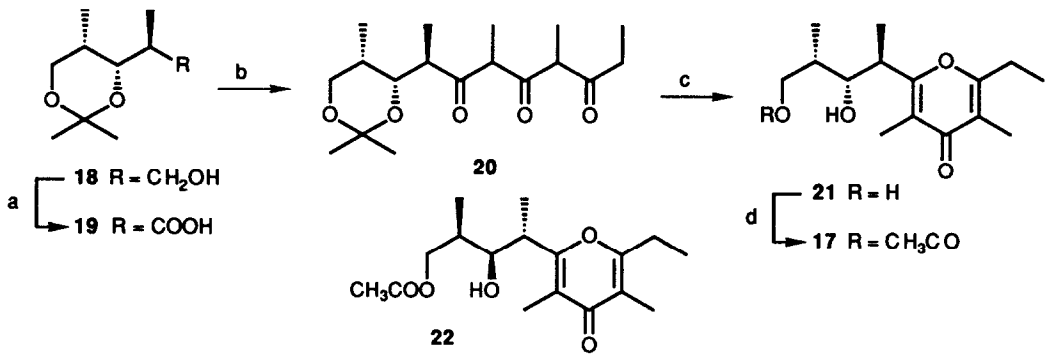


a. i) BnBr, NaH (66%); ii) Amberlyst H15 (83%); iii) MsCl, pyr (87%). b. CsOAc, 18-Crown-6 / PhH (96%). c. i) K_2CO_3 / MeOH (100%); ii) H_2, Pd-C (100%); iii) $PhCH(OMe)_2$ (66%); iv) TsCl, pyr (97%); v) Me_2CuLi (83%); vi) DIBAL (97%); Swern oxid., then Jones oxid. (63%). d. i) Imd_2CO; ii) **14**, LDA / THF-DMPU (37% in two steps). e. Ph_3P-CCl_4 / THF (75%). f. i) DDQ / CH_2Cl_2-H_2O (86%); ii) TBAF / THF (77%)

Scheme 2.

Absolute configurations of peroniatriols I and II (2 and 3). Our previous research[3] elucidated that **2** and **3** have the 3R,4S- and 3R,4R-configurations, and both of them share the same stereochemistry at the C_{10} position, although an absolute configuration is unsettled. At the outset, synthesis of **9** bearing the 10S-configuration was undertaken to establish the absolute structure of the left wing (C_1 - C_{11}) of peroniatriols I and II (**2** and **3**). Thus, the known diol (**10**)[7] was transformed into the acid (**13**) involving inversion of the oxygen function (**11** → **12**).[8] Compound **13** in hand was converted to its imidazolide, and coupled with the chiral dione (**14**) prepared by reaction of **6** with pentan-3-one by a similar procedure to the case of **7**, to yield the triketide (**15**). Cyclization under the Ph_3P - CCl_4 conditions furnished **16** in 75% yield, which on deprotection in two steps afforded the desired **9** {$[\alpha]_D$ +31.4°}.[6] Fortunately the ^1H NMR data were identical with those of the degradation product of **2** {$[\alpha]_D$ +4°}[2] and an enantiomer {$[\alpha]_D$ -18.8°} synthesized by us.[4] This observation indicated that both peroniatriols (**2** and **3**) possess the 10S-configuration.[9]

For structural determination of the right wing (C_{12} - C_{16}), we chose **17** as a synthetic target, based on the following information: 1) both peroniatriols (**2** and **3**) gave the same degradation product (**17**),[2] 2) the relative stereochemistry of the C_{10} - C_{16} sequence of **2** are same as that of **4a**, and the C_{13} - C_{16} position of **3** exhibits an identical NMR pattern to that of **4b**.[5] Thus, the known alcohol (**18**)[10] was oxidized to the acid (**19**), which was coupled with 4-methylheptan-3,5-dione to provide the triketide (**20**). Successful cyclization of **20** involving removal of the acetal group gave **21** in 54% yield. Upon selective acetylation at -20°C, **21** was converted to the target compound (**17**).[6] Additionally the enantiomer (**22**) of **17** was synthesized from an enantiomer of **18** to confirm the stereochemistry of **17**. Ultimately the ^1H NMR spectra of synthesized **17** and **22** were superimposable to the reported data,[2] and comparison of the optical rotations {$[\alpha]_D$ +7.8° (**17**); -8.4° (**22**); +29.4° (natural)} established the 14R,15R,16R-configuration of peroniatriols I and II (**2** and **3**). Although an absolute configuration of the C_{13} position could not be proved at this stage, the stereochemical relation[5] to **4a** and **4b** suggested 13R (**2**) and 13S (**3**) configurations as shown in Figure 1.



a. i) Swern oxid.; ii) $KMnO_4$ (quantitative). b. i) $(COCl)_2$; ii) 4-methylheptan-3,5-dione, LDA-DMPU, -70°C (55% in two steps). c. DMSO-$(COCl)_2$, -20°C (54%). d. Ac_2O-pyr., -20°C (40%).

Scheme 3.

In conclusion, our methodology for γ-pyrone construction could accomplish the absolute configurations of ilikonapyrone (**1**), as well as peroniatriols I and II (**2** and **3**) which are the C_3-epimer of **4a** and C_3,C_4,C_{10}-epimer of **4b**, respectively. Further studies on scope and limitation of the methodology toward γ-pyrone-containing natural products are in progress.

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6. **5**: $[\alpha]_D^{18}$ +32.8° (*c* 1.07, CH_2Cl_2); IR (film) 3610, 1660, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (6H, complex), 1.92 (3H, s), 1.95 (3H, s), 2.61 (2H, q, J= 7.5 Hz), 3.29 (1H, m), and 3.78 (2H, complex). **9**: $[\alpha]_D^{18}$ +31.4° (*c* 1.10, CH_2Cl_2); IR (film) 3400, 1645, 1585, and 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, J= 7.3 Hz), 1.22 (3H, d, J= 7.3 Hz), 1.29 (3H, d, J= 6.8 Hz), 1.39 (1H, ddq, J= 14.5, 8.3, 7.3 Hz), 1.50 (1H, ddq, J= 14.5, 3.9, 7.3 Hz), 1.97 (3H, s), 1.99 (3H, s), 3.01 (1H, dq, J= 6.8, 6.8 Hz), 3.22 (1H, ddq, J= 7, 5.4, 7.3 Hz), 3.74 (1H, m), and 3.79 (2H, complex). **17**: $[\alpha]_D^{18}$ +7.8° (*c* 0.20, CH_2Cl_2); IR (film) 3400, 1740, 1650, 1585, and 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (3H, d, J= 7 Hz), 1.14 (3H, d, J= 7 Hz), 1.22 (3H, t, J= 7 Hz), 1.94 (3H, s), 1.99 (3H, s), 2.09 (3H, s), 2.10 (1H, m), 2.62 (2H, q, J= 7 Hz), 3.13 (1H, m), 3.86 (1H, m), 3.97 (1H, dd, J= 6, 11 Hz), and 4.26 (1H, dd, J= 8, 11 Hz). The structures of other new compounds cited herein were supported by their spectral data.
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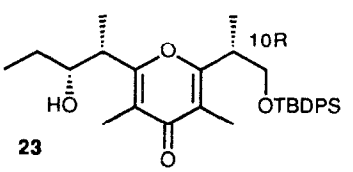
9. A possibility of epimerization at the C_{10} position during the synthetic process could be excluded by synthesis of the 10R derivative (**23**) using enantiomer of **14**. Compound **23** showed an entirely different spectrum from that of the 10S derivative (**24**). **23**: $[\alpha]_D^{20}$ -4° (*c* 0.20, $CHCl_3$); IR (film) 3400, 1650, and 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, J= 7 Hz), 0.99 (9H, s), 1.09 (3H, d, J= 7 Hz), 1.25 (3H, d, J= 7 Hz), 1.28 - 1.44 (2H, complex), 1.87 (3H, s), 1.98 (3H, s), 2.97 (1H, m), 3.08 (1H, m), 3.59 (1H, m), 3.68 (1H, dd, J= 6, 10 Hz), 3.83 (dd, J= 8, 10 Hz), 7.4 (6H, complex), and 7.6 (4H, complex). **24**: $[\alpha]_D^{20}$ +5° (*c* 1.03, $CHCl_3$); IR (film) 3430, 1655, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J= 7 Hz), 0.98 (9H, s), 1.12 (3H, d, J= 7 HZ), 1.15 (3H, d, J= 7 Hz), 1.32 (1H, m), 1.43 (1H, m), 1.94 (3H, s), 1.98 (3H, s), 2.95 (1H, m), 3.24 (1H, m), 3.64 (1H, m), 3.69 (1H, dd, J= 6, 10 Hz), 3.78 (dd, J= 10, 10 Hz), 7.4 (6H, complex), and 7.6 (4H, complex).



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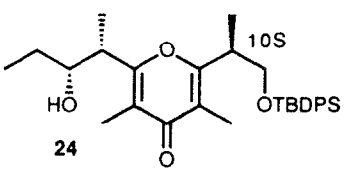

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