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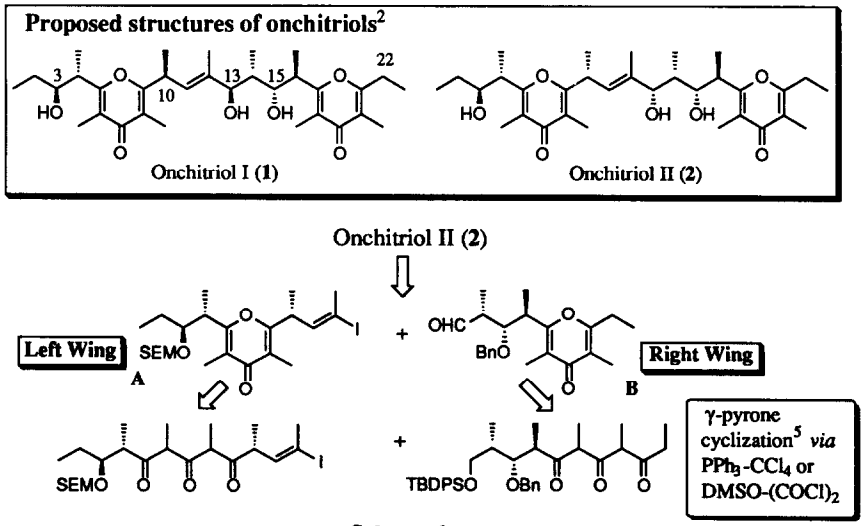
Synthetic Studies on Fully Substituted γ-Pyrone-Containing Natural Products: The First Total Synthesis of Onchitriol II

Hirokazu Arimoto, Shigeru Nishiyama,* and Shosuke Yamamura*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223 Japan

Summary: The first total synthesis of onchitriol II, a cytotoxic metabolite of mollusc *Onchidium* sp., is described. It employs mild cyclization method [DMSO - $(COCl)_2$ or Ph_3P - CCl_4] of triketides bearing optically active functional groups to the corresponding γ-pyrones as a key step. Additional synthesis of some diastereoisomers provided a possibility to revise the structure of closely related onchitriol I.

The cytotoxic metabolites of pulmonate of the family of *Onchidacea*, a shelless marine mollusc phylum, were extensively investigated by some research groups.[1] Onchitriols (**1**, **2**)[2] which were isolated from *Onchidium* sp. by Riguera and coworkers in 1992, are new members of the typical class; polyhydroxylated linear polypropionates with bis fully substituted γ-pyrone moiety, which include ilikonapyrone[3] and peroniatriols.[4] The structures of this family were in general, proposed by comparison with that of ilikonapyrone which had been determined by an X-ray crystallographic analysis,[3] but ambiguities on relative stereochemistries of asymmetric centers existing across γ-pyrone or trisubstituted olefin could not be avoided. In order to confirm these points, 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,[5] which enabled to establish the structures of peroniatriols and ilikonapyrone including absolute stereochemistries.[6] We report herein the first total synthesis of onchitriol II and some of its diastereoisomers, making use of the above mentioned efficient γ-pyrone formation. This synthesis allows the



Scheme 1.

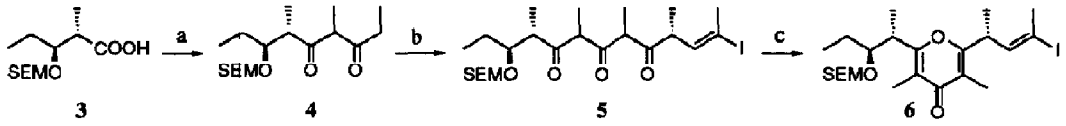
complete assignment of the stereochemistry for onchitriol II (2), and the structural revision of onchitriol I (1).

Synthetic strategies

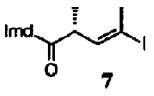
Retrosynthetic analysis of onchitriol II (2) formed our strategy in which functionalized vinyl iodide (left wing A) and aldehyde (right wing B) would be connected as seen in scheme 1. Both wings were further simplified to the corresponding carboxylic acids and ketones *via* β-triketone by applying our PPh_3-CCl_4 methodology (Scheme 2 and 3).

Construction of the C_1-C_{12} Left Wing

Our synthesis started with enantiomerically pure carboxylic acid **3**, which could be prepared from commercially available (*S*)-(+)-methyl 3-hydroxy-pentanoate by following the protocol of Fráter.[7] Condensation with 3-pentanone, followed by acylation with carboxylic acid **7**[8] gave β-triketone **5**, which was directly subjected to PPh_3-CCl_4 cyclization[5] to form the desired left wing **6** in acceptable yield.



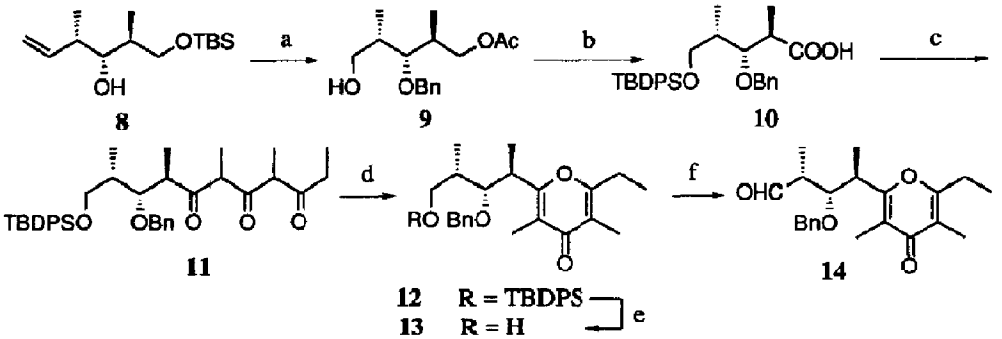
a. i) Imd_2CO; ii) 3-pentanone, LDA-DMPU, -70 °C (67%).
b. i) LDA (2eq.) -DMPU / THF, -70~-10 °C; ii) **7**, -73 °C (47%). c. PPh_3(3eq.) -CCl_4(10eq.) / THF (40%).



Scheme 2.

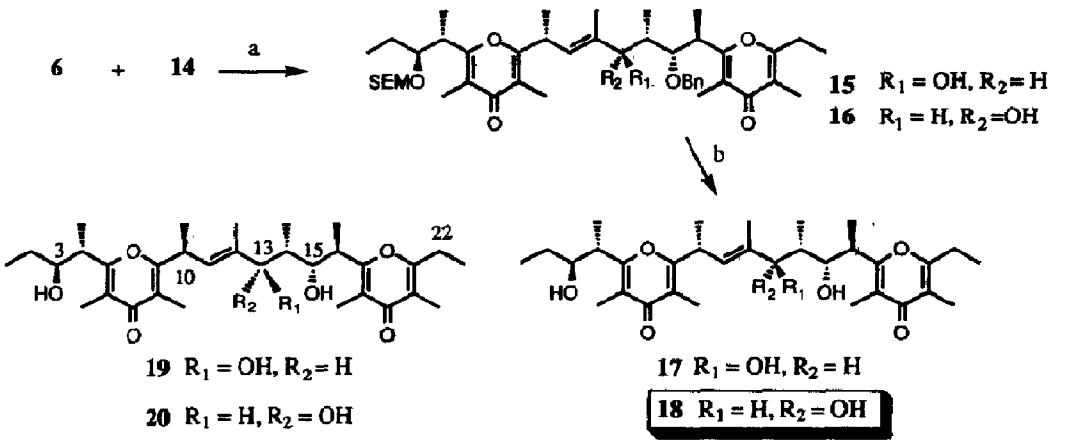
Construction of the C_{13}-C_{23} Right Wing

Assembly of the right wing was accomplished as follows. The known allyl alcohol **8**[9] was transformed to appropriately protected carboxylic acid **10**, which was condensed with β-diketone dienolate to give **11**. Cyclization to the γ-pyrone **12** proceeded in excellent yield. Further manipulation of **12** gave the right wing aldehyde **14**.



a. i) TBAF; ii) $PhCH(OMe)_2$, p-TsOH / CH_2Cl_2; iii) DIBAL-H / CH_2Cl_2, 0 °C (96%); iv) Ac_2O, Pyr. (100%); v) O_3 / CH_2Cl_2-MeOH, then Me_2S; vi) $NaBH_4$ (83% in 2steps). b. i) TBDPSCl, Imidazole (quant.); ii) K_2CO_3, MeOH (99%); iii) Swern oxid., then $KMnO_4$ (87%). c. i) $(COCl)_2$; ii) 4-methyl-heptane-3,5-dione, LDA-DMPU, -70 °C (56%). d. PPh_3-CCl_4 (86%). e. TBAF (quant.). f. Swern oxid. (99%).

Scheme 3.

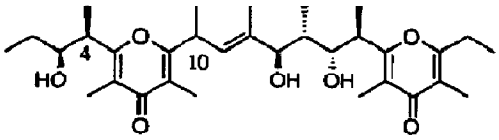


a. 0.5% $NiCl_2$-$CrCl_2$, DMSO room temp. 1 day (**15**: 23%, **16**: 27%, recovered aldehyde: ca. 30%). b. i) Ac_2O, Pyr.; ii) TFA / CH_2Cl_2, -10 °C; iii) DDQ / CH_2Cl_2-H_2O; iv) K_2CO_3 / MeOH (**17**: 64% in 4 steps from **15**, **18**: 97% in 4 steps from **16**)

Scheme 4.

Chromium-nickel coupling and transformations to onchitriol II

The $CrCl_2$-$NiCl_2$ coupling[10] of **6** and **14** in DMSO proceeded as intended to provide a mixture of **15** and **16**, although the reaction in DMF solution was unsuccessful. For deprotection of the coupling products, the following problems should be cleared: i) removal of the benzyl groups by DDQ oxidation provided a complex mixture in the presence of the C_{13} hydroxyl group, and ii) the pyrone units were sensitive to usual TBAF / MS 4Å conditions to remove a SEM group. Ultimately the above-mentioned difficulties could be excluded by the four steps manipulation (Scheme 4) to give **17** and **18**[11] in 64 and 97% yields, respectively. Related isomers (**19**, **20**)[11] were also synthesized in essentially the same way. Among the four isomers synthesized, the analytical data of **18** proved to be identical in all respects with those of natural onchitriol II (**2**). However, the spectral data of onchitriol I (**1**) were obviously different from those of synthetic **19** (the proposed structure for **1**), **17** and **20**. At this stage, we reexamined the reported data: relative stereochemistries of C_{13}-C_{16} would be reliable, and absolute configurations of the alcohol units were determined by Trost-Mosher methodology.[2] Combined with our results, it would be suggested that onchitriol I has probably the C_4 β geometry, although that of the C_{10} is still uncertain (Fig. 1). Synthesis of possible isomers is in progress to accomplish unambiguous structural determination of **1**.



Possible structure of onchitriol I

Figure 1.

In conclusion, our methodology for γ-pyrone construction could accomplish the total synthesis of onchitriol II (**2**), which was the first example for this class natural products, and a possibility of further structural revision of onchitriol I (**1**) was suggested.

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17: $[\alpha]_D^{19}$ +8° (*c* 0.59, CH_2Cl_2); HREIMS *m/z* (obs.) 544.3423 (M^+), calc. for $C_{32}H_{48}O_7$ 544.3397; IR (film) 3400, 1650, 1590, 1560 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.91 (3H, t, J= 7.3 Hz), 0.96 (3H, d, J= 6.9 Hz), 1.10 (3H, d, J= 7.0 Hz), 1.13 (3H, t, J= 7.7 Hz), 1.20 (3H, d, J= 7.4 Hz), 1.26 (1H, m), 1.35 (3H, d, J= 7.0 Hz), 1.58 (1H, m), 1.61 (3H, d, J= 1.5 Hz), 1.87 (1H, m), 1.90 (6H, s), 1.97 (3H, s), 2.03 (3H, s), 2.45 (1H, dq, J= 7.7, 7.7 Hz), 2.59 (1H, dq, J= 7.7, 7.7 Hz), 2.91 (1H, dq, J= 7.4, 7.3 Hz), 2.98 (1H, br.s), 3.10 (1H, dq, J= 9.9, 7.0 Hz), 3.46 (1H, br.s), 3.65 (1H, m), 3.78 (1H, dd, J= 1.7, 9.9 Hz), 3.90 (1H, dq, J= 9.1, 7.0 Hz), 4.16 (1H, br.d, J= 4.4 Hz), 5.70 (1H, dq, J= 9.1, 1.5 Hz); ^{13}C-NMR (100MHz, $CDCl_3$) δ 5.0, 9.3, 9,4, 9.5, 9.7(2C), 11.0,13.4, 14.3, 15.5, 19.3, 24.7, 27.9, 33.8, 35.7, 39.6, 41.1, 75.1, 76.4, 80.4, 116.4, 117.7, 118.8, 119.8, 127.0, 137.0, 164.2, 164.3, 164.5, 165.2, 179.8(2C). **18** (Onchitriol II): $[\alpha]_D^{19}$ +17° (*c* 0.98, CH_2Cl_2); HREIMS *m/z* (obs.) 545.3481 (M^++1), calc. for $C_{32}H_{49}O_7$ 545.3476; IR (film) 3500, 1650, 1590, 1558 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.87 (3H, t, J= 7.3 Hz), 1.01 (3H, t, J= 7.8 Hz), 1.02 (3H, d, J= 6.9 Hz), 1.14 (3H, d, J= 7.3 Hz), 1.15 (3H, d, J= 6.8 Hz), 1.18 (1H,m), 1.32 (3H, d, J= 6.8 Hz), 1.63 (3H,d, J= 0.9 Hz), 1.67 (1H, m), 1.86(3H, s), 1.87 (3H, s), 1.92 (3H, s), 1.95 (1H, m), 2.04 (3H, s), 2.25 (1H, dq, J= 15.6, 7.8 Hz), 2.54 (1H, dq, J= 15.6, 7.8 Hz), 2.81 (1H, dq, J= 8.7, 6.8 Hz), 3.07 (1H, dq, J= 9.8, 6.9 Hz), 3.56 (1H, m), 3.71 (1H, br.d, J= 9.8 Hz), 3.94 (1H, dq, J= 9.3, 6.9 Hz), 4.04 (1H, br.s, OH), 4.08 (1H, d, J= 2.9 Hz), 5.83 (1H, dq, J= 9.3, 0.9 Hz); ^{13}C-NMR (100MHz, $CDCl_3$) δ 9.2, 9.4 (2C), 9.6, 9.7, 9.8, 10.6, 13.6, 13.8, 15.4, 19.6, 24.5, 27.6, 34.0, 34.3, 39.5, 41.8, 73.0, 75.2, 79.9, 116.0, 117.3, 118.5, 120.0, 125.4, 137.4, 164.0, 164.5, 164.8, 165.5, 179.7, 179.8. **19**: $[\alpha]_D^{20}$ +14° (*c* 0.23, CH_2Cl_2); HREIMS *m/z* (obs.) 544.3379 (M^+), calc. for $C_{32}H_{48}O_7$ 544.3397; IR (film) 3420, 1650, 1590, 1555 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.94 (3H, d, J= 7.0 Hz), 1.00 (3H, t, J= 7.4 Hz), 1.20 (3H, d, J= 7.3 Hz), 1.21 (3H, t, J= 7.3 Hz), 1.33 (3H, t, J= 6.7 Hz), 1.45 (1H, m), ca.1.65 (1H, m, overlapped with the H_2O peak), 1.69 (3H,d, J= 1.3 Hz), 1.90 (1H, m), 1.94 (3H, s), 1.97 (3H,s), 1.98 (3H, s), 1.99 (3H, s), 2.60 (2H, complex), 3.05 (1H, dq, J= 7.2, 7.0 Hz), 3.11 (1H, dq, J= 9.5, 7.0 Hz), 3.71 (1H, ddd, J= 3.4, 7.2, 8.3 Hz), 3.92 (1H, dq, J= 9.1, 6.7 Hz), 4.08 (1H, d, J= 6.2 Hz), 4.15 (1H, dd, J= 1.9, 9.5 Hz), 5.64 (1H, dq, J= 9.5, 1.9 Hz); ^{13}C-NMR (100MHz, $CDCl_3$) δ 9.5, 9.6, 9.7 (3C), 9.8, 11.4, 12.7, 14.4, 14.6, 18.7, 24.8, 27.5, 34.3, 35.8, 39.0, 41.2, 72.0, 75.3, 79.9, 117.3, 117.9, 119.6, 119.8, 127.0, 137.4, 164.2, 164.3 (2C), 164.6, 179.8 (2C). **20**: $[\alpha]_D^{22}$ -13° (*c* 0.25, CH_2Cl_2); HREIMS *m/z* (obs.) 545.3462 (M^++1), calc. for $C_{32}H_{49}O_7$ 545.3475; IR (film) 3500, 1648, 1590, 1555 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.79 (3H, d, J= 6.9 Hz), 1.01 (3H, t, J= 7.3 Hz), 1.13 (3H, d, J= 7.0 Hz), 1.21 (3H, d, J= 7.0 Hz), 1.23 (3H, t, J= 7.7 Hz), 1.33 (3H, d, J= 7.0 Hz), 1.44 (1H, m), 1.66 (3H, d, J= 1.1 Hz), 1.67 (1H, m), 1.88 (1H, m), 1.94 (3H, s), 1.98 (3H, s), 1.98 (3H, s), 2.01 (3H, s), 2.62 (2H, m), 3.05 (1H, dq, J= 7.3, 7.3 Hz), 3.12 (1H, dq, J= 9.9, 6.9 Hz), 3.73 (1H, m), 3.91 (1H, dq, J= 9.1, 7.0 Hz), 4.01 (1H, dd, J= 9.9, 1.5 Hz), 4.25 (1H, d, J= 2.2 Hz), 5.66 (1H, dq, J= 9.2, 1.1 Hz).

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