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Total Synthesis of (±)-Actinophyllic Acid

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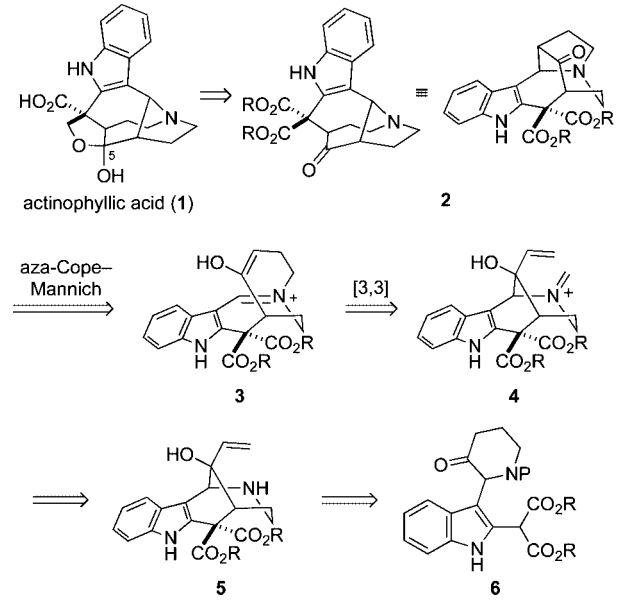
During a search for new natural product structures as potential leads for developing agents for treating cardiovascular disorders, Quinn, Carroll, and co-workers reported in 2005 the isolation and relative configuration of actinophyllic acid (**1**).[1] This structurally unique indole alkaloid was obtained 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 dienolate[4] generated from indole-2-malonate precursor **6**.

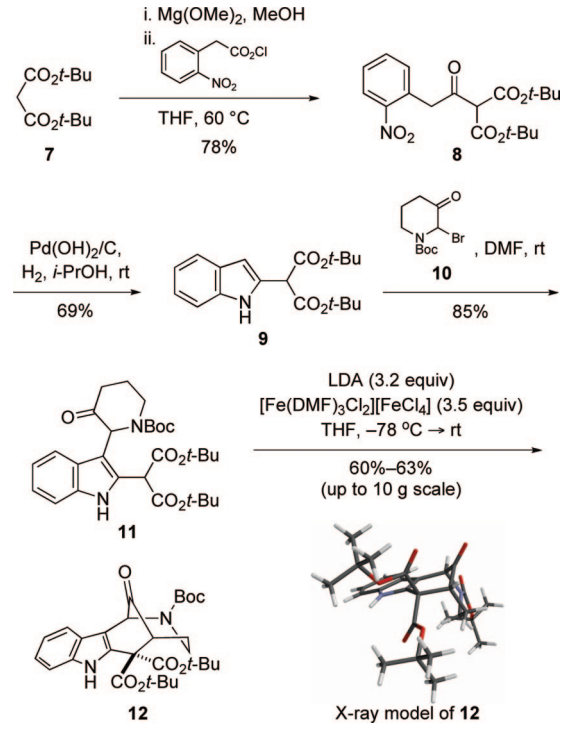
The synthesis commenced with the preparation of indole di-*tert*-butyl malonate **9** using a standard sequence (Scheme 2).[5] Reaction of the magnesium enolate of di-*tert*-butyl malonate (**7**) with 2-nitrophenylacetyl chloride, generated in situ from the corresponding acid, gave keto diester **8** 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 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 $[Fe(DMF)_3Cl_2][FeCl_4]$,[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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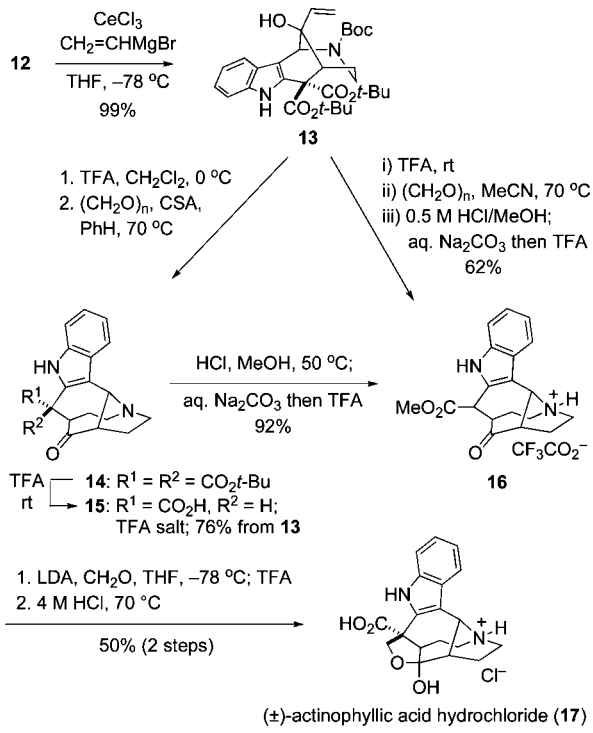
Scheme 3



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 °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 °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 formaldehyde[13] installed the tetrahydrofuran ring to provide actinophyllic acid methyl ester. Acidic hydrolysis then provided (±)-actinophyllic acid, which was most conveniently isolated and characterized as its hydrochloride salt **17**.[14]

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 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 ^{1}H 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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(14) Final purification of salt **17** by HPLC, as reported for the natural product,[1] does not reproducibly give samples of **1** that show identical ^{1}H NMR spectra nor samples whose spectra precisely match those reported for natural **1** (in DMSO-d_6); we believe such samples are variable mixtures of zwitterionic **1** and salt **17**. Addition of incremental amounts of sodium methylsulfinylmethylide-d_5 to hydrochloride salt **17** in DMSO-d_6 revealed incremental shifts in most resonances. When ca. 1 equiv of base was added, a ^{1}H NMR spectrum identical to that reported[1] 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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