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The first total synthesis of putaminoxin and determination of its absolute configuration

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ABSTRACT

Asymmetric synthesis of putaminoxin, a phytotoxic macrolide from the cultured dinoflagellate *Amphidinium* sp., has been accomplished. Absolute configuration of putaminoxin was concluded to be **1** from comparison of the NMR data and $[\alpha]_D$ values of synthetic and natural putaminoxin.

Putaminoxin **1**,[1] a phytotoxic lactone, was isolated from the culture of *Phoma putaminum* fungus. This fungal pathogen is responsible for a necrotic leaf disease of *Erigeron annuus* (L), a weed widely found in fields and pastures all over Europe, including Italy. Related 10-membered lactones[2] such as putaminoxin B and putaminoxin E have also been isolated from fungi with phytotoxic activity (Fig. 1). The structure of **1** was characterized using spectroscopic and chemical methods as (5*S*) 5-hydroxy-9-propyl-6-nonen-9-olide. However, the relative and absolute stereochemistry at C9 remained unresolved. Considering that the new phytotoxic lactones could be directly used as herbicides or as leads for the preparation of analogues, research was carried out to isolate and characterize the toxic macrolides produced by *P. Putaminum*.

In view of its interesting phytotoxic activity and in order to determine the absolute stereochemistry at C9 of putaminoxin, we planned an asymmetric total synthesis of **1** as shown in Scheme 1. Putaminoxin **1** could be obtained by ring-closing metathesis (RCM) of **2** through esterification of the segment **3** and the segment **4**. In this Letter, we describe the first total synthesis of putaminoxin **1** and its absolute configuration to be **1**.

We commenced the synthesis from the commercially available *n*-butyraldehyde **5,** which was subjected to an enantioselective Keck allylation[3] using (*S*)-Binol and allyl-tri-*n*-butyltin to furnish the homoallylic alcohol **4** with the known stereochemistry in 75% yield with excellent enantioselectivity of 95% ee (determined by chiral HPLC) (Scheme 2).

The synthesis of the other fragment began with the epoxy alcohol **6** prepared as reported by us earlier.[4] The alcohol **6** was converted to the corresponding epoxy iodide in 78% yield by treating with triphenylphosphine, iodine, and imidazole in a mixture of dry ether and acetonitrile. The compound was converted into a secondary allylic alcohol **8** in 85% yield by refluxing with activated zinc in dry ethanol. After protecting the secondary hydroxyl group as its 4-methoxybenzyl ether using sodium hydride and 4-methoxybenzyl bromide, the compound **9** was subjected to deprotection of the tetrahydropyran to give alcohol **10**. The alcohol **10** was oxidized to aldehyde by using 2-iodoxybenzoic acid followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **3** in 80% yield (Scheme 3).

Next the union of the two fragments **3** and **4** was achieved by using *N*,*N*′-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in dichloromethane to furnish the diene ester **2**. Treatment of **2** with the Grubbs' first generation catalyst (20% mol) under high dilution furnished a 9:1 *E*:*Z* mixture of macrocyclic lactones, from which the (*E*)-isomer **11** was isolated in 60% yield by silica gel column chromatography. Oxidative removal of 4-methoxybenzyl ether in compound **11** gave the target molecule **1** (Scheme 4).

The prepared synthetic putaminoxin is identical (IR, ^1H and ^{13}C NMR) with the natural product and also has an optical rotation $[\alpha]_D^{25}$ −25.2 (*c* 1, $CHCl_3$) which is in good agreement with the literature value [lit.[1] $[\alpha]_D^{25}$ −23.1 (*c* 1.6, $CHCl_3$)]. Thus, the absolute stereochemistry of putaminoxin **1** was established as 5*S* and 9*R*.

In summary, this Letter describes the first total synthesis of (5*S*,9*R*)-(−)-putaminoxin and its absolute configuration has been fixed.

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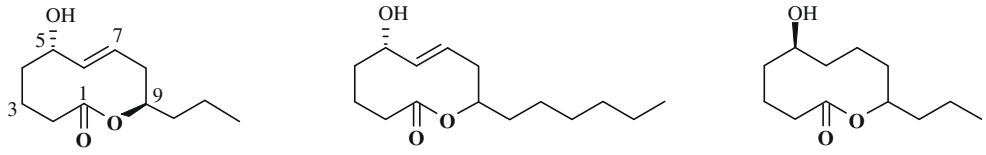
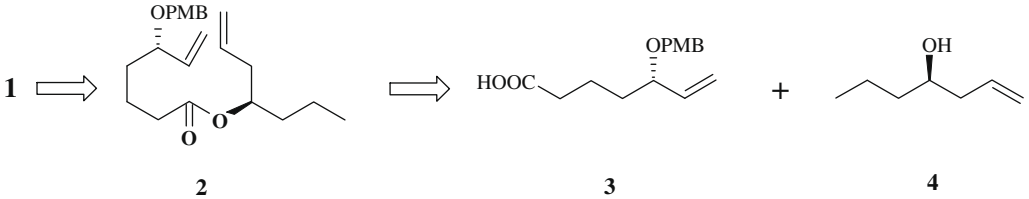
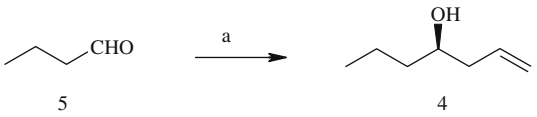


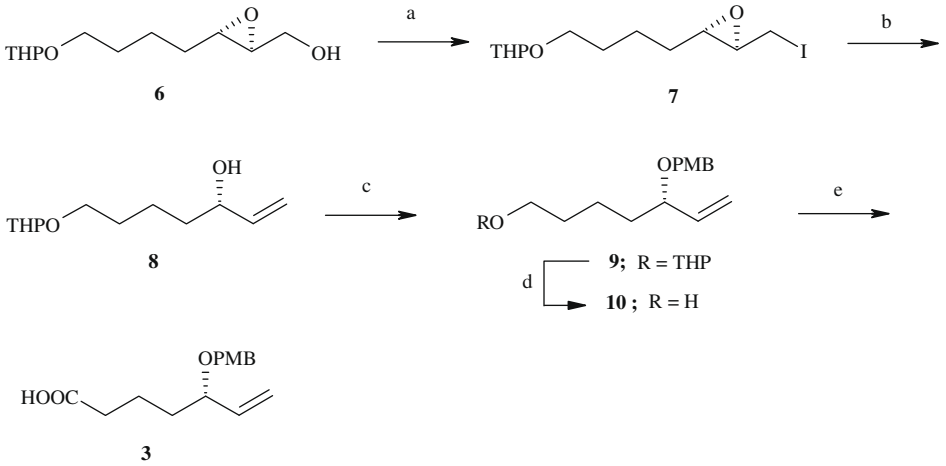
Figure 1.



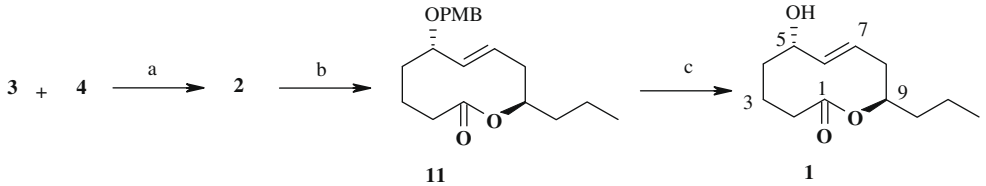
Scheme 1. Retrosynthesis



Scheme 2. Reagents and conditions: (a) $SnBu_3$, $Ti(O^iPr)_4$, (*S*)-binol, dry DCM, −78 to −20 °C, 72 h, 75%, 95% ee.



Scheme 3. Reagents and conditions: (a) imidazole, TPP, iodine, ether/acetonitrile (3:1), 0 °C to rt, 2 h, 78%; (b) Zn, dry ethanol, reflux, 4 h, 85%; (c) NaH, PMBBr, dry THF, 0 °C to rt, 4 h, 86%; (d) PPTS, MeOH, 0 °C to rt, 6 h, 72%; (e) (i) IBX, dry DMSO, dry DCM, rt, 2 h; (ii) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 0 °C to rt, 1 h, 80%.



Scheme 4. Reagents and conditions: (a) DCC, DMAP, DCM, 0 °C to rt, 18 h, 73%; (b) $(PCy_3)_2RuCH{=}Ph$ (20 mol %), DCM, reflux, 28 h, 60%; (c) DDQ, H_2O/DCM (1:9), 0 °C to rt, 1 h, 80%.

Acknowledgment

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References and notes

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2. Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Zonno, M. C. *Nat. Toxins* **1998**, *6*, 183–188.
3. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
4. Sabitha, G.; Reddy, E.V.; Giri, K.Y. and Yadav, J. S. *Synthesis* **2006**, *19*, 3270–3274.Spectral data**:** *(4R)-1-hepten-4-ol* (**4**): IR (neat); 3438, 2940, 2866, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.80 (m, 1H), 5.11 (td, 2H, J = 1.5, 3.1, 13.5 Hz), 3.61 (m, 1H), 2.26 (m, 1H), 2.11 (m, 1H), 1.43 (m, 4H), 0.94 (t, 3H, J = 7.5 Hz).
(5S)-5-[(4-Methoxybenzyl)oxy]-6-heptenoic acid (**3**): $[\alpha]_D^{25}$ +25.2 (c 1, $CHCl_3$); IR (neat): 3412, 2930, 1709, 1609, 1513, 1249, 1172, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, 2H, J = 8.7 Hz), 6.81(d, 2H, J = 8.7 Hz), 5.70 (m, 1H), 5.22 (d, 1H, J = 2.9 Hz), 5.19 (d, 1H, J = 10.2 Hz), 4.49 (d, 1H, J = 11.7 Hz), 4.23 (d, 1H, J = 11.7 Hz), 3.78 (s, 3H), 3.68 (q, 1H, J = 12.4, 6.5 Hz), 2.30 (dt, 2H, J = 1.4, 7.3, 8.7 Hz), 1.74–1.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.37, 159.09, 138.58, 129.64, 129.4, 117.26, 113.68, 79.66, 69.76, 55.17, 33.47, 33.89, 20.65; ESIMS: 265 (M^++1).
(1R)-1-Propyl-3-butenyl (5S)-5-[(4-methoxybenzyl)oxy]-6-heptenoate (**2**): $[\alpha]_D^{25}$ +4.5 (c 1, $CHCl_3$); IR (neat): 2925, 2854, 1732, 1610, 1512, 1247, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, J = 8.6 Hz), 6.81(d, 2H, J = 8.6 Hz), 5.68 (m, 2H), 5.19 (m, 2H), 5.03 (m, 2H), 4.89 (p, 1H, J = 5.8, 12.4, 18.6 Hz), 4.49 (d, 1H, J = 11.5 Hz), 4.23 (d 1H, J = 11.5 Hz), 3.79 (s, 3H), 3.67 (q, 1H, J = 6.4, 13.3 Hz), 2.25 (m, 2H), 1.64–1.23 (m, 10H), 0.91 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.33, 159.11, 138.75, 133.71, 130.71, 129.27, 177.55, 117.19, 113.75, 79.72, 73.04, 69.66, 55.21, 38.69, 34.87, 34.32, 33.54, 31.59, 24.94, 22.49, 21.04, 13.92; ESIMS: 283 (M^++Na).
(5S,9R)-(−)-Putaminoxin (**1**): $[\alpha]_D^{25}$ − 25.2 (c 1, $CHCl_3$); IR (neat): 3432, 2959, 2930, 2871, 1729, 1670, 1443, 1364, 1180, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.55 (ddd, 1H, J = 4.9, 10.5, 15.2 Hz), 5.32 (dd, 1H, J = 9.2, 15.2 Hz), 5.03 (m, 1H), 4.01 (dt,1H, J = 3.9, 7.9, 14.9), 2.44 (ddd, 1H, J = 3.9, 7.9, 14.9 Hz), 2.36 (dt, 1H, J = 3.9, 4.9, 12.4 Hz), 2.06–1.97 (m, 2H), 1.95–1.87 (m, 4H), 1.64–1.24 (m, 4H), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.63, 137.14, 131.66, 75.34, 74.13, 40.36, 38.72, 36.42, 35.69, 22.29, 19.14, 13.86. ESIMS: 235 (M^++Na).