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Total Synthesis of (±)-Actinophyllic Acid

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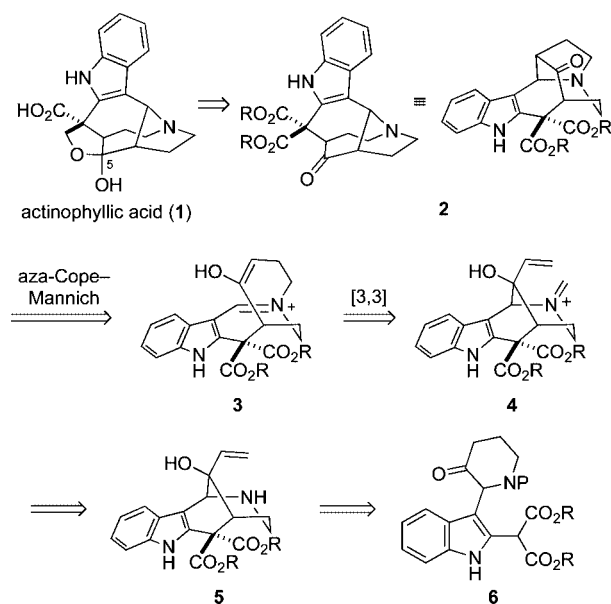
During a search for new natural product structures as potential leads for developing agents for treating cardiovascular disorders, Quinn, Carroll, and co-workers reported in 2005 the isolation and relative configuration of actinophyllic acid (**1**).¹ This structurally unique indole alkaloid was obtained 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**.

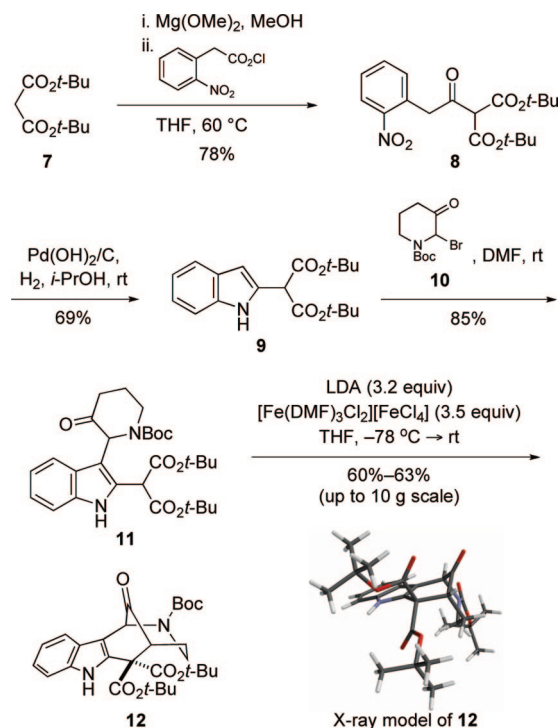
The synthesis commenced with the preparation of indole di-*tert*-butyl malonate **9** using a standard sequence (Scheme 2).⁵ Reaction of the magnesium enolate of di-*tert*-butyl malonate (**7**) with 2-nitrophenylacetyl chloride, generated in situ from the corresponding acid, gave keto diester **8** in 78% yield. Reduction of the nitro group and concomitant cyclization delivered indole **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 keto-bridged hexahydroazocino[4,3-*b*]indole ring system was constructed in one step by regioselective intramolecular oxidative coupling of malonate and 3-piperidone enolates. Thus, deprotonation of **11** with 3.2 equiv of lithium diisopropylamide (LDA) at -78 °C, followed by addition of 3.5 equiv of the Fe(III) oxidant $[\text{Fe}(\text{DMF})_3\text{Cl}_2][\text{FeCl}_4]$,⁸ provided tetracyclic ketone **12** in 60–63% yield. To our knowledge, this is the first example of intramolecular oxidative coupling of ketone and malonic ester enolates.^{9,10} It is noteworthy that this oxidative coupling proceeded in the presence of an unprotected indole, providing good yields of **12** on scales up to 10 g.

Scheme 1



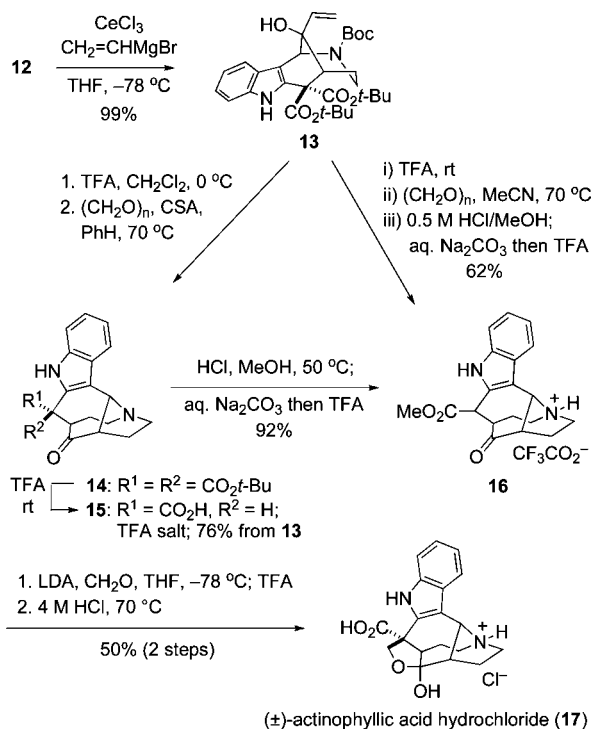
Scheme 2



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

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Scheme 3



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 ketone **12** with cerium trichloride,¹¹ followed by reaction with vinylmagnesium bromide at $-78\text{ }^\circ\text{C}$ in THF, provided a single allylic alcohol product, **13**, in nearly quantitative yield. Selective removal of the Boc group from this product, followed by reaction of the resulting secondary amine with 1 equiv of paraformaldehyde and a catalytic amount of camphorsulfonic acid (CSA) in benzene at $70\text{ }^\circ\text{C}$, cleanly promoted aza-Cope–Mannich reorganization to provide pentacyclic diester **14**. Exposure of this crude product to neat trifluoroacetic acid (TFA) gave amino acid trifluoroacetate salt **15** in 76% overall yield from allylic alcohol **13**. Fischer esterification of **15**, followed by counterion exchange, provided ester **16**, a 2:1 mixture of α and β ester epimers, in 92% yield.¹²

We eventually discovered that the transformation of tetracyclic allylic alcohol **13** to pentacyclic ester **16** could be carried out conveniently in a one-pot process by initially exposing **13** to TFA at room temperature, which cleaved the Boc and *tert*-butyl esters and promoted decarboxylation. Removal of TFA in vacuo, dilution with acetonitrile, and exposure of the resulting amino acid trifluoroacetate salt to paraformaldehyde promoted aza-Cope–Mannich transformation to the carboxylic acid congener of **16**, which after removal of acetonitrile was esterified to provide **16** in 62% yield as 1:1 mixture of ester epimers.

In two additional steps, pentacyclic ester **16** was transformed to actinophyllic acid (**1**). Stereoselective aldol reaction of the lithium enolate derived from ester **16** with monomeric formaldehyde¹³

installed the tetrahydrofuran ring to provide actinophyllic acid methyl ester. Acidic hydrolysis then provided (\pm)-actinophyllic acid, which was most conveniently isolated and characterized as its hydrochloride salt **17**.¹⁴

In conclusion, the first total synthesis of (\pm)-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 an aza-Cope–Mannich rearrangement to construct the unprecedented actinophyllic acid ring system.

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Supporting Information Available: Experimental details for key steps; copies of ^1H and ^{13}C 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>.

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- Final purification of salt **17** by HPLC, as reported for the natural product,¹ 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 $\text{DMSO}-d_6$); we believe such samples are variable mixtures of zwitterionic **1** and salt **17**. Addition of incremental amounts of sodium methylsulfonfylmethylide- d_5 to hydrochloride salt **17** in $\text{DMSO}-d_6$ revealed incremental shifts in most resonances. When ca. 1 equiv of base was added, a ^1H NMR spectrum identical to that reported¹ 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.

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