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Total Synthesis and Structural Revision of (±)-Tricholomalides A and B

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Abstract

The neurotrophic diterpenoids, tricholomalides A (**1**) and B (**2**), were synthesized in a concise fashion. Key transformations include a ketene [2+2] cycloaddition and a Grignard-type reaction. In the course of the synthesis, it was determined that the structures of tricholomalides A and B had originally been mis-assigned.

A focus of our laboratory is on the total synthesis and evaluation of small molecule natural products possessing neurotrophic activity.¹ Such compounds may serve as promising lead agents in the treatment of neurodegenerative disease, the progression of which is marked by diminishing levels of neuronal support.² In this context, we took note of a report by Ohta et. al. of a class of neurotrophically active diterpenes, termed the tricholomalides. Isolated from the mushroom *tricholoma* sp., tricholomalides A-C were found to induce neurite outgrowth in rat pheochromocytoma cells at micromolar levels.³ The promising neurotrophic activity and complexity of the target structures prompted us to undertake the syntheses of tricholomalides A and B. As shown below, in the course of our total synthesis effort, we found that the structures of tricholomalides A (**1'**) and B (**2'**) had been mis-assigned. Our revised assignments are shown in formulas **1** and **2** (Scheme 1). We describe below the total syntheses of tricholomalides A (**1**) and B (**2**) using chemistry recently developed in our laboratory.

Our synthetic strategy, outlined in Scheme 2, centered around a homo-Robinson annulation to construct the hydroazulene core (**4**→**5**). We envisioned installing the lactone moiety of **6**

through a sequence initiated by [2+2] dichloroketene cycloaddition. Finally, Grignard-type reaction of **6**, or a suitable derivative thereof, would provide tricholomalide B, and subsequent Michael reaction was expected to furnish tricholomalide A.

As described previously,⁴ the synthesis of **10** was accomplished through a progression involving homo-Robinson annulation (**4**→**8**), followed by DIBAL-H mediated ketone reduction, to afford a diastereomeric mixture of alcohols **9** and **10** (1:3.8).⁵ Isomer **10** was protected as a TIPS ether (**11**) and subjected to [2+2] addition with dichloroketene, which occurred at the more reactive olefin to afford cyclobutanone **12** as a single diastereomer.⁶ As anticipated, ketene addition occurred from the less hindered α -face of the olefin.⁷ Next, dechlorinated product, **13** was advanced to **15** in a straightforward manner.⁸ The latter was subjected to hydroxyl-directed epoxidation to furnish **16** in 93% yield. The structure assignment of **16** was confirmed by X-ray diffraction. Finally, Dess-Martin oxidation, followed by base-promoted β -elimination of the resultant ketone and TES protection of the γ -hydroxyl enone, as shown, afforded **17** (Scheme 3).

As outlined in Scheme 4, **17** was subjected to Grignard-type conditions to provide **18** (31-66% yield).⁹ The latter was advanced to **20** as shown. Surprisingly, X-ray crystallographic analysis of **20** showed that the isopropenyl group had approached from the β -face of the molecule, *syn* to the α -angular methyl group. Although, at the time, we were disappointed in this stereochemical outcome, we nevertheless decided to continue with the synthesis, with the intention of exploring conditions for allylic oxidation. Thus, upon exposure to SeO₂, **20** was converted to diol **2** in 53% yield. To our surprise, the ¹H and ¹³C NMR spectra of synthetic **2** matched those reported for tricholomalide B. Furthermore, attempts to transform **2** to tricholomalide C under basic conditions afforded compound **1** (72% yield), which exhibited ¹H and ¹³C NMR spectra identical to those reported for tricholomalide A. The structures of **2** and **1** were confirmed by X-ray diffraction, although the assignment of the hydroxyisopropenyl group in **2** was based on NMR data, due to the disorder of the hydroxyisopropenyl in the crystal.

Comparative analysis of the tricholomalides and their structurally close relatives, the trichoaurantianolides (**21-24**), led us to hypothesize that tricholomalides A and B may actually have the same stereochemistry at C₂ as tricholomalide C and the trichoaurantianolides.^{3, 10} Since natural samples of the tricholomalides were not available to us, we decided to synthesize the originally proposed tricholomalide B (**2'**) for further structural clarification.

Our unoptimized route to **2'** is presented in Scheme 6. Thus, **6** was advanced to **25** as shown.¹¹ Ketone **25** was converted to its vinyl triflate, and a modified Stille coupling served to append the isopropenyl moiety, providing **26**.¹² Following deprotection,¹³ the intermediate was subjected to a hydroxyl directed epoxidation/oxidation/ β -elimination sequence to furnish **28**.¹⁴ Finally, allylic oxidation of **28** gave **2'**, whose structure was unambiguously confirmed by X-ray diffraction.

As expected, the ¹H and ¹³C NMR of **2'** were clearly different from those reported for tricholomalide B. Thus, we can conclude that the structure of tricholomalide B is **2**, rather than **2'**. Furthermore, since the Ohta group reported that tricholomalide B could be transformed into tricholomalide A (in DMSO at 4 °C), we may infer that the two compounds possess the same stereochemistry at C₂; and based on the NOE data shown by the Ohta group (as well as our own observation), the stereochemistry of C₁ and C₁₁ of tricholomalide A should be as originally reported. Thus, the structure of tricholomalide A is **1**, rather than **1'**. We note that the tetrahydrofuran-cycloheptane system of **1** is, surprisingly, in a *trans* junction. This may reflect thermodynamic control in the cyclization of **2**.

In summary, a concise synthesis of the neurotrophically active tricholomalides A and B has been accomplished, and the structures of these natural products have been reassigned. We are confident that an enantiopure synthesis of **1** and **2** is achievable, since substantially enantiopure **7** has been synthesized in our laboratory.¹⁵ The biological evaluations of the tricholomalides will be disclosed in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- (1). Wilson RM, Danishefsky SJ. *Acc. Chem. Res* 2006;39:539–549. [PubMed: 16906750]
- (2). (a) Bennett MR, Gibson WG, Lemon G. *Auton. Neurosci* 2002;95:1–23. [PubMed: 11871773] (b) Dawbarn D, Allen S. J. *Neuropathol. Appl. Neurobiol* 2003;29:211–230.
- (3). Tsukamoto S, Macabalang AD, Nakatani K, Obara Y, Nakahata N, Ohta T. *J. Nat. Prod* 2003;66:1578–1581. [PubMed: 14695800]
- (4). Min S-J, Danishefsky SJ. *Tetrahedron Lett* 2008;49:3496–3499. [PubMed: 19461989]
- (5). These modified reduction conditions afford a more favorable product distribution in comparison to our earlier disclosure. In addition, the undesired isomer, **9**, was recycled to enone **8** through DMP oxidation
- (6). Mehta G, Rao HSP. *Syn. Comm* 1985;15:991–1000.
- (7). Many thanks to Prof. E. J. Corey for suggesting that the siloxy group may stabilize the C₅ cation in the zwitterionic intermediate during ketene [2+2], rendering the olefin in the 7-membered ring was more reactive
- (8). Nemoto H, Fujita S, Nagai M, Fukumoto K, Kametani T. *J. Am. Chem. Soc* 1988;110:2931–2938.
- (9). Imamoto T, Takiyama N, Nakamura K, Hatajima T, Kamiya Y. *J. Am. Chem. Soc* 1989;111:4392–4398.
- (10). (a) Invernizzi AG, Vidari G, Vita-Finzi P. *Tetrahedron Lett* 1995;36:1905–1908. (b) Benevelli F, Carugo O, Invernizzi AG, Vidari G. *Tetrahedron Lett* 1995;36:3035–3038.
- (11). Mehta G, Umarye JD, Srinivas K. *Tetrahedron Lett* 2003;44:4233–4237.
- (12). Han XJ, Stoltz BM, Corey EJ. *J. Am. Chem. Soc* 1999;121:7600–7605.
- (13). Ireland RE, Varney MD. *J. Org. Chem* 1986;51:635–648.
- (14). Mihelich ED, Daniels K, Eickhoff DJ. *J. Am. Chem. Soc* 1981;103:7690–7692.
- (15). Mandal M, Yun H, Dudley GB, Lin S, Tan DS, Danishefsky SJ. *J. Org. Chem* 2005;70:10619–10637. [PubMed: 16355979]

Scheme 1.
Original and Revised Tricholomalide Structures.

Scheme 2.
Synthetic Strategy Toward Tricholomalides A and B.

Scheme 3. Synthesis of Intermediate 17.^a

^aKey: (a) ref. 4, 3 steps, 90%; (b) ref. 4, 3 steps, 45%; (c) ref. 4, 53%; (d) DIBAL-H, -78 °C, DCM, 81%, **9:10** = 1:3.8; (e) TIPSOTf, Et₃N, DCM, 89%; (f) Zn, CCl₃COCl, Et₂O, sonication; (g) Zn, HOAc, 100 °C; (h) aq. NaOH, TBHP, THF, 0 °C; (i) TBAF, THF, 85% from **11**; (j) mCPBA, DCM, 93%; (k) DMP, DCM; (l) i-Pr₂NEt, DCM, 30 min; (m) add TESCl, 84% from **16**.

Scheme 4. Synthesis of Tricholomalides A and B.^a

^aKey: (a) isopropenylmagnesium bromide, CeCl_3 , THF, $-78\text{ }^\circ\text{C}$, 20 min to 1 h, 31% - 66%; (b) HF-py, THF, $0\text{ }^\circ\text{C}$, 80%; (c) MnO_2 , THF, 51%; (d) SeO_2 , TBHP, py, DCM, 4 days, 53%; (e) NaOMe, MeOH, 72%.

Scheme 5.
The Trichaurantianolides.

Scheme 6.

Synthesis of the Originally Proposed Tricholomalide B^a

^aKey: (a) *i*-Pr₂NEt, MOMCl, DCM; (b) H₂, 10% Pd-C, EtOAc, 89% from **6**; (c) KHMDS, *N,N*-Bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine, THF, 0 °C, 20 min, 57%; (d) Tributyl(isopropenyl)-stannane, LiCl, CuCl, Pd(PPh₃)₄, DMSO, 60 °C, 1 h, 79%; (e) LiBF₄, wet CH₃CN, 72 °C, 73%; (f) VO(acac)₂, TBHP, DCM, 4 Å mol. sieves, 3 days, 43%; (g) DMP, DCM; (h) *i*-Pr₂NEt, DCM, 20 min, 61% from **27**; (i) SeO₂, TBHP (anhyd.), DCM, 16%.