Total Synthesis of (±)-Actinophyllic Acid

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During a search for new natural product structures as potential leads for developing agents for treating cardiovascular disorders, Quinn, Carroll, and co-workers reported in 2005 the isolation and relative configuration of actinophyllic acid (1).1 This structurally unique indole alkaloid was obtained from the leaves of the tree Alstonia actinophylla collected on the Cape York Peninsula, Far North Queensland, Australia. It was identified in a coupled CPU/hippuricase assay as an inhibitor of carboxypeptidase U (CPU), an endogenous inhibitor of the process the body uses to clear fibrin clots (fibrinolysis).2 The structure of actinophyllic acid (1) is unique because the 1-azabicyclo[4.4.2]dodecane and 1-azabicyclo[4.2.1]nonane fragments that define its structure are found in no other indole alkaloid. We report herein the first total synthesis of (±)-actinophyllic acid (1) by a route that is sufficiently concise that it would be suitable for production of gram quantities of the natural product.

Our plan for preparing actinophyllic acid (1) is outlined in retrosynthetic format in Scheme 1. Initial disconnection of the C5 hemiketal and oxidation state adjustments reveals pentacyclic ketone 2, which we envisaged arising from allylic alcohol 5 by aza-Cope–Mannich rearrangement of formaldiminium ion derivative 4.3 The hexahydro-1,5-methanoazocino[4,3-b]indole ring system of the ketone precursor of allylic alcohol 5 we saw deriving from intramolecular oxidative coupling of a dienolate4 generated from indole-2-malonate precursor 6.

The synthesis commenced with the preparation of indole di-tert-butyl malonate 9 using a standard sequence (Scheme 2).5 Reaction of the magnesium enolate of di-tert-butyl malonate (7) with 2-nitrophenylacetyl chloride, generated in situ from the corresponding acid, gave keto diester 8 in 78% yield. Reduction of the nitro group and concomitant cyclization delivered indole-2-malonate 9 in 69% yield. After examining several alternate ways to append a 3-piperidone fragment to intermediate 9, we discovered that this junction was readily accomplished by simply allowing indole 9 to react at room temperature in N,N-dimethylformamide (DMF) with the crude bromopiperidone 10,6 generated by bromination of 1-tert-butoxycarbonyl-3-piperidone.7 In this way, indole 11 was prepared on multigram scale in 85% yield.

The elaboration of indole keto diester 12 to (±)-actinophyllic acid is summarized in Scheme 3. tert-Butyl ester substituents had been incorporated into intermediate 12 with the hope, bolstered

![Scheme 1](image1)

![Scheme 2](image2)

![Scheme 3](image3)

Note: The images of the schemes are not directly translatable to text in this format. The schemes are essential for understanding the synthesis process.
eventually by its X-ray model (see Scheme 2), that these bulky groups would shield the Si face of the ketone in the addition of a vinyl nucleophile. This expectation was verified when premixing of the resulting secondary amine with 1 equiv of paraformaldehyde and a catalytic amount of camphorsulfonic acid (CSA) in benzene provided pentacyclic ester C, cleanly promoted aza-Cope reorganization to 17. Stereoselective aldol reaction of the lithium methylide-actinophyllic acid is no longer available for direct comparison. In conclusion, the first total synthesis of (±)-actinophyllic acid (1) was accomplished from di-tert-butyl malonate in an overall yield of 8% by a concise sequence that proceeds by way of only seven isolated intermediates. Of the eight stages of the synthesis, all but one construct C−C or C−N bonds. Key bond formations include an intramolecular oxidative coupling of ketone and malonate enolates and anaza-Cope−Mannich rearrangement to construct the unprecedented actinophyllic acid ring system.

Acknowledgment. This research was supported by the NIH Neurological Disorders & Stroke Institute (NS-12389). NMR and mass spectra were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation programs. We thank Professor Phil Baran for discussion and samples of metal salts, and Dr. Joe Ziller for X-ray analyses.

Supporting Information Available: Experimental details for key steps; copies of 1H and 13C NMR spectra of new compounds (PDF); CIF file for compound 12. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(9) This conversion was initially optimized with the dimethyl ester congener of 17. These studies showed that yields of the cyclized product were much lower using 2.0 equiv of LDA and 2.2 equiv of oxidant, or if Ketac®), Fe(cp)2PF6, or Cu(O2CC5H11)2 was employed as the oxidant.
(12) The constitution and relative configuration of the α epimer was confirmed by single-crystal X-ray analysis.
(13) Schlosser, M.; Coffinet, D. Synthesis 1971, 380–381.
(14) Final purification of salt 17 by HPLC, as reported for the natural product, does not reproducibly give samples of 1 that show identical 1H NMR spectra nor samples whose spectra precisely match those reported for natural 1 (in DMSO-d6), we believe such samples are variable mixtures of zwitterionic 1 and salt 17. Addition of incremental amounts of sodium methylsulfinylmethylide-d6 to hydrochloride salt 17 in DMSO-d6 revealed incremental shifts in most resonances. When ca. 1 equiv of base was added, a 1H NMR spectrum identical to that reported for natural 1 was obtained; see the Supporting Information for details. Unfortunately, a sample of natural actinophyllic acid is no longer available for direct comparison.

JA803158Y