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

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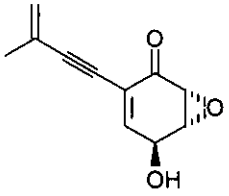
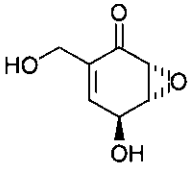
Abstract —— Absolute configuration of (+)-PT-toxin, isolated from the tea gray blight fungi, *Pestalotiopsis longiseta* and *Pestalotiopsis theae*, has been determined unambiguously by enantiocontrolled synthesis of both enantiomers starting from the common chiral-building block.

(+)-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 ^{1}H and ^{13}C-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 us[3] in 1996 (**Figure 1**). In relation to our recent synthesis[4] 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.

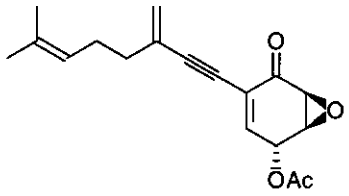
Employing the same procedure for the synthesis[4] of (–)-tricholomenyn A (**3**), the (+)-monoacetate (**4**)[6] was converted into the epoxyiodocyclohexenone [(–)-**8**][7] in 56% overall yield in a six-step reaction sequence. Thus, (+)-**4** was first transformed into the enone [(+)-**5**] by sequential 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.



(+)-PT-toxin (**1**)



(+)-epiepoxydon (**2**)



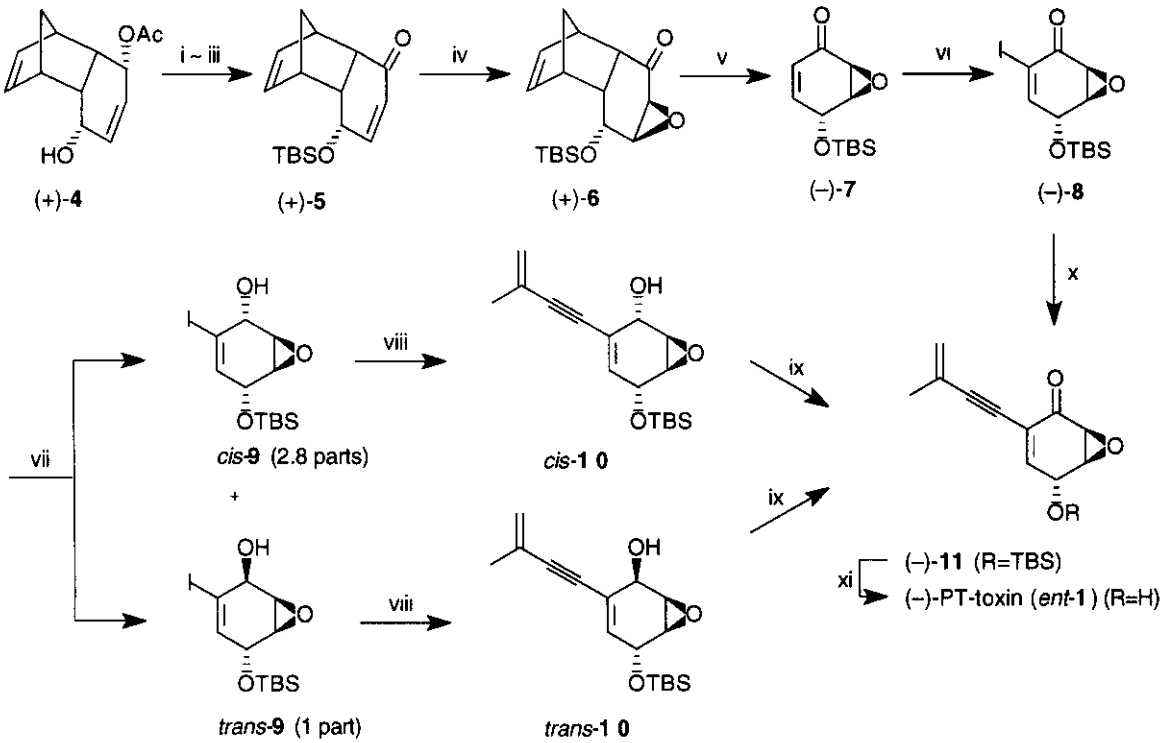
(–)-tricholomenyn A (**3**)

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° (*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° (*c* 1.0, $CHCl_3$), and the minor *trans*-allyl alcohol (*trans*-**9**),[10] $[\alpha]_D^{29}$ –14.8° (*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° (*c* 0.6, $CHCl_3$), and *trans*-**10**, $[\alpha]_D^{29}$ –22.9° (*c* 0.4, $CHCl_3$), in quantitative yields, which gave the same ketone [(–)-**11**], $[\alpha]_D^{29}$ –195.7° (*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 acetonitrile[13] afforded the secondary alcohol (*ent*-**1**), mp 78-79 °C, $[\alpha]_D^{29}$ –200.3° (*c* 0.4, $CHCl_3$); $[\alpha]_D^{29}$

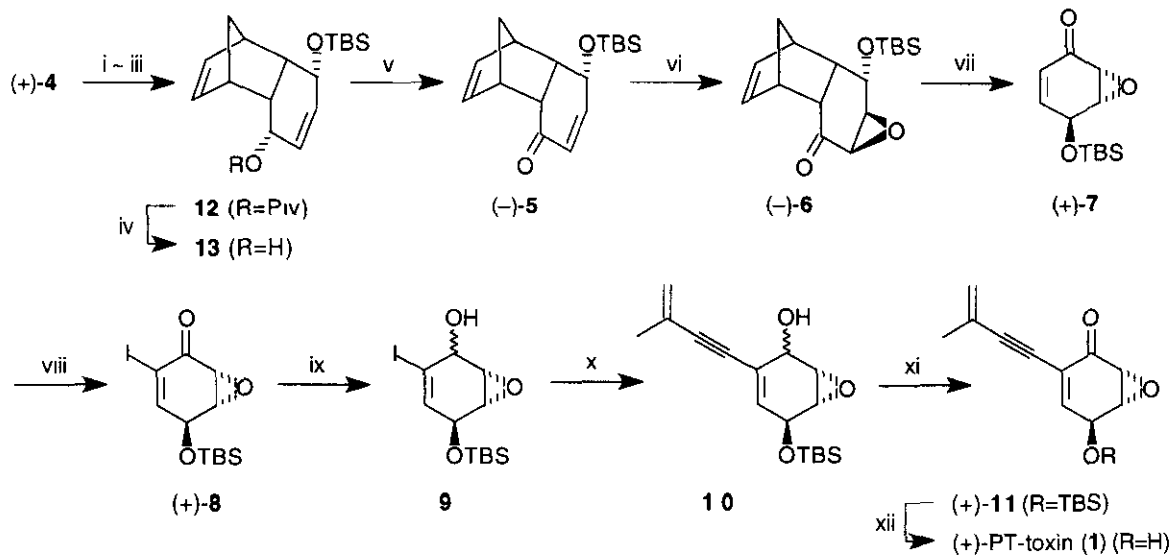


Scheme 1

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, PhOPh, reflux (93%); vi, I_2, Py-CH_2Cl_2 (1:5 v/v), 0 °C (89%); vii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0 °C (96%); viii, $PdCl_2(PPh_3)_2$ (5 mol%); CuI (5 mol%), 2-methyl-1-buten-3-yne, Et_3N (98%); ix, Dess-Martin oxidation, CH_2Cl_2 (86%); x, $PdCl_2(PPh_3)_2$ (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%).

$-156\pm22°$ (*c* 0.4, MeOH)[14] [natural: $[\alpha]_D$ +147° (*c* 0.82, MeOH)], which possessed the same spectroscopic data[15] 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 mushroom[5] (**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**][3] 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° (*c* 1.4, $CHCl_3$), *via* the tricyclic epoxide [(–)-**6**] and the cyclohexene epoxide [(+)-**7**] in a comparable 62% overall yield. Reduction of (+)-**8** with sodium borohydride-cerium(III) chloride[11] 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 periodinate[12] gave the single enone (**11**), $[\alpha]_D^{28}$ +195.7° (*c* 1.3, $CHCl_3$), which, on desilylation,[13] afforded natural (+)-PT-toxin (**1**),[1,15] mp 78-79 °C, $[\alpha]_D^{29}$ +200.3° (*c* 0.9, $CHCl_3$),[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, Et_3N, DMAP (cat.), CH_2Cl_2; ii, K_2CO_3, MeOH (89%, 2 steps); iii, TBSCl, imidazole, DMF (~100%); iv, MeLi, THF, –12 °C; v, PDC, CH_2Cl_2 (95%, 2 steps); vi, 30% H_2O_2, Triton B, THF, 0 °C (80.5%); vii, PhOPh, reflux (78%); viii, I_2, Py-CH_2Cl_2 (1:5 v/v), 0 °C (99%); ix, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0 °C (97%); x, $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), 2-methyl-1-buten-3-yne, Et_3N (97%); xi, Dess-Martin oxidation, CH_2Cl_2 (82%); xii, 46% HF-MeCN (1:19 v/v) (92%).

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