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# ASYMMETRIC TOTAL SYNTHESES OF (+)- AND (-)-PULO'UPONE

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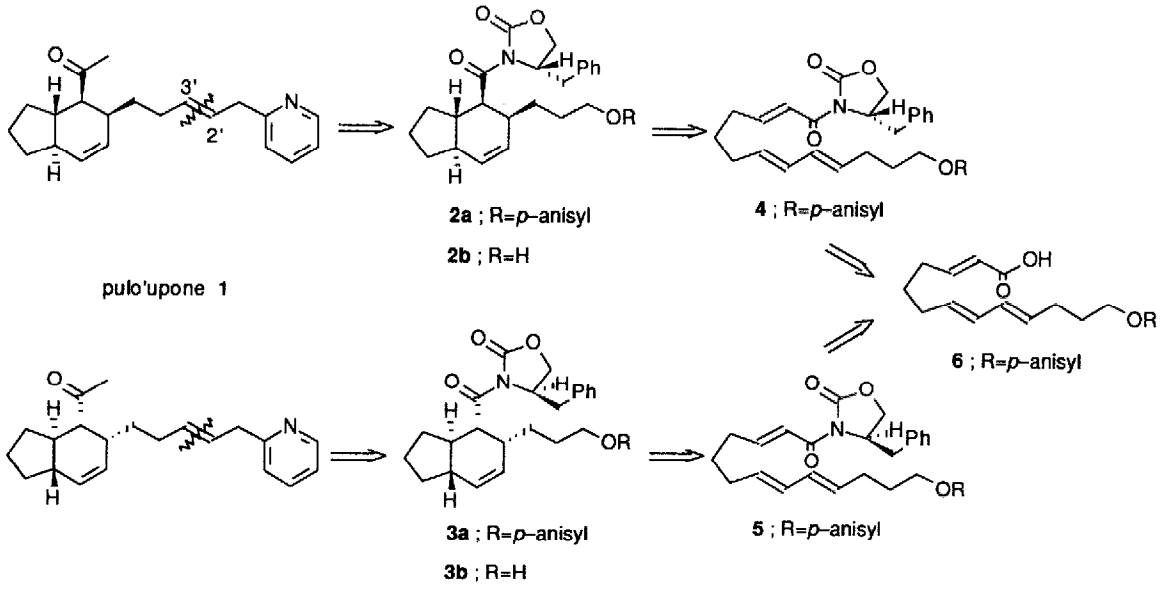
Summary: Asymmetric total syntheses of both enantiomers of marine mollusk metabolite pulo'upone 1 have been achieved by Evans' asymmetric Diels-Alder reaction.

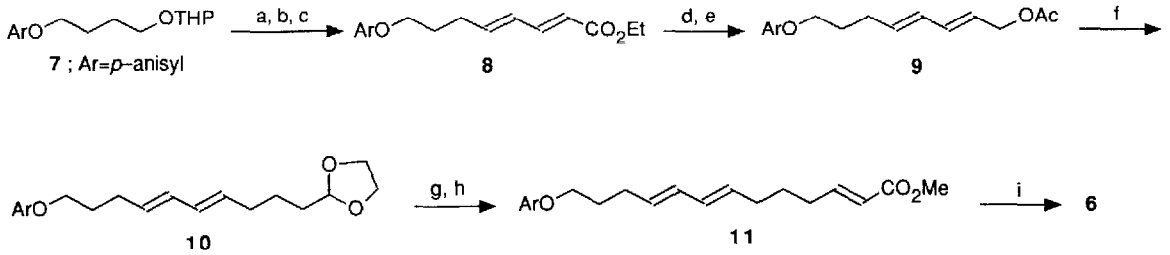
Pulo'upone **1** isolated from the Hawaiian mollusk Philinopsis speciosa is an uncommon pyridine derivative substituted at C-2 by a bicyclic $C_{16}$-polyketide and its structure was determined by spectral analysis.[1] Recently there has been confirmation of its structural assignment by a total synthesis of (±)-pulo'upone **1**.[2] We wish to report herein asymmetric total syntheses of (+)- and (-)-pulo'upone **1** which revealed the absolute stereochemistry of their structures. Our approach to both enantiomers of **1** is shown in Scheme 1. C2'-C3' bond could be formed by using a Wittig reaction and the both chiral trans-hydrindene nuclei in **2** and **3** could be prepared from the chiral trienimides **4**, **5** by Evans' asymmetric Diels-Alder reaction.[3] **4**, **5** could be introduced from the common trienoic acid **6**.




Scheme 1

The synthesis of trienoic acid **6** is summarized in Scheme 2. Removal of THP group from the p-anisyl ether **7**[4] with p-toluenesulfonic acid provided an alcohol

in 95% yield, oxidation of which with pyridinium chlorochromate[5] followed by treatment with lithio triethyl 4-phosphonocrotonate[6] gave the diene ester **8**[7] in 45% overall yield. Reduction of **8** with diisobutylaluminum hydride and subsequent acetylation with acetic anhydride provided the acetate **9** in 97% overall yield. Reaction of **9**[8] with the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxolane in the presence of a catalytic amount of $Li_2CuCl_4$ afforded the ketal **10** in 74% yield. Hydrolysis of the ketal **10** with aqueous acetic acid followed by Wadsworth-Emmons coupling with the potassium salt of methyl diisopropylphosphonoacetate afforded the triene ester **11** in 74% overall yield. Hydrolysis of **11** with aqueous sodium hydroxide gave the trienoic acid **6** in 57% yield.

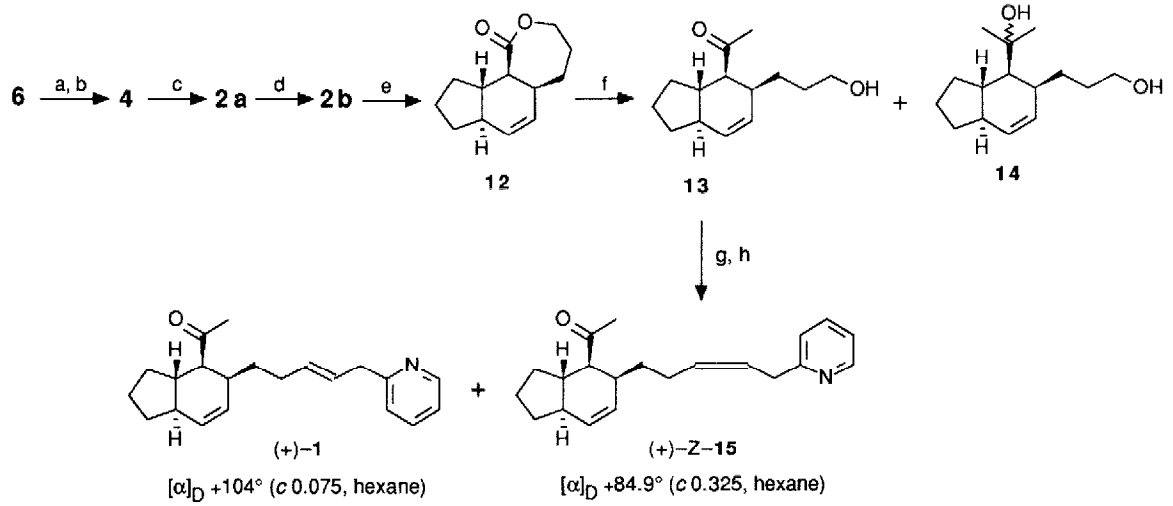



Scheme 2

**Reagents and conditions;** (a) p-TsOH, MeOH, room temp., 13 h, (b) PCC, MS3A, $CH_2Cl_2$, room temp., 15 min., (c) triethyl 4-phosphonocrotonate, LHMDS, THF, -40 °C to room temp., 12 h, (d) i-$Bu_2AlH$, $Et_2O$, -78 °C, 1h, (e) $Ac_2O$, pyridine, room temp., 14 h, (f) 2-(2-bromoethyl)-1,3-dioxolane, cat. $Li_2CuCl_4$, -30 °C, 2 h, (g) AcOH-$H_2O$-THF, 80 °C, 4 h, (h) methyl diisopropylphosphonoacetate, t-BuOK, THF, -20 °C, 5 h, (i) 10% NaOH, MeOH, THF, room temp., 10 h.

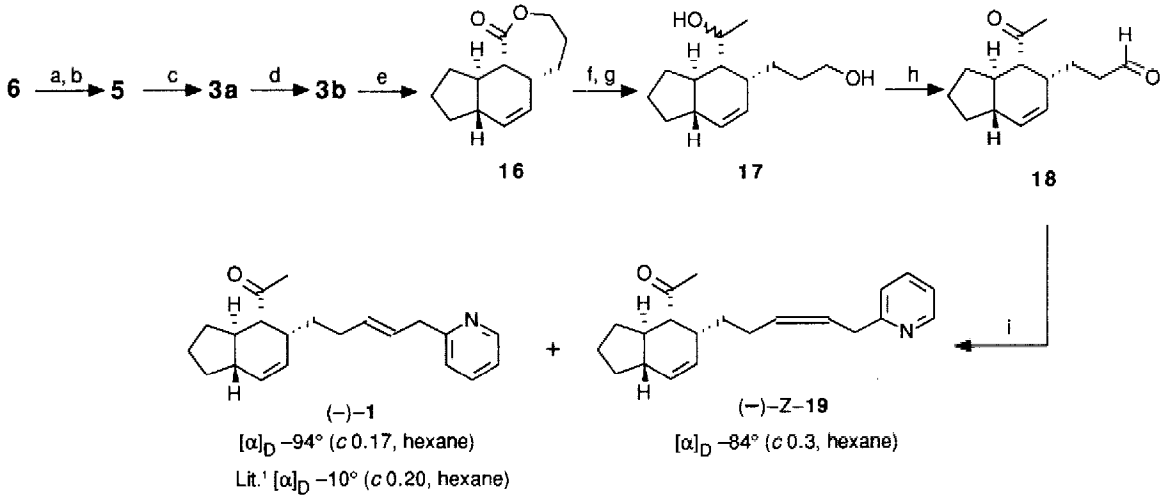
The synthesis of optical active pulo'upone **1** began with using (4S)-4-(phenylmethyl)-2-oxazolidinone[9] as a chiral auxiliary which was prepared from (S)-phenylalanine (Scheme 3). Treatment of the trienoic acid **6** with oxalylchloride provided an acid chloride, addition of which to a preformed solution of 3-lithio-(S)-(+)-2-oxazolidinone (1 equiv.) gave the trienimide **4** in 59% overall yield. Intramolecular Diels-Alder reaction of **4** with 1.3 equiv. of dimethylaluminum chloride in a dilute dichloromethane solution provided the trans-hydrindene **2a** in 52% yield. Since selective removal of the chiral auxiliary of **2a** with lithium hydroxide or potassium hydroxide was unseccessful because of its steric crowding, the p-anisyl group of **2a** was removed with ceric ammonium nitrate[4] to give the alcohol **2b** in quantitative yield, treatment of which with n-butyllithium (1 equiv.) provided the lactone **12** [$[\alpha]_D$ +182° (c, 0.96, $CHCl_3$)] in 76% yield. Addition of methyllithium (1 equiv.) to the lactone **12** gave the methyl ketone **13** in 12% yield together with the diol **14** in 31% yield (23% and 60% yields for **13** and **14** based on the recovered starting material, respectively). Oxidation of **13** with pyridinium chlorochromate[5] (95%) followed by Wittig reaction with the lithium salt of 2-(2-pyridyl)ethyltriphenylphosphonium

iodide[10] afforded, in 44% yield, a separable mixture of (+)-pulo'upone **1** and (+)-Z-isomer **15** in a ratio of 1:3.




Scheme 3

**Reagents and conditions;** (a) $(COCl)_2$, toluene, room temp., 20 h, (b) (4S)-4-(phenylmethyl)-2-oxazolidinone, n-BuLi, THF, -78 °C, 1.5 h, (c) 1.3 equiv. $Me_2AlCl$, $CH_2Cl_2$, -30 °C, 5 h, (d) CAN, $CH_3CN$-$H_2O$, 0 °C, 15 min., (e) 1 equiv. n-BuLi, THF, 0 °C, 1 h, (f) 1 equiv. MeLi, THF, -78 °C, 1 h, (g) PCC, MS3A, $CH_2Cl_2$, room temp., 15 min, (h) 1.2 equiv. 2-(2-pyridyl)ethyltriphenylphosphonium iodide, 1.15 equiv. n-BuLi, THF, 0 °C, 5 h.




Scheme 4

**Reagents and conditions;** (a) $(COCl)_2$, toluene, room temp., 20 h, (b) (4R)-4-(phenylmethyl)-2-oxazolidinone, n-BuLi, THF, -78 °C, 1.5 h, 62% (2 steps), (c) 1.3 equiv. $Me_2AlCl$, $CH_2Cl_2$, -30 °C, 5 h, 57%, (d) CAN, $CH_3CN$-$H_2O$, 0 °C, 15 min, 100%, (e) 1 equiv. n-BuLi, THF, 0 °C, 1 h, 72%, (f) 1.1 equiv. i-$Bu_2AlH$, THF, -78 °C, (g) 6 equiv. MeLi, THF-$Et_2O$, -78 °C to room temp., (h) PCC, MS3A,

$CH_2Cl_2$, room temp., 30 min, (i) 1.2 equiv. 2-(2-pyridyl)ethyltriphenylphosphonium iodide, 1.15 equiv. n-BuLi, THF, 0 °C, 5 h.

Then we investigated the synthesis of (-)-pulo'upone **1** and also attempted to improve the low yield observed in the formation of **13** (Scheme 4). Use of (4R)-4-(phenylmethyl)-2-oxazolidinone[9] was prepared from (R)-phenylalanine yielded the lactone **16** [$[\alpha]_D$ -180.3° (c 0.944, $CHCl_3$)] in the same sequence of reactions. Reduction of **16** with diisobutylaluminum hydride (1.1 equiv.) followed by treatment of the resulting lactol with methyl lithium (6 equiv.) provided the diol **17** in 70% overall yield. Oxidation of **17** with pyridinium chlorochromate[5] gave ketoaldehyde **18** in 60% yield. Finally the same Wittig reaction of **18** afforded in 45% yield a separable mixture of (-)-pulo'upone **1**[11] and (-)-Z-isomer **19** in a ratio of 1:3. Spectral properties ($^1H$ NMR, IR, UV, mass) of synthetic (+)-**1** and (-)-**1** were identical with those of natural **1** in all respects except the value of specific rotation. The absolute stereochemistry of (-)-pulo'upone was thus revealed as shown in Scheme **4**.

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References and Notes

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7. All new compounds exhibited satisfactory spectroscopic (IR, $^1H$ NMR, low and high resolution mass) data.
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10. 2-(2-pyridyl)ethyltriphenylphosphonium iodide was prepared on heating 2-(2-iodoethyl)pyridine with triphenylphosphine in $CH_3CN$ at 80 °C for 22 h.
11. The endo/exo ratios of intramolecular Diels-Alder reaction products of **4** and **5** were determined as >99:1 by silica gel chromatography and the analysis of synthetic (-)-**1** and (+)-**1** by capillary gas chromatography (0.3 mm x 20 m DB-5, 200 °C) revealed the synthetic (-)-**1** to be a 88:12 mixture of enantiomers.

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