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Synthesis and Revised Structure of Vallartanone B

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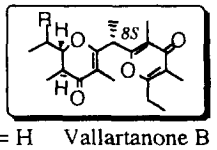
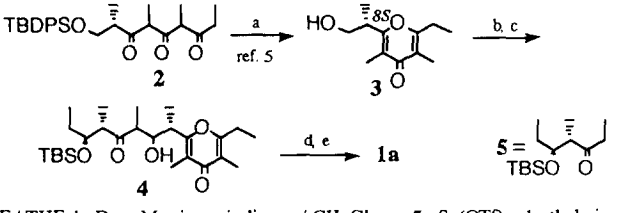
Abstract: The synthesis and revised structure of vallartanone B, a γ-pyrone-containing polypropionate from a marine mollusc, are described. Copyright © 1996 Elsevier Science Ltd

Cytotoxic polypropionates, produced by marine pulmonate molluscs, have attracted considerable attention as possible defense allomones,[1] although not all of them possess ichthyodeterrent properties. We previously reported efficient methods for constructing tetraalkylsubstituted γ-pyrones,[2] which have enabled the total synthesis of onchitriols.[3] Vallartanone B(**1a**), isolated from *Siphonaria maura*, deters feeding of the fish *Thallasoma lunare*, and may be a defensive allomone of pulmonate molluscs.[4] The structure of **1a** was proposed based on an interpretation of spectral data. Although the absolute configuration was determined by analogy with that of the related vallartanone A(**1b**), a CD exciton coupling method for the bis-pyrone system has not been fully established. We report here the synthesis of vallartanone B and its C8 epimer, and a revision of its stereochemistry.



R= H Vallartanone B (**1a**)
R= Me Vallartanone A (**1b**)

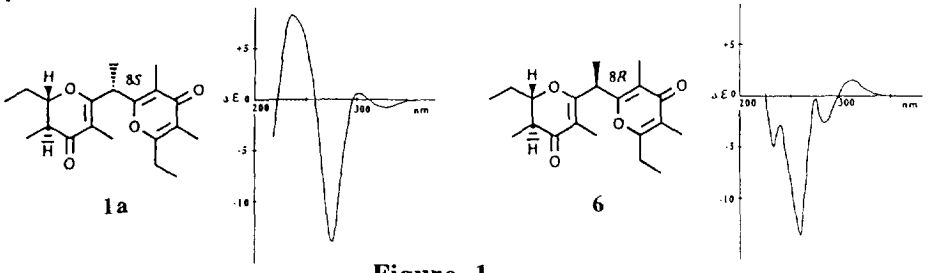


a. Ph_3P-CCl_4 / THF then TBAF / THF. b. Dess-Martin periodinane / CH_2Cl_2. c. **5**, $Sn(OTf)_2$, 1-ethyl piperidine /CH_2Cl_2, -78°C (82 % in 2 steps). d. Dess-Martin periodinane / CH_2Cl_2. e. TFA / $CHCl_3$ (44 % in 2 steps).

Scheme 1

β-Triketone (**2**), prepared from methyl (*S*)-3-hydroxy 2-methylpropionate, was converted to a pyrone (**3**) as in our previous study.[5] Dess-Martin oxidation of **3** gave crude aldehyde,[6] which was directly subjected to aldol reaction with a ketone (**5**).[7] The resulting mixture of **4** was further oxidized to β-diketones,[6] and immediately treated with TFA to give **1a**. Similarly the 8*R* isomer (**6**), which was originally proposed to be vallartanone B, was stereospecifically synthesized from methyl (*R*)-3-hydroxy 2-methylpropionate. In either case, the final product contained up to 13 % of its C8 epimer, which could be separated by HPLC (CHIRALCEL, Daicel Co., 75 % aq.MeOH). Although the epimers exhibited very

similar ^{1}H and ^{13}C NMR spectra,[8] a detailed comparison with that of natural vallartanone B suggested that the natural product had an 8*S* configuration. Furthermore, the CD spectrum of **6** did not show a distinct split Cotton effect, while that of 8*S* isomer (**1a**) agreed with the reported spectra[4] of natural vallartanone A(Figure 1.). The optical rotation of **1a** was of the same sign and magnitude as that of the natural product. Thus, we concluded that the stereochemistry of vallartanone B should be revised to **1a**. These results also suggest the possibility that the strucre of vallartanone A should also be reconsidered.



1a **6**

Figure 1.

In conclusion, the total synthesis of vallartanone B has led to structural revision at C8.[9] Further studies on its role as a defensive allomone are in progress.

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3. a) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 9581-9584. b) Arimoto, H.; Okumura, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 5357-5358.
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6. Since the product was prone to racemization under silica gel chromatography, the reaction mixture was washed with $NaHCO_3$aq. and concentrated under reduced pressure at 20°C. The residue was used for the next step without further purification.
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8. **1a**(synth.): $[\alpha]_D^{20}$ -129° (*c* 0.35, $CHCl_3$); HREIMS; *m/z* 332.1977, calc. for $C_{20}H_{28}O_4$ 332.1987; IR (film) 1650, 1600 cm^{-1}; UV(MeOH) 217 nm (ε 12715), 265 nm (ε 21663), ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.97 (3H, t, J= 7.3 Hz), 1.09 (3H, d, J= 6.9 Hz), 1.23 (3H, t, J= 7.6 Hz), 1.47 (3H, d, J= 7.1 Hz), 1.64 (1H, m), 1.76 (3H, s), 1.81 (1H, m), 1.93 (3H, s), 1.96 (3H, s), 2.30 (1H, dq, J= 12.3, 6.9 Hz), 2.63 (2H, q, J= 7.6 Hz), 3.86 (1H, ddd, J= 3.3, 8.1, 12.3 Hz), 4.16 (1H, q, J= 7.1 Hz); ^{13}C-NMR (75MHz, $CDCl_3$) δ 8.9, 9.0, 9.3, 9.5, 10.6, 11.2, 14.3, 24.8, 25.5, 38.6, 42.7, 84.4, 108.7, 118.2, 118.9, 160.8, 164.5, 168.6, 179.6, 195.3: **6**: $[\alpha]_D^{20}$ -52° (*c* 0.42, $CHCl_3$); HREIMS; *m/z* 332.1970, calc. for $C_{20}H_{28}O_4$ 332.1987; IR (film) 1650, 1600 cm^{-1}; UV(MeOH) 217 nm (ε 7503), 268 nm (ε 10967), ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.96 (3H, t, J= 7.3 Hz), 1.08 (3H, d, J= 6.9 Hz), 1.23 (3H, t, J= 7.8 Hz), 1.49 (3H, d, J= 7.2 Hz), 1.69 (1H, m), 1.74 (3H, s), 1.78 (1H, m), 1.96 (3H, s), 1.96 (3H, s), 2.36 (1H, dq, J= 11.8, 6.9 Hz), 2.62 (2H, q, J= 7.8 Hz), 3.80 (1H, ddd, J= 3.4, 7.9, 11.8 Hz), 4.14 (1H, q, J= 7.2 Hz); ^{13}C-NMR (75MHz, $CDCl_3$) δ 8.9, 8.9, 9.3, 9.5, 10.7, 11.3, 14.4, 24.8, 25.5, 38.7, 42.8, 84.3, 109.1, 118.2, 118.7, 161.0, 164.5, 168.6, 179.6, 195.2
9. A conformational study of vallartanone derivatives is in progress.

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