The enantiocontrolled synthesis of (−)-tricholomenyn A, a novel antimitotic enynylcyclohexenone from *Tricholoma acerbum*

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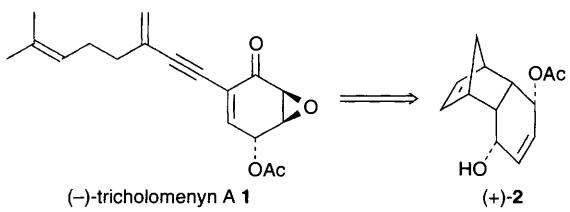
(−)-Tricholomenyn A, a structurally novel antimitotic enynylcyclohexenone from *Tricholoma acerbum*, is synthesized in an enantiocontrolled manner from a chiral synthon of *cis*-1,4-dihydroxycyclohexa-2,5-diene and verifies the relative and the absolute structures of the natural product.

(−)-Tricholomenyn A **1** is isolated from the fruiting bodies of the mushroom *Tricholoma acerbum* as a mitotic inhibitor.[1] Its relative structure, having an enyne side chain on the polyoxygenated cyclohexene framework, was determined mostly by NMR spectroscopy and its absolute configuration was tentatively assigned by correlation of its CD spectrum to those of simpler natural products possessing the same epoxycyclohexenone chromophore.[2] Since we have been interested in utilizing the tricyclic monoacetate **2**, accessible in optically pure forms by enzymatic asymmetrization of the *meso*-enediol precursor,[3] as chiral synthon of 1,4-dihydroxycyclohexa-2,5-diene,[4] we chose (−)-tricholomenyn A **1** as an appropriate target molecule for the demonstration of the potential of the chiral synthon as well as for the determination of the configuration of this physiologically and structurally interesting natural product. Here we report the successful conversion of the synthon **2** into (−)-tricholomenyn A **1** which verified the proposed relative and absolute structures (Scheme 1).

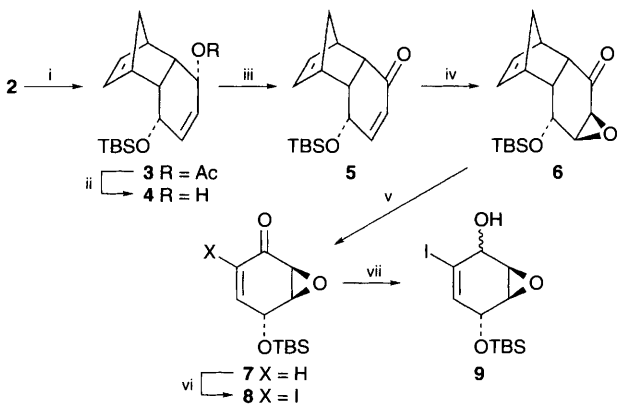
Employing the established procedure,[5] (−)-acetate‡,[3] **2** was first transformed to the tricyclic dienone **5** in 77% overall yield *via* the siloxy acetate **3** and the siloxy alcohol **4**. Treatment of **5** with 30% hydrogen peroxide in the presence of Triton B gave stereoselectively the single *exo*-epoxide **6**, mp 66–67 °C, $[\alpha]_D^{28}$ +56.2 (*c* 1.19, $CHCl_3$), in 89% yield. The epoxide **6** was then heated in boiling diphenyl ether (*ca.* 260 °C) to give rise to the epoxycyclohexenone **7**,§ $[\alpha]_D^{28}$ −333.3 (*c* 1.32, $CHCl_3$), having three stereogenic centres required for the target molecule in 92.5% yield after 30 min by a retro-Diels–Alder reaction. The product was exposed to iodine in the presence of pyridine[6] to furnish the α-iodoenone **8**, $[\alpha]_D^{29}$ −109.7 (*c* 1.29, $CHCl_3$). The epoxy functionality was found to be stable under these thermolysis and halogenation conditions. Since the ketone functionality was turned out to inhibit the palladium-mediated cross-coupling reaction (see below), **8** was reduced with sodium borohydride–cerium(III) chloride[7] to give the allyl alcohol **9** as an inseparable mixture (Scheme 2).

On the other hand, 6-methylhept-5-en-2-one was first transformed to the enol triflate **10** on treatment with *N*-phenyltrifluoromethanesulfonimide in the presence of lithium diisopropylamide (LDA).[8] Reaction of **10** with trimethylsilylacetylene in the presence of dichlorobis(triphenylphosphine)palladium(II) $[PdCl_2(PPh_3)_2]$[9] afforded the conjugated enyne **11** whose trimethylsilyl group was then replaced by tributylstannyl group to give **13** *via* the terminal acetylene **12** by sequential desilylation[10] and stannylation[11] (Scheme 3).

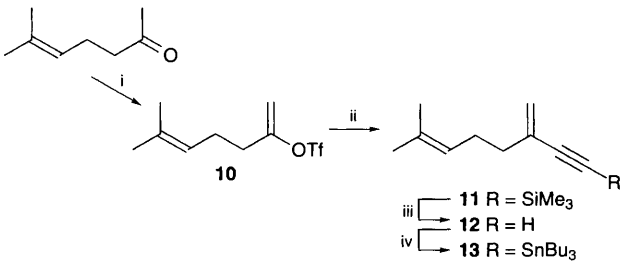
Having obtained the requisite segments, we first examined the coupling of the iodoenone **8** with stannane **13** in the presence of $PdCl_2(PPh_3)_2$.[12,13] The expected reaction did occur in the presence of the palladium catalyst (5 mol%) and copper(I) iodide in *N*-methylpyrrolidine at room temperature to give the coupling product **14**. But, the yield did not exceed 40% owing to facile aromatization of the coupling product under the conditions. The reaction did not proceed at all when the terminal acetylene **12** in place of the stannane **13** was used.[13] However, it was found that the reaction proceeded neatly with minimum aromatization to give the coupling product when the iodo alcohol **9** and the terminal acetylene **12** were used as the substrates. Thus, stirring **9** and **12** in triethylamine in the presence of copper(I) iodide and $PdCl_2(PPh_3)$ (6 mol%) at room temperature furnished the coupling product **17** in 98% yield as a mixture of epimers. Without separation the mixture was



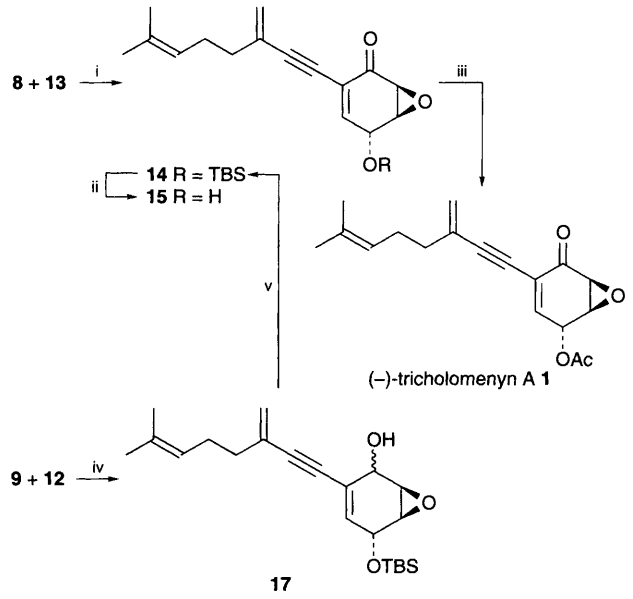
Scheme 1



Scheme 2 *Reagents and conditions*: i, Bu^tMe_2SiCl, imidazole, DMF (88%); ii, K_2CO_3, MeOH; iii, PDC, CH_2Cl_2 (87% from **3**); 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 (100%)



Scheme 3 *Reagents and conditions*: i, LDA, THF, −78 °C, then, Tf_2NPh, −78 to −10 °C; ii, trimethylsilyl acetylene, $PdCl_2(PPh_3)_2$ (3 mol%), CuI (3 mol%), Et_3N; iii, K_2CO_3, MeOH; iv, BuLi, HMPA, Bu_3SnCl, THF, −78 °C



Scheme 4 *Reagents and conditions*: i, $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), *N*-methylpyrrolidone (39%); ii, 46% HF–MeCN (1 : 19 *v/v*) (86%); iii, Ac_2O, py–CH_2Cl_2 (1 : 5 *v/v*), 0 °C (59%); iv, $PdCl_2(PPh_3)_2$ (6 mol%), CuI (8 mol%), Et_3N (98%); v, Dess–Martin oxidation, CH_2Cl_2, room temp., (90%)

oxidized with the Dess–Martin periodinate[14] to give the single enone **14**, $[\alpha]_D^{29}$ −129.6 (*c* 1.17, CH_2Cl_2), in 90% yield which was identical with that obtained by the reaction between **8** and **13**.

Conversion of **14** into the target molecule was accomplished without difficulty in 51% overall yield by sequential desilylation and acetylation. Thus, on exposure to hydrofluoric acid in acetonitrile,[15] **14** afforded the secondary alcohol **15**, $[\alpha]_D^{27}$ −130.5 (*c* 0.64, CH_2Cl_2), which was acetylated with acetic anhydride in the presence of pyridine¶ to give (−)-tricholomenyn A **1**, $[\alpha]_D^{29}$ −235.7 (*c* 1.47, CH_2Cl_2)‖ {natural[1]: $[\alpha]_D^{20}$ −148.1 (*c* 0.35, CH_2Cl_2)}. Overall yield of the natural product **1** from the chiral *cis*-1,4-dihydroxyhexa-2,5-diene synthon **2** was 25% in 11 steps. Since the direction of the optical rotations and spectroscopic data are identical with those reported for natural (−)-tricholomenyn A[1] **1**, the proposed structure deduced spectroscopically has been verified at this point and at the same time the first enantiocontrolled synthesis of the natural product has been accomplished (Scheme 4).

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Footnotes

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‡ Optically pure material (>99% ee by HPLC) was used.

§ Spectral (IR, ^1H NMR, MS) and analytical (combustion and/or high resolution MS) data were obtained for all new isolable compounds.

¶ When triethylamine was used in place of pyridine aromatization occurred.

‖ Optical purity was determined by HPLC (>99% ee, CHIRALCELOD, Pr^iOH–hexane, 1 : 20).

References

1 L. Garlaschelli, E. Magistrali, G. Vidari and O. Zuffardi, *Tetrahedron Lett.*, 1995, **36**, 5633.
2 J. Sekiguchi and G. M. Gaucher, *Biochem. J.*, 1979, **182**, 445; T. Kamikubo, K. Hiroya and K. Ogasawara, *Tetrahedron Lett.*, 1996, **37**, 499.
3 S. Takano, Y. Higashi, T. Kamikubo, M. Moriya and K. Ogasawara, *Synthesis*, 1993, 948.
4 K. Ogasawara, *Pure Appl. Chem.*, 1994, **66**, 2119.
5 T. Kamikubo and K. Ogasawara, *Tetrahedron Lett.*, 1995, **36**, 1685.
6 C. R. Johnson, P. A. Adams, M. P. Braun, C. B. W. Senanayake, P. M. Wovkulich and M. R. Uskokovic, *Tetrahedron Lett.*, 1992, **33**, 917.
7 A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
8 J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.
9 W. J. Scott, M. R. Pena, K. Sward, S. J. Stoessel and J. K. Stille, *J. Org. Chem.*, 1985, **50**, 2302; E. J. Corey, M.-C. Kang, M. C. Desai, A. K. Ghosh and I. N. Houpis, *J. Am. Chem. Soc.*, 1988, **110**, 649.
10 P. A. Wender, J. A. McKinney and C. Mukai, *J. Am. Chem. Soc.*, 1990, **112**, 5369; J. Suffert, *Tetrahedron Lett.*, 1990, **31**, 7437.
11 J. C. Bottavo, R. N. Hanson and D. E. Seitz, *J. Org. Chem.*, 1981, **46**, 5221.
12 J. K. Stille and J. H. Simpson, *J. Am. Chem. Soc.*, 1987, **109**, 2138.
13 K. Sonogashira, Y. Toda and N. Hagiwara, *Tetrahedron Lett.*, 1975, 4467; C. R. Johnson, J. P. Adams, M. P. Braun and C. B. W. Senanayake, *Tetrahedron Lett.*, 1992, **33**, 919.
14 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155; *J. Am. Chem. Soc.*, 1991, **113**, 7277.
15 R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly and S. M. Roberts, *Tetrahedron Lett.*, 1979, 3981.

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