First Synthesis of (+)-Pteroenone: A Defensive Metabolite of the Abducted Antarctic Pteropod *Clione antarctica*

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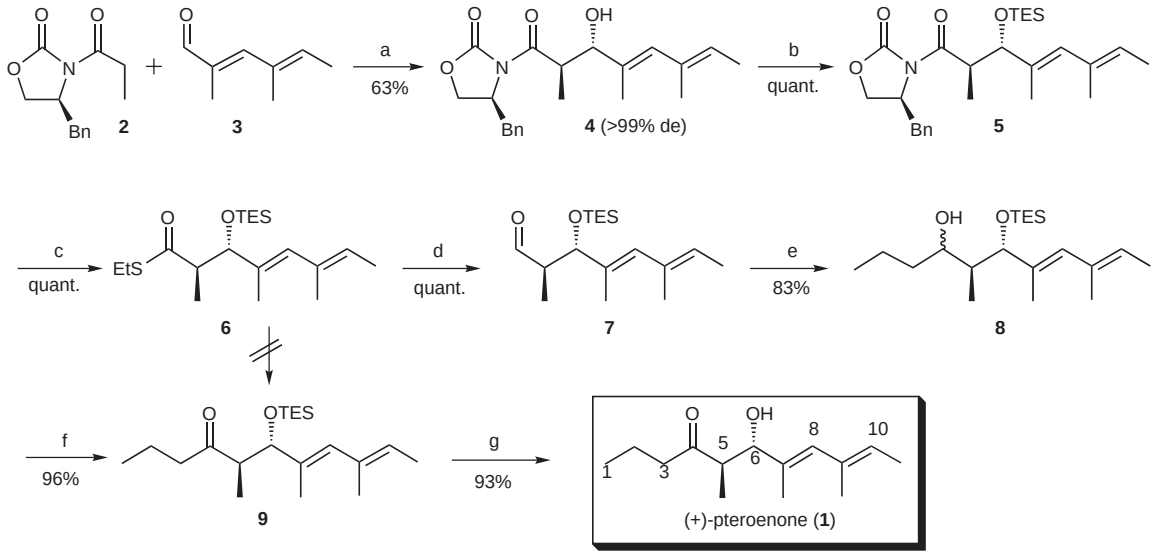
This paper is dedicated to Professor Steven V. Ley FRS CBE on the occasion of his 60th birthday.

Abstract: (+)-Pteroenone, a defensive metabolite of the abducted antarctic pteropod *Clione antarctica*, was firstly and efficiently synthesized by employing *anti*-selective aldol reaction as the key step.

Key words: pteroenone, defensive metabolite, *Clione antarctica*, marine natural products, *anti*-aldol reaction

The pteropod *Clione antarctica* is a shell-less, pelagic mollusc, which blooms each austral summer in McMurdo Sound, Antarctica. There has been known the curious relationship between *C. antarctica* and an Antarctic hyperiid amphipod, *Hyperiella dilatata*, which is a prey of several antarctic fishes. Predatory fishes do not eat the amphipod grasping a pteropod on its dorsum, due to a feeding deterrent produced by the pteropod.[1,2] Yoshida et al. searched for this defensive chemical substance, and isolated a compound named pteroenone [(+)-**1**].[2] Here, the first synthesis of (+)-**1** is described.

As shown in Scheme 1, our synthesis of (+)-**1** started from the Evans *anti*-selective aldol reaction[3] of **2** with the known aldehyde **3**,[4] giving aldol **4**. This aldol **4** was purified (>99% de) by recrystallization. The absolute configuration was confirmed by converting **4** to the final compound. The hydroxy group of **4** was protected as TES ether to give **5**. Since substitution of the chiral auxiliary with propyl group via the Weinreb amide was not efficient,[5] the compound **5** was converted to thiol ester **6** with lithium thioethoxide in quantitative yield.[6] Since direct conversion of thiol ester **6** to ketone **9** failed under a variety of Fukuyama coupling conditions[7] and organocopper



Scheme 1 Synthesis of (+)-pteroenone. *Reagents and conditions*: a) $MgCl_2$ (0.2 equiv), TMSCl (1.5 equiv), Et_3N (2 equiv), EtOAc, r.t., 1 d, recrystallization; b) TESOTf (1.2 equiv), 2,6-lutidine (1.2 equiv), CH_2Cl_2, –55 °C, 3 h; c) EtSH (3.8 equiv), *n*-BuLi (2.6 equiv), THF, –78 °C to 7 °C, 6 h; d) DIBAL (1.01 equiv), CH_2Cl_2, –80 °C, 20 min; e) *n*-PrLi (1.1 equiv), Et_2O, –80 °C, 30 min; f) IBX (4 equiv), DMSO, r.t., 5 h; g) HF–TBAF (pH 7, excess), THF–H_2O, r.t., 2 h.

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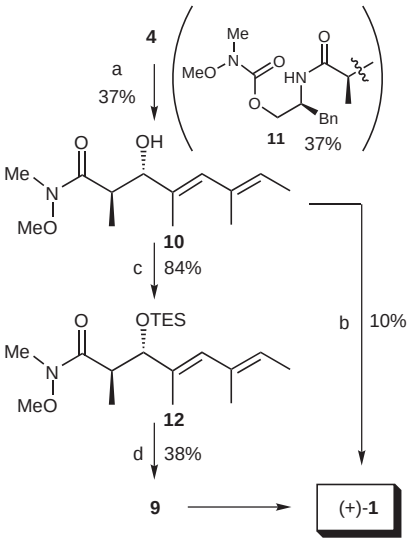
reagents,[8] this transformation was achieved in 3 steps: reduction using DIBAL, alkylation with *n*-PrLi and IBX oxidation. Use of *n*-PrMgBr or *n*-PrCeCl$_2$ lowered the yield (<65%). The stereochemistry was retained through these steps, however, deprotection of the TES group was troublesome: usual conditions such as HF·pyridine, HF–MeCN, TBAF, and HOAc–THF–H$_2$O resulted in decomposition or epimerization. Finally, neutral conditions (pH 6–7) by mixing aqueous HF and TBAF–THF[9] gave (+)-**1** without epimerization of 5- or 6-position. The purity of the final compound (+)-**1** was 98% ee and 96% de.[10] The overall yield was 47%. The ^{1}H NMR and ^{13}C NMR spectral data and the value of optical rotation were identical with those reported.[2,11]

In conclusion, the first efficient synthesis of a marine defensive metabolite, (+)-pteroenone was achieved in high yield using the Evans *anti*-aldol reaction as the key step. Synthesis of all four diastereoisomers is under way and their bioassays will make clear the curious ecological relationships and generality of this marine repellent.



Scheme 2 Other synthetic routes to (+)-**1**. *Reagents and conditions*: a) Me(MeO)NH·HCl (3 equiv), AlCl$_3$ (3 equiv), CH$_2$Cl$_2$, –20 °C to 20 °C; b) *n*-PrMgBr (3 equiv), THF, 0 °C; c) TESOTf (1.2 equiv), 2,6-lutidine (1.2 equiv), CH$_2$Cl$_2$, –55 °C; d) *n*-PrLi (3 equiv), THF, –78 °C.

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(5) At first, we tried shortcut routes (Scheme 2). The chiral auxiliary was removed by transamidation to afford Weinreb amide **10**, accompanied by undesired ring-opening compound **11**. A variety of conditions were tried but formation of **11** could not be suppressed, and all attempts to convert **11** into **10** or **1** failed. Amide **10** was treated with excess *n*-PrMgBr without protecting the hydroxy group to give the desired compound **1**, but only in 10% yield. The major impurities were retro-aldol reaction products. Although the hydroxy group was protected, the corresponding TES ether **12** also gave the ketone **9** in low yield, accompanied by the over-reacted tertiary alcohol.
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(10) Determined by HPLC analysis (98% ee and 96% de): column, Daicel Chiralcel® OJ (4.6 × 250 mm); solvent, hexane–*i*-PrOH (100:1) 0.5 mL/min, 20 °C; detection, 234 nm; t_R = 18.9, 19.6 (diastereomers, Σ = 2%), 22.6 (enantiomer, 1%) and 24.7 [(+)-**1**, 97%] min. These retention times of the peaks were identified by the separate synthesis of other three diastereomers.
(11) Compound (+)-**1**: colorless oil, $[\alpha]_D^{26}$ +47 (*c* 0.30, hexane) {Lit.[2], $[\alpha]_D$ +48 (*c* 0.6, hexane)}. ^{1}H NMR (500 MHz, C$_6$D$_6$): δ = 0.82 (3 H, d, *J* = 7.5 Hz, 5-Me), 0.84 (1 H, t, *J* = 7.5 Hz, H-1), 1.58 (3 H, d, *J* = 7.0 Hz, H-11), 1.62 (2 H, sextet, *J* = 7.5 Hz, H-2), 1.65 (3 H, s, 9-Me), 1.67 (1 H, d, *J* = 3.5 Hz, OH), 1.71 (3 H, s, 7-Me), 2.19 (1 H, td, *J* = 7.3, 17.5 Hz, H-3), 2.31 (1 H, td, *J* = 7.3, 17.5 Hz, H-3), 2.60 (1 H, qd, *J* = 7.0, 9.5 Hz, H-5), 4.07 (1 H, dd, *J* = 2.5, 9.0 Hz, H-6), 5.40 (1 H, q, *J* = 6.7 Hz, H-10), 5.78 (1 H, s, H-8). All the signals were fully assigned by HH-COSY, HSQC and HMBC spectra. In the ^{1}H NMR, signal at δ = 2.31 ppm was misdescribed in ref.[2] as 2.21 ppm. ^{13}C NMR (125 MHz in C$_6$D$_6$): δ = 12.5 (7-Me), 13.7 (C-1), 13.9 (C-11), 14.1 (5-Me), 16.5 (9-Me), 17.0 (C-2), 45.6 (C-3), 48.8 (C-5), 81.3 (C-6), 124.9 (C-10), 132.4 (C-8), 133.2 (C-9), 134.5 (C-7), 213.2 (C-4). HRMS (EI) [M$^+$]: *m*/*z* calcd for C$_{14}$H$_{24}$O$_2$: 224.1776; found: 224.1779.