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

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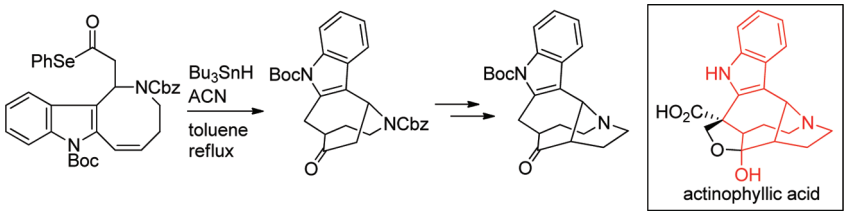
ABSTRACT



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.[1] 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).[2] Actinophyllic acid exhibits inhibitory activity in the coupled enzyme assay of carboxypeptidase U (CPU) /hippuricase (IC_{50} = 0.84 μM).[2a] 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-(methanetriyloxymethano)pyrrolo[1′,2′:1,2]azocino[4,3-b]indole-8(5H)-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.[3] However, exploration of new flexible routes to actinophyllic acid still remains important as long as its derivatives have the potential to be medicinal candidates.[4] 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**.

(1) Reviews:(a) Seigler, D. S. *Plant Secondary Metabolism*; Springer: New York, 2001; Chapters 34 and 35, pp 628−667. (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148–180.

(2) (a) Carroll, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. *J. Org. Chem.* **2005**, *70*, 1096–1099. Recently, absolute configuration of natural actinophyllic acid was determined by Berova and co-workers, see: (b) Taniguchi, T.; Martin, C. L.; Monde, K.; Nakanishi, K.; Berova, N.; Overman, L. E. *J. Nat. Prod.* **2009**, *72*, 430–432.

(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.

(4) A report of a synthetic study of actinophyllic acid: Vaswani, R. G.; Day, J. J.; Wood, J. L. *Org. Lett.* **2009**, *11*, 4532–4535.

(5) Reviews on acyl radicals: (a) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2070. (b) Schiesser, C. H.; Wille, U.; Matsubara, H.; Ryu, I. *Acc. Chem. Res.* **2007**, *40*, 303–313. Recent examples of acyl radical cyclizations: (c) Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 681–683. (d) Grant, W. S.; Zhu, K.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867–1870. (e) Inoue, M.; Ishihara, Y.; Yamashita, S.; Hirama, M. *Org. Lett.* **2006**, *8*, 5801–5804. (f) Roca, T.; Bennasar, M.-L. *J. Org. Chem.* **2011**, *76*, 4213–4218.

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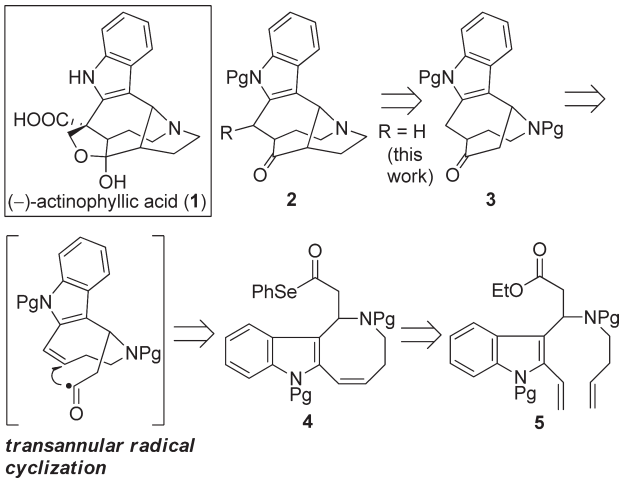
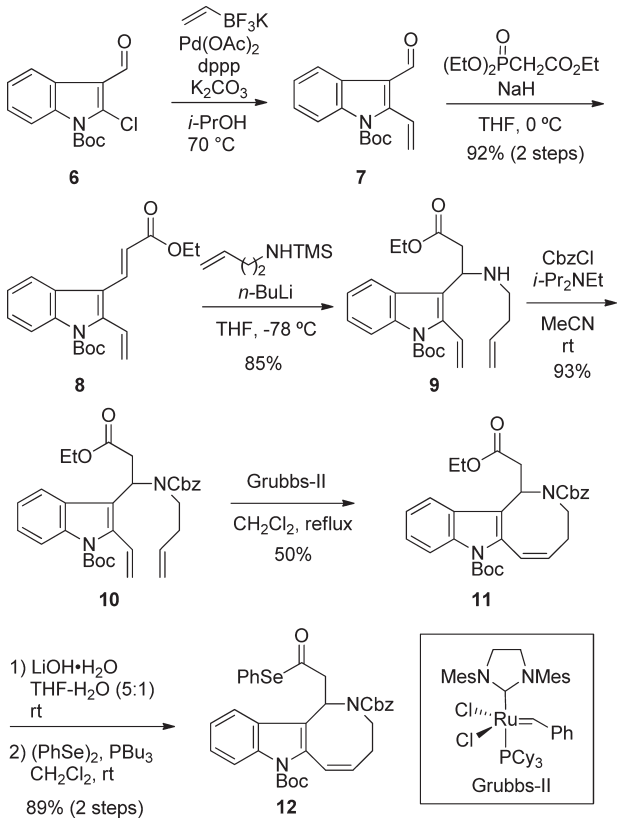
We proposed the transannular acyl radical cyclization of selenoester **4** to obtain compound **3**. Although many examples of efficient transannular acyl radical cyclizations for the construction of complex cyclic natural products have been reported, the synthesis of an azabicyclo[3.3.2] compound using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

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



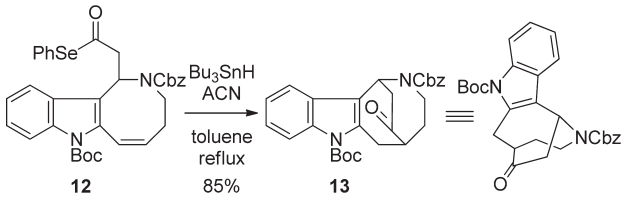
Scheme 2. Synthesis of Radical Precursor **12**



Easily available indole derivative **6**[10] 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**.[11] Subsequently, crude compound **7** was subjected to a Horner−Wadsworth−Emmons reaction to obtain the α,*β*-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**.[12] 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.[13]

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.[5a] Therefore, the exclusive formation of compound **13** via a more stable α-indolyl radical (*π*-radical) intermediate would be reasonable in the present cyclization.

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



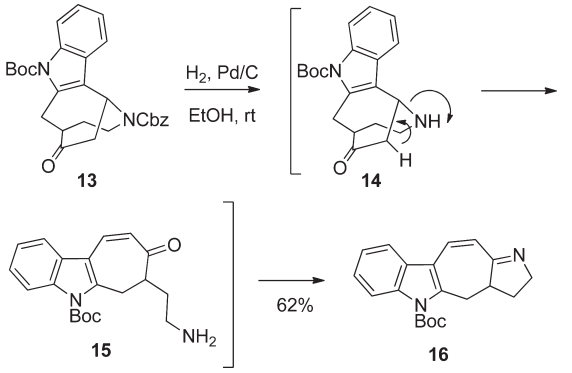
(6) Reviews on transannular cyclizations: (a) Clarke, P. A.; Reeder, A. T.; Winn, J. *Synthesis* **2009**, 691–709. (b) Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993–1018.

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

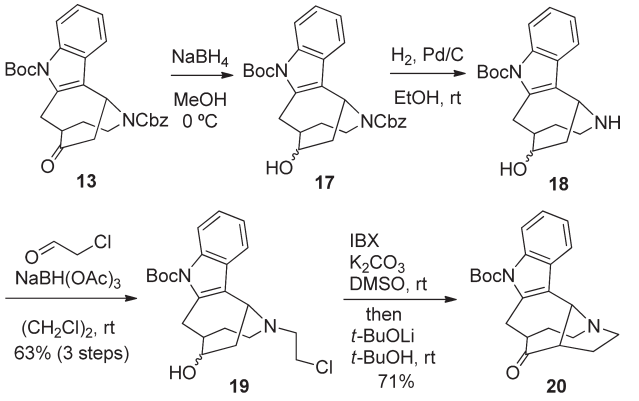
(8) Dowd and co-workers have reported the synthesis of a bicyclo-[3.3.2] compound using a transannular radical reaction: (a) Dowd, P.; Zhang, W. *J. Am. Chem. Soc.* **1992**, *114*, 10084–10085. (b) Dowd, P.; Zhang, W.; Geib, S. J. *Tetrahedron* **1995**, *51*, 3435–3454.

(9) Examples of the similar strategy: (a) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Roca, T.; García-Díaz, D.; Alonso, S. *J. Org. Chem.* **2009**, *74*, 8359–8368. (b) Bennasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Org. Lett.* **2011**, *13*, 2042–2045.

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



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



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

In conclusion, we have succeeded in synthesizing a core **20** bearing most of the components of (±)-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**.[14] Further studies toward the total synthesis of (−)-actinophyllic acid using this strategy are currently ongoing in our laboratory.

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

(10) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Véliz, E. A.; Yang, Z.-C. *Synlett* **1995**, 609–611. Compound **6** also seems to be commercially available from some suppliers.

(11) Reviews on Suzuki-Miyaura reaction: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49–56.

(12) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1988**, *44*, 4173–4180.

(13) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.

(14) Examples of asymmetric aza-Michael reactions: (a) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886–2887. (b) Doi, H.; Sakai, T.; Yamada, K.; Tomioka, K. *Chem. Commun.* **2004**, 1850–1851.

The authors declare no competing financial interest.