

# Synthesis of the Core of Actinophyllic Acid Using a Transannular Acyl Radical Cyclization

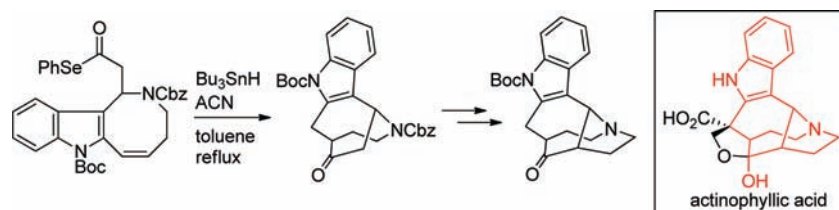
Hisaaki Zaimoku, Tsuyoshi Taniguchi,\* and Hiroyuki Ishibashi

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

tsuyoshi@p.kanazawa-u.ac.jp

Received February 4, 2012

## ABSTRACT



A synthetic study of actinophyllic acid based on an original strategy has been described. A transannular acyl radical cyclization allowed us to obtain a key bicyclo[3.3.2] framework, and construction of a core of the target alkaloid has been accomplished by subsequent introduction of a C2 unit.

A number of classes of indole alkaloid with unusual structures and biological activity have recently attracted the widespread interest of synthetic and medicinal chemists.<sup>1</sup> One of these, (–)-actinophyllic acid (**1**), was isolated by Carroll and co-workers in 2005 from leaves of the Australian tree *Alstonia actinophylla* (Scheme 1).<sup>2</sup> Actinophyllic acid exhibits inhibitory activity in the coupled enzyme assay of carboxypeptidase U (CPU) /hippuricase (IC<sub>50</sub> = 0.84 μM).<sup>2a</sup> Since CPU is an inhibitor of the blood fibrinolysis process, actinophyllic acid might become the seed of an agent for treatment of thrombotic diseases. Actinophyllic acid has a unique 2,3,6,7,9,13c-hexahydro-1*H*-1,7,8-(methanetrioxymethano)pyrrolo[1',2':1,2]azocino[4,3-*b*]indole-8(5*H*)-carboxylic acid skeleton, and an elegant total synthesis of this alkaloid based on a

biomimetic aza-Cope/Mannich cascade strategy has recently been reported by Overman and co-workers.<sup>3</sup> However, exploration of new flexible routes to actinophyllic acid still remains important as long as its derivatives have the potential to be medicinal candidates.<sup>4</sup> In this regard, we envisaged an alternative approach for the synthesis of actinophyllic acid that would facilitate the search for potential derivatives. Herein we report a synthesis of the core of (±)-actinophyllic acid using a well-designed radical cyclization as a milestone in our synthetic study of this alkaloid.

Our synthetic strategy for actinophyllic acid is outlined in Scheme 1. It targeted the core compound (±)-**2** (R = H). The pyrrolidine ring of compound (±)-**2** (R = H) would be constructed by two alkylations at a nitrogen atom and the α-position of the ketone in azabicyclo[3.3.2] structure **3**.

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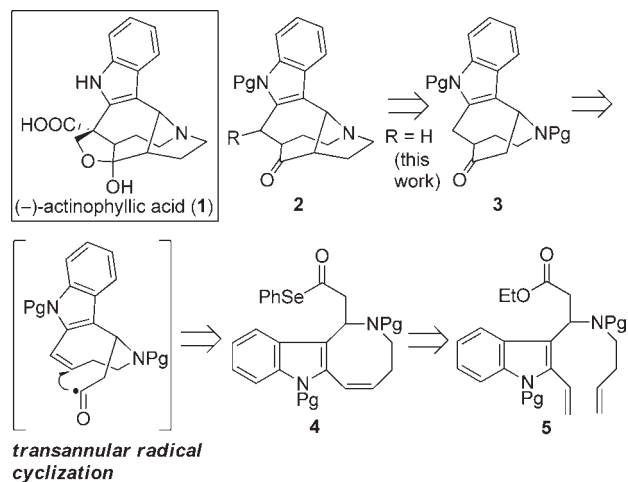
(3) (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569. (b) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906.

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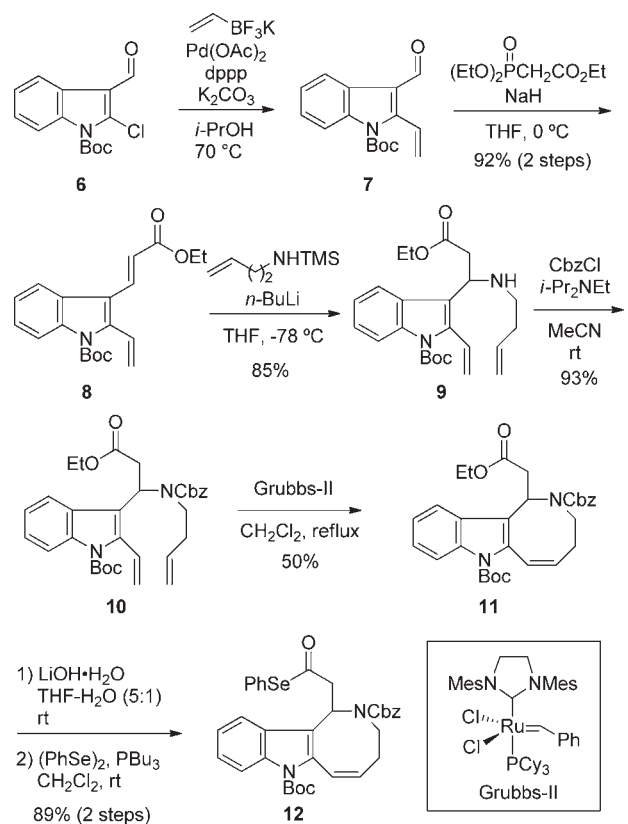
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We proposed the transannular acyl radical cyclization of selenoester **4** to obtain compound **3**. Although many examples of efficient transannular acyl radical cyclizations for the construction of complex cyclic natural products have been reported, the synthesis of an azabicyclo[3.3.2] compound using this methodology has been hardly investigated.<sup>5–8</sup> A ring-closing metathesis of diene **5** would be a reliable method for the construction of an eight-membered ring of radical precursor **4**.<sup>9</sup>

**Scheme 1.** Structure and Synthetic Strategy of **1**



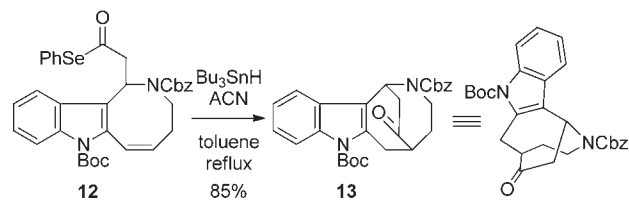
**Scheme 2.** Synthesis of Radical Precursor **12**



Easily available indole derivative **6**<sup>10</sup> was chosen as a starting material for our synthesis (Scheme 2). Suzuki–Miyaura coupling of 2-chloroindole derivative **6** with potassium vinyltrifluoroborate (1.5 equiv) in the presence of palladium acetate (1 mol %) and a bidentate phosphine ligand (1 mol %) gave 2-vinylindole compound **7**.<sup>11</sup> Subsequently, crude compound **7** was subjected to a Horner–Wadsworth–Emmons reaction to obtain the  $\alpha,\beta$ -unsaturated ester **8** in good overall yield. The 3-butenylamine moiety of diene **9** was readily introduced by aza-Michael addition of the corresponding lithium silylamide (2 equiv) to compound **8**.<sup>12</sup> After protection of the secondary amine of compound **9** with a Cbz group, ring-closing metathesis of compound **10** using Grubbs second-generation catalyst (2 mol %) afforded eight-membered ring compound **11**. The moderate yield of **11** was due to competitive dimerization of compound **10**, and improvement in the yield may be possible by further optimization of the reaction conditions in the future. Compound **11** was transformed into selenoester **12** through an ester hydrolysis followed by a selenation using a combination of diphenyldiselenide and tributylphosphine.<sup>13</sup>

With selenoester **12** in hand, we examined the key transannular radical cyclization to construct the caged skeleton of actinophyllic acid. Treatment of compound **12** with tributyltin hydride (1.5 equiv) and 1,1'-azobiscyclohexanecarbonitrile (ACN) (0.2 equiv) in toluene at reflux caused a transannular cyclization of an intermediary acyl radical to give the desired azabicyclo[3.3.2] compound **13** in a perfectly regioselective manner (Scheme 3). This result did not surprise us because the regioselectivity of acyl radical cyclizations has ostensibly tended to be thermodynamically controlled.<sup>5a</sup> Therefore, the exclusive formation of compound **13** via a more stable  $\alpha$ -indolyl radical ( $\pi$ -radical) intermediate would be reasonable in the present cyclization.

**Scheme 3.** Transannular Radical Cyclization of **12**



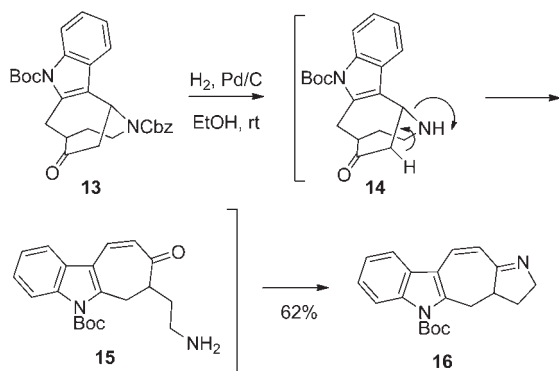
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(7) Examples of transannular acyl radical cyclizations: (a) Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 2323–2328. (b) Bannasar, M.-L.; Roca, T.; Garcia-Diaz, D. *J. Org. Chem.* **2008**, *73*, 9033–9039.

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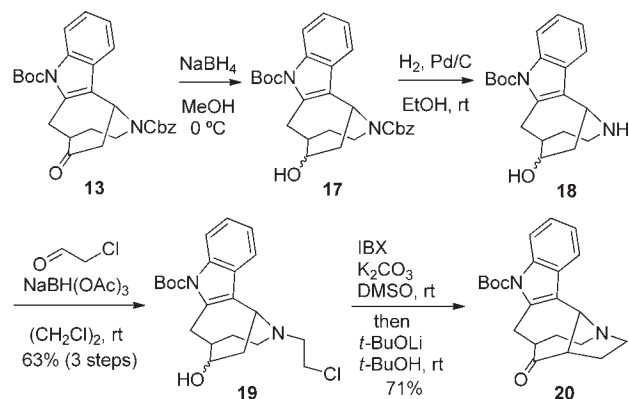
**Scheme 4.** Unexpected Formation of **16** from **13**



Next, we focused on constructing the pyrrolidine ring of the actinophyllic acid core. When compound **13** was exposed to palladium-catalyzed hydrogenolysis, its Cbz group was removed and the unexpected tetracyclic compound **16** was obtained (Scheme 4). Probably, deprotection of the Cbz group set off a ring-opening reaction by elimination of the hydrogen atom at the  $\alpha$ -position of ketone **14** to give tricyclic intermediate **15** which, following intramolecular condensation, would afford the corresponding imine **16**. Hence, we realized that the ketone group of compound **13** needed to be masked prior to the deprotection of the Cbz group.

The ketone group of compound **13** was reduced to alcohol **17** with sodium borohydride (1 equiv), and we now succeeded in removing the Cbz group of compound **17** by hydrogenolysis and we obtained the secondary amine **18** (Scheme 5). Without isolation of compound **18**, it underwent reductive amination with 2-chloroacetaldehyde (2 equiv) to give *N*-alkylated compound **19** in good overall yield. Finally, oxidation of alcohol **19** with 2-iodoxybenzoic acid (IBX) (3 equiv) and subsequent treatment with an

**Scheme 5.** Synthesis of Actinophyllic Acid Core **20**



excessive amount of lithium *tert*-butoxide (5 equiv), in one-pot, led to the ( $\pm$ )-actinophyllic acid core **20** via an intramolecular alkylation.

In conclusion, we have succeeded in synthesizing a core **20** bearing most of the components of ( $\pm$ )-actinophyllic acid. The most remarkable step in our synthetic strategy is the transannular acyl radical cyclization that provides an access to the azabicyclo[3.3.2] system **13**. We anticipate that synthesis of an optically active derivative will be possible by an asymmetric aza-Michael reaction of compound **8**.<sup>14</sup> Further studies toward the total synthesis of ( $-$ )-actinophyllic acid using this strategy are currently ongoing in our laboratory.

**Acknowledgment.** This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

**Supporting Information Available.** Experimental detail and spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.

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