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SYNTHETIC STUDIES ON FULLY SUBSTITUTED γ-PYRONE-CONTAINING NATURAL PRODUCTS: SYNTHESIS OF γ-PYRONE DERIVATIVES OBTAINED BY DECOMPOSITION OF PERONIATRIOLS

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Summary: In connection with the two γ-pyrones obtained by decomposition reactions of peroniatriols I and II, γ-pyrone derivatives have been synthesized by newly developed mild cyclization methods, and this result revised the partial structures of these natural products.

Of metabolites of marine molluscs exhibiting remarkable biological activities, the family of propionate-derived pyrone derivatives has intrigued synthetic chemists for their varieties of structures carrying pyrone rings with chiral substituents.[1] Among these natural products, probable defense allomone ilikonapyrone (1) isolated from *Onchidium verruculatum*,[2] and cytotoxic peroniatriols I and II (2 and 3) isolated from the saponified extracts of *Peronia peronii*,[3] have possessed similar bispyrone structures, though their absolute configurations have still

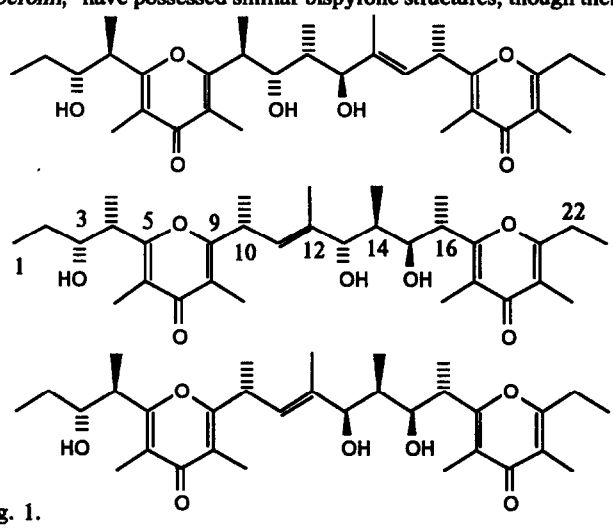
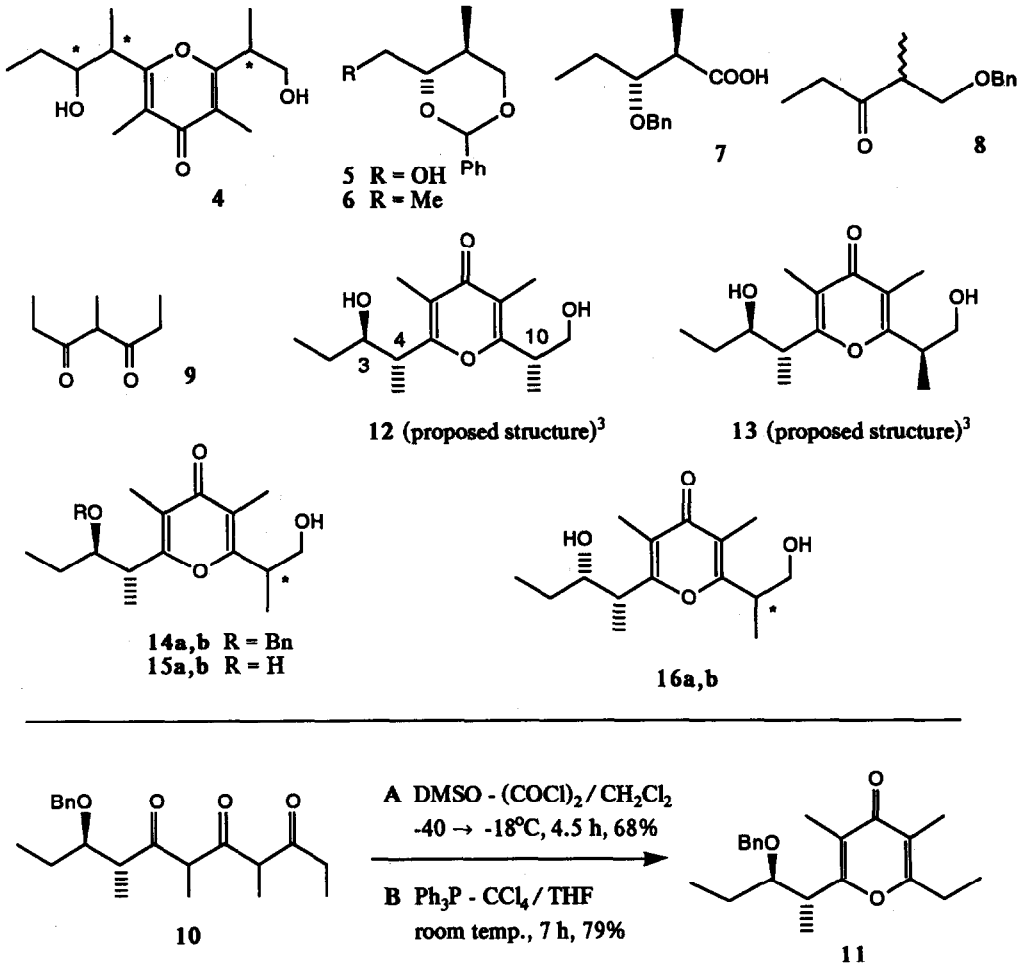


Fig. 1.

been uncertain.[4] We have planed to synthesize these pyrone derivatives in optically active forms, and a crucial step might be a formation of the pyrone ring from acyclic precursors carrying the continuous chiral centers. Related to this synthetic problem, we have reported in the preceeding paper the two mild conditions using DMSO - $(COCl)_2$ and Ph_3P - CCl_4 or CBr_4, which effected conversion of β-triketide to the corresponding γ-pyrone without unexpected side-reactions of the adjacent chiral centers. We describe herein synthetic process of optically active left wing segments (type 4) of ilikonapyrone (1) and peroniatriols I and II (2, 3). These compounds were obtained on decomposition of 2 and 3 involving ozonolysis followed by $NaBH_4$ reduction,[3] and our synthetic result would be expected to determine the absolute configurations of the left wings in 2 and 3.



Scheme 1.

Synthesis of the chiral segment (7) was started from the known benzylidene derivative (5).[5] Treatment of 5 with TsCl - pyridine in a usual manner gave an unstable tosylate in 98% yield, C_1-unit elongation of which was accomplished with Me_2CuLi (Et_2O, -30 → -20 °C) to give 6[6] in 89% yield. Compound 6 was transformed into a mixture of benzyl derivatives, which was oxidized to give the desired carboxylic acid (7)[6] and a ketone (8). (1. DIBAL-H, CH_2Cl_2, -10 °C, 95%. 2. Jones oxid., 7 in 72%, 8 in 8%). The carboxylic acid (7) thus obtained was converted to the corresponding imidazolide *via* its acid chloride, and the crude product was immediately reacted with a dianion of a diketone (9) to give a triketide (10)[6] in 46% yield from 7. [1. $(COCl)_2$ / PhH, then imidazole; 2. 9, LDA / THF, -78 °C]. In the next key step, cyclization of 10 to a γ-pyrone (11)[6] was performed by the two methods (A and B) as shown in Scheme 1. It was noted that any other γ-pyrone products could not be detected under these two conditions.

Upon introduction of a hydroxymethyl unit, the γ-pyrone (11) in hand would be derivatized to derivatives of type 4, which was obtained as above-mentioned from peroniatriols I and II (2, 3), and Ireland had proposed these structures as 12 from 2 and 13 from 3.[3] To realize this synthetic plan, 11 was transformed into alcohols

(**14a**, **14b**).[6] [1. LDA, HCOOEt / THF, -50 → -10 °C, 44%. 2. $NaBH_4$ / MeOH, 0 °C, **14a** 24% and **14b**, 23%). Both compounds were then subjected to oxidative deprotection [DDQ / moist. CH_2Cl_2, room temp.], to give **15a**[6] and **15b**[6] in 40 and 49% yields respectively. At this stage, the synthesized **15a** and **15b** should be identified with **12** and **13**, which were epimers at C_{10} position, and actually **15a** indicated a good agreement with **13** by comparison of their spectral data along with optical rotations {$[\alpha]_D$ +7° (CH_2Cl_2)},[3] while **15b** had a different structure from the remaining **12**.[7] Then, the secondary OH groups in **15a** and **15b** were epimerized to obtain all the possible isomers except their enantiomers; both **15a** and **15b** were converted in four steps to **16a**[8] and **16b**[8], respectively [1. TBDPSCl, Imd; 2. Swern oxid.; 3. $NaBH_4$ / EtOH; 4. nBu_4NF]. Consequently, comparison of the ^1H NMR spectra suggested that **16b** is equal to **12**, while its optical rotation showed an opposite sign to **12** {$[\alpha]_D$ +4° (CH_2Cl_2)}.[3] Therefore, the stereochemistry at C_3 position in **12** should be inverted, and the C_{10}-methyl group has the same stereochemistry as that of **13**, and at least the stereochemistry at C_3 - C_{10} positions of peroniatriol I (**2**) might be as depicted in Figure 1.[9]

In conclusion, stereostructures of peroniatriols I and II proposed by Ireland must be revised and presented as shown in **2** and **3**.

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6. **6**: $C_{13}H_{18}O_2$ [m/z 206.1305 (M^+)]; δ ($CDCl_3$) 0.78 (3H, d, J= 6 Hz), 1.03 (3H, t, J= 7 Hz), 1.40 - 2.10 (3H, complex), 3.35 (1H, m), 3.48 (1H, t, J= 11 Hz), 4.10 (1H, dd, J= 5, 11 Hz), 5.49(1H, s), and 7.25 - 7.60 (5H, complex). **7**: $C_{13}H_{18}O_3$ [m/z 223.1346 (M^++1)]; $[\alpha]_D^{25}$ -24.3° (c 1.02, $CHCl_3$); IR (film) 1710 and 1500 cm^{-1}; δ ($CDCl_3$) 0.96 (3H, t, J= 7 Hz), 1.18 (3H, d, J= 7 Hz), 1.63 ((2H, complex), 2.81 (1H, m), 3.65 (1H, m), 4.53 (1H, d, J= 11 Hz), 4.59 (1H, d, J= 11 Hz), and 7.30 (5H, complex). **10**: IR (film) 3420, 1725, 1700, 1660, and 1608 cm^{-1}. This compound might be a mixture of stereoisomers in the triketide moiety *via* the corresponding enols. **11**: $C_{21}H_{29}O_3$ [m/z 329.2127 (M^++1)]; $[\alpha]_D^{27}$ -15.9° (c 0.81, $CHCl_3$); IR (film) 1656, 1609, and 1553 cm^{-1}; δ ($CDCl_3$) 0.98 (3H, t, J= 7 Hz), 1.14 (3H, t, J= 8 Hz), 1.16 (3H, d, J= 7 Hz), 1.57 (1H, m), 1.73 (1H, m), 1.94 (3H, s), 1.99 (3H, s), 2.46 (1H, dq, J= 15, 7 Hz), 2.56 (1H, dq, J= 15, 7 Hz), 3.26 (1H, m), 3.55 (1H, m), 4.30 (1H, d, J= 11 Hz), 4.48 (1H, d, J= 11 Hz), 7.13 (2H, complex), and 7.24 (3H, complex). **14a**: δ ($CDCl_3$) 0.95 (3H, t, J= 7.3 Hz), 1.15 (3H, d, J= 6.8 Hz), 1.22 (3H, d, J= 6.8 Hz), 1.55 (2H, complex), 1.9 (3H, s), 1.98 (3H, s), 2.42

(1H, t, J= 6.5 Hz), 3.20 (2H, complex), 3.55 (2H, complex), 3.65 (1H, m), 4.39 (1H, d, J= 11.2 Hz), and 4.55 (1H, d, J= 11.2 Hz). **14b**: δ ($CDCl_3$) 0.95 (3H, t, J= 7 Hz), 1.13 (3H, d, J= 7 Hz), 1.19 (3H, d, J= 7 Hz), 1.60 (2H, m), 1.97 (3H, s), 1.98 (3H, s), 3.21 (1H, m), 3.25 (1H, dq, J= 7, 7 Hz), 3.50 (1H, m), 3.75 (2H, complex), 4.33 (1H, d, J= 11.7 Hz), and 4.51 (1H, d, J= 11.7 Hz). **15a**: $C_{12}H_{18}O_3$ [m/z 210.1236 (M^+-C_3H_6O)]; , $[\alpha]_D^{23}$ +8.0° (c 0.25, CH_2Cl_2); IR (film) 3360, 1647, 1584, and 1557 cm^{-1}; δ ($CDCl_3$) 0.99 (3H, t, J= 7.3 Hz), 1.22 (3H, d, J= 7 Hz), 1.28 (3H, d, J= 7 Hz), 1.37 (1H, ddq, J= 14.2, 8.8, 7.3 Hz), 1.61 (1H, ddq, J= 14.2, 3.4, 7.3 Hz), 1.951 (3H, s), 1.954 (3H, s), 3.03 (1H, dq, J= 7, 7 Hz), 3.23 (1H, ddq, J= 8, 4.4, 7 Hz), 3.70 (1H, ddd, J= 8.8, 7, 3.4 Hz), 3.75 (1H, dd, J= 11.2, 4.4 Hz), and 3.84 (1H, dd, J= 11.2, 8 Hz). **15b**: $C_{12}H_{18}O_3$ [m/z 210.1253 (M^+-C_3H_6O)]; $[\alpha]_D^{23}$ -24.6° (c 0.23, CH_2Cl_2); IR (film) 3400, 1650, 1582, and 1557 cm^{-1}; δ ($CDCl_3$) 0.99 (3H, t, J= 7.3 Hz), 1.258 (3H, d, J= 6.8 Hz), 1.260 (3H, d, J= 6.8 Hz), 1.46 (1H, ddq, J= 10, 8, 7.3 Hz), 1.58 (1H, ddq, J= 10, 4, 7.3 Hz), 1.976 (3H, s), 1.981 (3H, s), 3.07 (1H, dq, J= 6.8, 6.8 Hz), 3.20 (1H, ddq, J= 6.8, 5, 6.8 Hz), 3.70 (1H, ddd, J= 8, 6.8, 4 Hz), 3.78 (1H, dd, J= 11, 6.8 Hz), and 3.84 (1H, dd, J= 11, 5 Hz).

7. Unfortunately, Prof. Ireland could not provide authentic samples and the ^1H NMR spectra to us.
8. **16a**: $[\alpha]_D^{22}$ +19.6° (c 0.16, CH_2Cl_2); δ ($CDCl_3$) 0.98 (3H, t, J= 7.3 Hz), 1.21 (3H, d, J= 6.7 Hz), 1.28 (3H, d, J= 6.8 Hz), 1.54 (2H, m), 1.97 (3H, s), 1.98 (3H, s), 3.06 (1H, dq, J= 3.9, 6.8 Hz), 3.23 (1H, ddq, J= 8, 4.9, 6.7 Hz), 3.72 (1H, m), 3.75 (1H, dd, J= 11, 4.9 Hz), and 3.85 (1H, dd, J= 11, 8 Hz). **16b**: $[\alpha]_D^{21}$ -18.8° (c 0.17, CH_2Cl_2); δ ($CDCl_3$) 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, m).
9. A possibility of inversion of the stereochemistry at C_{10} position in **2** as well as **3** could not be necessarily ruled out.

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