

ABSOLUTE CONFIGURATION OF (+)-PT-TOXIN: ENANTIODIVERGENT SYNTHESIS OF (+)- AND (-)-PT-TOXINS†

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Abstract — Absolute configuration of (+)-PT-toxin, isolated from the tea gray blight fungi, *Pestalotiopsis longiseta* and *Pestalotiopsis theae*, has been determined unambiguously by enantiocontrolled synthesis of both enantiomers starting from the common chiral-building block.

(+)-PT-toxin (**1**)^{1,2} is a phytotoxin isolated from the tea gray blight fungi, *Pestalotiopsis theae*. Its relative structure was determined based on the ¹H and ¹³C-NMR data by comparison with those of (+)-epiepoxydon (**2**) having the same oxygenated cyclohexenone chromophore. Its absolute configuration was also proposed based on the direction of the optical rotations of (+)-epiepoxydon (**2**) whose absolute configuration was confirmed unambiguously by us³ in 1996 (**Figure 1**). In relation to our recent synthesis⁴ of an antimitotic natural product, (-)-tricholomenyn A (**3**),⁵ having an extra prenyl group on the side chain of the *O*-acetyl form of PT-toxin (**1**) with the enantiomeric cyclohexene configuration, we investigated the enantiocontrolled synthesis of PT-toxin (**1**) using the same starting material (**4**)⁶ so as to determine the absolute configuration.

Employing the same procedure for the synthesis⁴ of (-)-tricholomenyn A (**3**), the (+)-monoacetate (**4**)⁶ was converted into the epoxyiodocyclohexenone [(**-**)-**8**]⁷ in 56% overall yield in a six-step reaction sequence. Thus, (+)-**4** was first transformed into the enone [(**+**)-**5**] by sequential silylation, methanolysis and oxidation. On treatment with alkaline aqueous hydrogen peroxide, (+)-**5**³ yielded stereoselectively the *exo*-epoxide [(**+**)-**6**]³ as a single product. Thermolysis of (+)-**6** in diphenyl ether at reflux temperature (260 °C) occurred without difficulty to give the monocyclic epoxide [(**-**)-**7**]³ with the epoxy functionality intact.

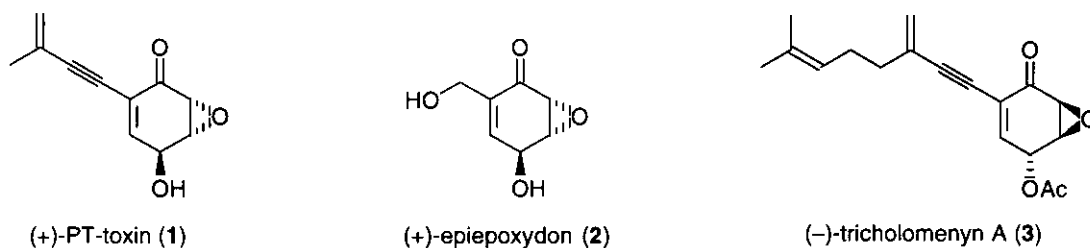
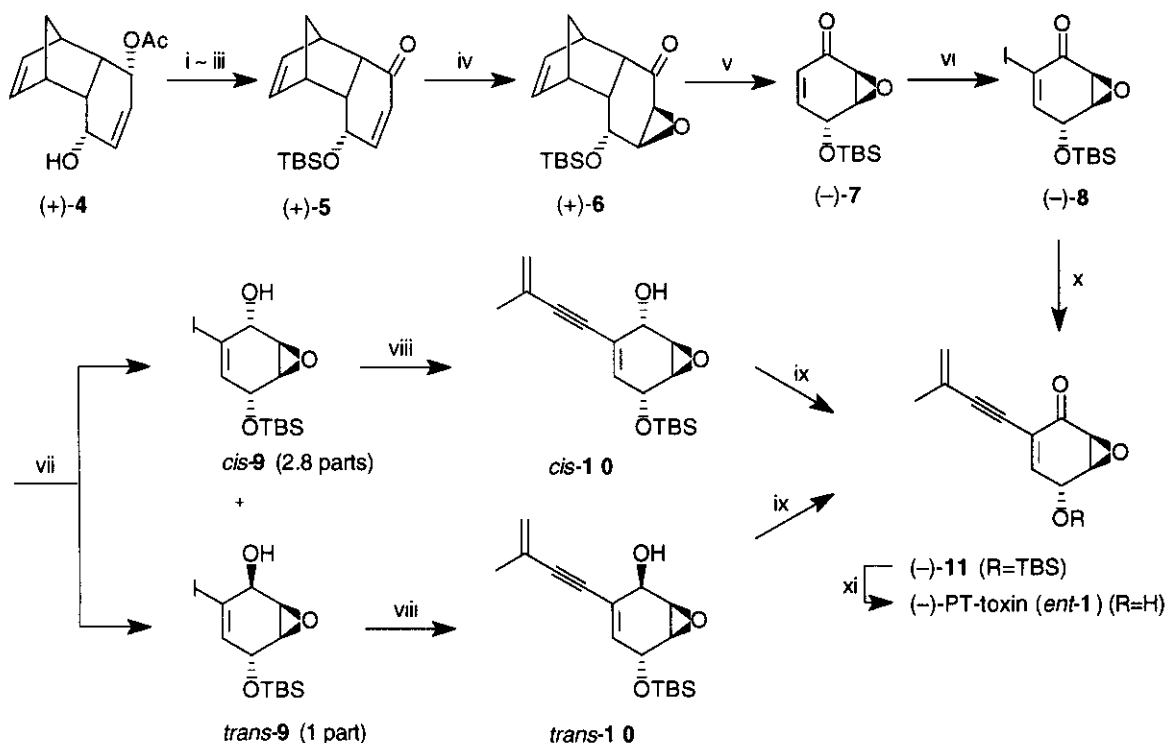


Figure 1

† Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Exposure of (-)-7 to iodine in dichloromethane in the presence of pyridine^{4,8} allowed a facile olefin halogenation to give the α -iodoenone [(-)-8], $[\alpha]_D^{29} -109.7^\circ$ (*c* 1.3, CHCl_3), without affecting the epoxy functionality.

Disappointingly, the palladium-mediated cross-coupling reaction^{4,9} between the α -iodoenone [(-)-8] and 2-methyl-1-buten-3-yne failed to give the expected product (11). However, we found that the coupling took place in an excellent manner when the α -iodoallyl alcohol (9) in place of the α -iodoenone (8) was used under the same conditions.⁴ Namely, both the major *cis*-allyl alcohol (*cis*-9),¹⁰ $[\alpha]_D^{29} +8.9^\circ$ (*c* 1.0, CHCl_3), and the minor *trans*-allyl alcohol (*trans*-9),¹⁰ $[\alpha]_D^{29} -14.8^\circ$ (*c* 0.3, CHCl_3), obtained in a ratio of 2.8:1 in 96% yield by sodium borohydride-cerium(III) chloride,¹¹ furnished the corresponding coupling products *cis*-10, $[\alpha]_D^{28} -19.0^\circ$ (*c* 0.6, CHCl_3), and *trans*-10, $[\alpha]_D^{29} -22.9^\circ$ (*c* 0.4, CHCl_3), in quantitative yields, which gave the same ketone [(-)-11], $[\alpha]_D^{29} -195.7^\circ$ (*c* 0.5, CHCl_3), in excellent yields on oxidation with the Dess-Martin periodinate reagent.¹² We also found that the direct cross-coupling of the iodoenone [(-)-8] took place in 82% yield when 4-tributylstannyl-2-methyl-1-buten-3-yne^{9d} was used in place of the terminal acetylene. Finally, exposure of the silyl ether [(-)-11] to hydrogen fluoride in acetonitrile¹³ afforded the secondary alcohol (*ent*-1), mp $78-79^\circ\text{C}$, $[\alpha]_D^{29} -200.3^\circ$ (*c* 0.4, CHCl_3); $[\alpha]_D^{29}$

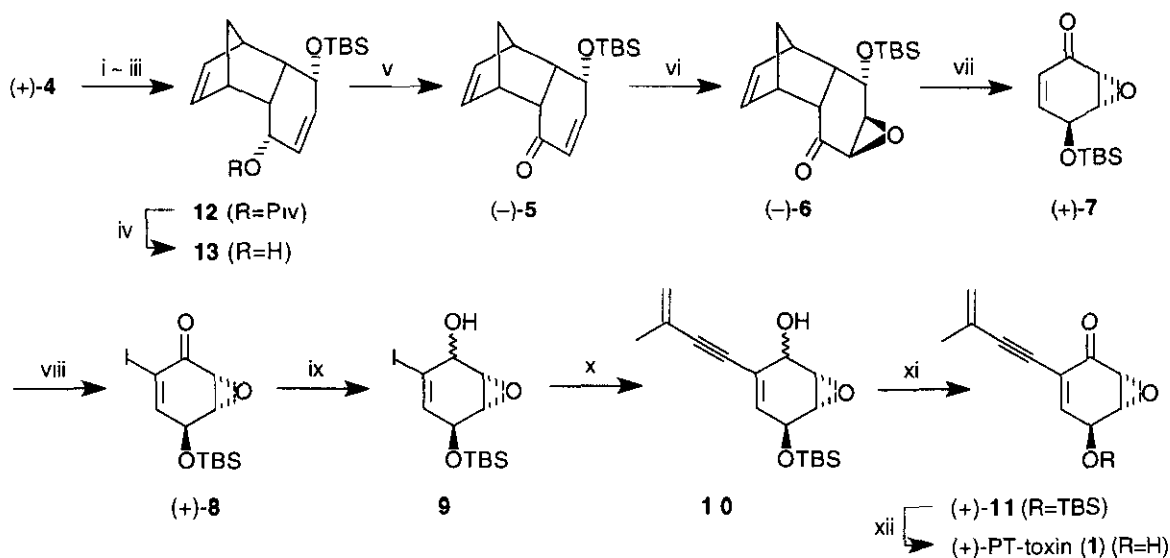


Scheme 1

Reagents and conditions: i, TBSCl, imidazole, DMF (88%); ii, K_2CO_3 , MeOH; iii, PDC, CH_2Cl_2 (87%, 2 steps); iv, 30% H_2O_2 , Triton B, THF, 0°C (89%); v, PhPh, reflux (93%); vi, I_2 , Py- CH_2Cl_2 (1:5 v/v), 0°C (89%); vii, NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, 0°C (96%); viii, $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), CuI (5 mol%), 2-methyl-1-buten-3-yne, Et_3N (98%); ix, Dess-Martin oxidation, CH_2Cl_2 (86%); x, $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), CuI (10 mol%), 4-tributylstannyl-2-methyl-1-buten-3-yne, *N*-methyl-2-pyrrolidone; xi, 46% HF-MeCN (1:19 v/v) (87%).

$-156 \pm 22^\circ$ (c 0.4, MeOH)¹⁴ [natural: $[\alpha]_D +147^\circ$ (c 0.82, MeOH)], which possessed the same spectroscopic data¹⁵ with those of natural (+)-PT-toxin (**1**) except the direction of optical rotations. Thus, the product was found to be the unnatural enantiomeric (–)-PT-toxin (*ent*-**1**). These findings led us to conclude that the absolute configuration proposed for the natural (+)-PT-toxin (**1**) is correct and that it has the opposite cyclohexene core stereochemistry to that of natural (–)-tricholomenyn A (**3**)⁴ isolated from the Italian mushroom⁵ (Scheme 1).

To obtain natural (+)-PT-toxin (**1**), the same starting material [(+)-**4**] was first transformed into the pivalate (**12**)^{6a} in 89% overall yield in three steps by sequential pivaloylation, deacetylation and silylation. On reductive removal of the pivaloyl group followed by oxidation with pyridinium dichromate (PDC), **12** afforded the (–)-enone [(–)-**5**] in 95% yield, *via* the secondary alcohol (**13**), which was found to be the enantiomer of the above (+)-enone [(+)-**5**]. Employing the same procedure for the synthesis of the unnatural enantiomer *ent*-**1**, (–)-**5** was transformed into the α -iodoenone [(+)-**8**], $[\alpha]_D^{28} +106.3^\circ$ (c 1.4, CHCl₃), *via* the tricyclic epoxide [(–)-**6**] and the cyclohexene epoxide [(+)-**7**] in a comparable 62% overall yield. Reduction of (+)-**8** with sodium borohydride-cerium(III) chloride¹¹ gave a 2.8:1 mixture of the allyl alcohols (**9**) which, without separation, was coupled with 2-methyl-1-buten-3-yne in the presence of the palladium catalyst^{4,9} to afford the enynol (**10**) in excellent yield as a mixture of two epimers. Oxidation of the mixture with the Dess-Martin periodinate¹² gave the single enone (**11**), $[\alpha]_D^{28} +195.7^\circ$ (c 1.3, CHCl₃), which, on desilylation,¹³ afforded natural (+)-PT-toxin (**1**),^{1,15} mp 78–79 °C, $[\alpha]_D^{29} +200.3^\circ$ (c 0.9, CHCl₃),¹⁴ in excellent yield. Thus, the proposed structure of (+)-PT-toxin (**1**) has been confirmed and the first enantiocontrolled synthesis of the natural product has been achieved (Scheme 2).



Scheme 2

Reagents and conditions: i, pivalic anhydride, Et₃N, DMAP (cat.), CH₂Cl₂; ii, K₂CO₃, MeOH (89%, 2 steps); iii, TBSCl, imidazole, DMF (~100%); iv, MeLi, THF, –12 °C; v, PDC, CH₂Cl₂ (95%, 2 steps); vi, 30% H₂O₂, Triton B, THF, 0 °C (80.5%); vii, PhOPh, reflux (78%); viii, I₂, Py-CH₂Cl₂ (1:5 v/v), 0 °C (99%); ix, NaBH₄, CeCl₃·7H₂O, 0 °C (97%); x, PdCl₂(PPh₃)₂ (5 mol%), CuI (5 mol%), 2-methyl-1-buten-3-yne, Et₃N (97%); xi, Dess-Martin oxidation, CH₂Cl₂ (82%); xii, 46% HF-MeCN (1:19 v/v) (92%).

ACKNOWLEDGEMENTS

We are grateful to the Japan Society for the Promotion of Science for Japanese Junior Scientists for a fellowship (to T. K.).

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Received, 4th February, 1997