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Catalytic Asymmetric Total Synthesis of (−)-Actinophyllic Acid

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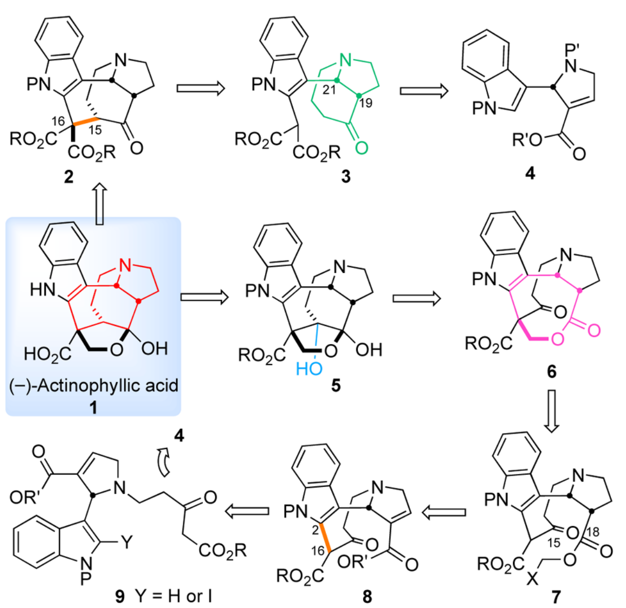
Supporting Information

ABSTRACT: Described herein is a catalytic asymmetric total synthesis of (−)-actinophyllic acid, with the key step being a chiral phosphine-catalyzed [3 + 2] annulation between an imine and an allenoate to form a pyrroline intermediate in 99% yield and 94% ee. The synthesis also features CuI-catalyzed coupling between a ketoester and a 2-iodoindole to shape the tetrahydroazocine ring; intramolecular alkylative lactonization; SmI_2-mediated intramolecular pinacol coupling between ketone and lactone subunits to assemble the complex skeleton of (−)-actinophyllic acid; and an unprecedented regioselective dehydroxylation.

In a search for therapeutic agents for the treatment of cardiovascular disorders, Quinn, Carroll, et al. isolated (−)-actinophyllic acid (**1**) from the leaves of the tree *Alstonia actinophylla* growing in Cape York Peninsula, Far North Queensland, Australia (Scheme 1).[1] (−)-Actinophyllic acid was reported to be a potent inhibitor of the zinc-dependent carboxypeptidase U (CPU), with an IC_{50} of 0.84 μM. CPU is an endogenous inhibitor of fibrinolysis, the breakage of fibrin clots. Consequently, inhibitors of CPU can facilitate fibrinolysis and inhibit the blood clot formation that is a cause of various cardiovascular disorders.[2] There have not, however, been any subsequent biological studies reported, presumably because of the scarcity of the natural product, due to its low isolation yield (0.0072%).[3] Therefore, any efficient de novo syntheses of this potent CPU inhibitor should benefit explorations of its biomedical potential.

Scheme 1. Retrosynthesis of (−)-Actinophyllic Acid



Structurally, (−)-actinophyllic acid contains the cage-like scaffold of a 1,2,3,5,6,7,8,10a-octahydro-1,7-methanopyrrolo-[1,2-*a*]azocine, highlighted in red in Scheme 1, with five contiguous stereogenic centers, one of which is a quaternary carbon, bridged by a tetrahydrofuran lactol.[4] This unprecedented architecture, along with great biomedical potential, has garnered widespread attention from the synthetic community. In 2008, Overman et al. accomplished an elegant total synthesis of (±)-actinophyllic acid through aza−Cope/Mannich cascade strategy (Figure 1).[5a] Later, the same group reported a second-generation synthesis toward (−)-actinophyllic acid based on diastereoselective coupling between a 2-indole malonate and diacetoxypiperidine.[5b,6] In 2013, Martin's group revealed an alternative synthesis of (±)-actinophyllic acid, spotlighting a remarkable cascade reaction between a seven-membered ring dienamine and a tertiary 2-indolyl acetoxylate.[7] Contemporarily, the Wood, Taniguchi, Maldonado, and Coldham groups reported their synthetic studies toward this novel monoterpene

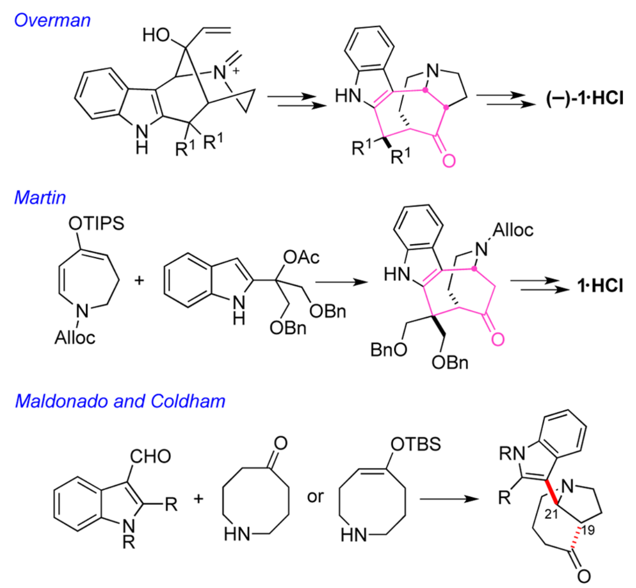


Figure 1. Key steps in previous attempts toward actinophyllic acid.

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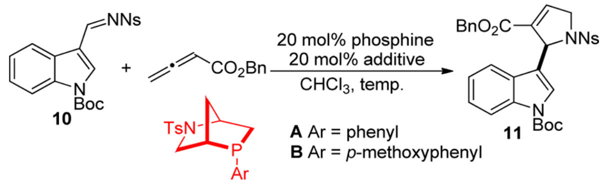
indole alkaloid.[8] Previous efforts, and our own experience, exposed that establishing the cis stereochemistry between the C19 ketone and the C21 indole substituents on the pyrrolidine ring (**4** to **3**, Scheme 1) is challenging. In both Maldonado's and Coldham's synthetic attempts, intramolecular Mannich reactions between an indole-3-carboxaldehyde and an azocinone resulted in the 1-azabicyclo[4.2.1]nonane scaffold with incorrect trans stereochemistry between the C19 ketone and the C21 indole (actinophyllic acid numbering), presumably due to steric congestion between the indoyl substituent and the adjacent C19 acyl chain.[7c,7d] Both Overman and Martin brought this challenge under control through their early stage construction of the indole-fused heptenone (in pink, Figure 1). We, on the other hand, addressed it through intramolecular lactonization (from **7** to **6**, Scheme 1). Herein, we report a catalytic asymmetric synthesis of (−)-actinophyllic acid, featuring a chiral phosphine-catalyzed [3 + 2] annulation between an imine and an electron-deficient allene.

In the retrosynthetic sense, we originally envisioned that (−)-actinophyllic acid could be obtained from the diester **2** through Overman's decarboxylation, hydroxymethylation, and lactol formation sequence (Scheme 1). We targeted forming the C15−C16 bond in **2** through oxidative coupling between the malonate and ketone units of intermediate **3**. The 1-azabicyclo[4.2.1]nonan-5-one scaffold (in green) of compound **3** was to be fashioned from pyrroline **4** via azepinone ring formation. The pyrroline **4**, in turn, could be assembled through a well-established phosphine-catalyzed [3 + 2] annulation between an indole imine and an electron-deficient allene.[9] While reduction of the pyrroline **4** to the 2,3-*cis*-substituted pyrrolidine was readily accomplished, the formation of the bridged 1-azabicycl[4.2.1]nonan-5-one system (in green) proved difficult, due to epimerization at C19, even under mild conditions.[10] To circumvent these obstacles, we devised an alternative route in which the hexahydroazocine ring would be built first (from **9** to **8**). Diastereoselective hydrogenation of the pyrroline should, then, bring the carbonyl groups at C15 and C18 in close proximity to form the azepane ring through pinacol coupling (from **6** to **5**). The two carbonyl groups would be brought even closer, we surmised, after intramolecular alkylative lactonization (from **7** to **6**). The azocinone ring in compound **8** should be accessible through coupling between the indole C2 atom and the C16 atom of the *β*-ketoester in **9**, which should be readily preparable from intermediate **4**.

Our synthetic campaign commenced with an exploration of the key [3 + 2] annulation between benzyl allenoate and the *N*-(*o*-nitrobenzenesulfonyl) (*o*-nosyl) imine **10**, which could be synthesized according to the known procedure from indole 3-carboxaldehyde.[9c] Initially, when using PPh_3, the desired racemic pyrroline was obtained in 99% yield after 6 h (Table 1, entry 1). Our previous studies on the enantioselective synthesis of pyrrolines foretold that the *endo*-phenyl Kwon [2.2.1] bicyclic phosphine **A** should produce the desired (*S*)-enantiomer **11**.[9c,d] When we applied 20 mol % of phosphine **A** to the reaction, the (*S*)-enantiomer was indeed formed in 97% yield and 75% ee after 5 h at room temperature in $CHCl_3$ (entry 2).[11,12] The more nucleophilic phosphine **B** improved the enantioselectivity to 83% ee. The ee increased further, to 91%, after decreasing the reaction temperature to 0 °C (entries 3 and 4). Further lowering of the temperature did not improve the ee.[13] From a mechanistic perspective, we suspected that hydrogen bonding would facilitate the proton-transfer steps[14] and rigidify the transition-state assembly,[15] thereby improving the enantioselectivity. Among a variety of tested hydrogen-bond donors, we found that phenol and derivatives accelerated the reaction and improved the enantioselectivity. Addition of 20 mol % phenol or biphenol decreased the reaction time to 2 h, albeit without improving the enantioselectivity (entries 5 and 6). When 20 mol % *s*-BINOL or *r*-BINOL was used as the additive, the enantioselectivity improved to 94% without decreasing the yield, with the reaction occurring within 2 h (entries 7 and 8).[15]

Table 1. Phosphine-Catalyzed Pyrrolidine Synthesis

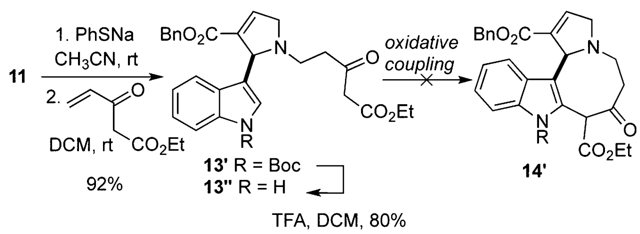


entry	cat.	temp. (°C)	additive	time (h)	yield (%)[a]	ee (%)[b]
1	PPh_3	rt		6	99	
2	A	rt		5	97	75
3	B	rt		5	99	83
4	B	0		5	99	91
5	B	0	phenol	2	99	91
6	B	0	biphenol	2	99	91
7	B	0	*s*-BINOL	2	99	94
8	B	0	*r*-BINOL	2	99	94

[a]Isolated yield after silica gel FCC. [b]Determined using HPLC.

With the annulation product in hand, we attempted to form the hexahydroazocinone ring through oxidative coupling between the ketoester and the C2 atom of indole.[16] Quick access to the ketoester **13′** was secured in 92% yield through deprotection of the *o*-nosyl group, performed with sodium benzenethiolate in MeCN at room temperature, followed by reaction with ethyl 3-oxopent-4-enoate (Scheme 2).[17] We examined a list of oxidants, including Fe^{3+}, Cu^{2+}, Mn^{3+}, Co^{2+}, Ag^{+}, and I_2, to facilitate the oxidative coupling of the substrates **13′** and **13″**, but obtained no fruitful results.

Scheme 2. Attempted Oxidative Coupling



Instead of using an oxidative coupling approach, we anticipated that a redox-neutral coupling reaction between indole 2-iodide and ketoester subunits might give the desired cyclization product **14′**.[18] Following the procedure used for the synthesis of **13′**, the iodoketoester **13** was obtained in 80% yield over two steps (Scheme 3). Having efficient access to the necessary iodoketoester **13**, several transition-metal catalysts were probed. Pleasingly, subjecting the iodoketoester **13** to CuI in DMSO at room temperature yielded (82%) the desired cyclization product **14**, which existed exclusively in its enol form. One recrystallization increased the ee to 99%.[19] As far as we know, this CuI-catalyzed coupling is the first between a 2-iodoindole and a ketoester to generate a tetrahydroazocine cycle.[18d] To our delight, a high pressure of H_2 gas over Pd/C

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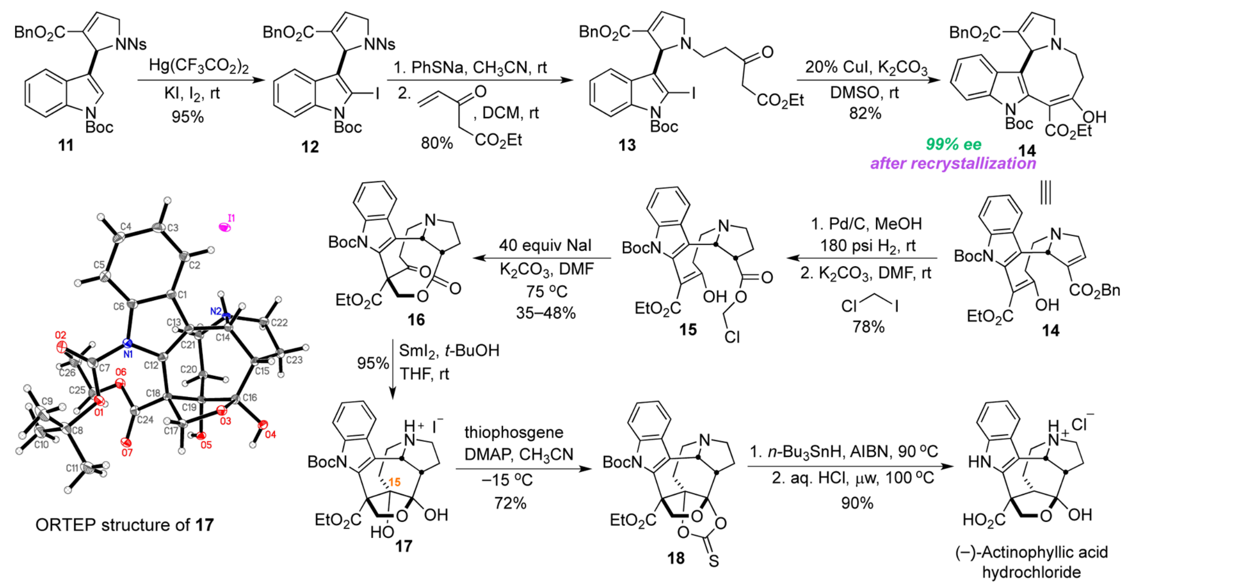
Scheme 3. Synthesis of (−)-Actinophyllic Acid Hydrochloride



formed the cis hydrogenation product along with deprotection of the benzyl group in one pot. Exchanging the solvent to DMF and treating the resulting carboxylic acid with chloroiodomethane and K_2CO_3 readily manufactured the chloromethyl ester **15** in 78% yield for the two steps. After significant experimentation, we found that 40 equiv of NaI in DMF with K_2CO_3 as base furnished the lactone **16** in 35−48% yield. Although modestly yielded, this alkylative lactonization framed another challenging eight-membered tetrahydrooxocine portion of (−)-actinophyllic acid and set the stage for the final azepane segment, and concomitant tetrahydrofuran part, formation through intramolecular ketone−lactone pinacol coupling. The pinacol coupling strategy departs significantly from the lactol formation approach adopted by Overman and Martin.

Continuing with the synthetic venture, we evaluated the effects of several single-electron-transfer reagents, including Ti^{3+}, Li, Na, and Sm^{2+}, on the pinacol coupling.[20] Only SmI_2 combined with 10 equiv of *t*-BuOH provided the desired coupling product **17**, in quantitative yield; its structure was confirmed through X-ray crystallographic analysis.[21] At this stage, the complete heavy atom arrangement of (−)-actinophyllic acid was in place. What remained was regioselective removal of the hindered C15 hydroxyl group from compound **17**.

To this end, we turned our attention to radical dehydroxylation.[22] The idea was that the thiocarbonate **18**, when treated with a tributyltin radical, would undergo homolytic cleavage of the tertiary carbon−oxygen bond preferably, due to electronic differentiation (the rigid multicyclic framework of actinophyllic acid would not allow the necessary stereoelectronic alignment of the lone pair of electrons on the tetrahydrofuran oxygen with the ensuing α-radical). The dihydroxy compound **17** was reacted with thiophosgene in the presence of DMAP at −15 °C, transforming into the thionocarbonate **18** in 72% yield. The standard conditions of *n*-Bu_3SnH and AIBN at 90 °C in toluene worked efficiently to furnish the desired lactol product. Finally, global deprotection, through the effect of aqueous HCl under microwave heating at 100 °C for 30 min, furnished (−)-actinophyllic acid hydrochloride in 90% yield over two steps $\{[\alpha]_{589}^{22.8}$ −175.8° (*c* 1.0, MeOH)}. The spectral data of our synthetic sample matched those reported in the literature.[5]

In conclusion, we have successfully completed a catalytic asymmetric total synthesis of (−)-actinophyllic acid in 13 steps from a known aldehyde in 12.4% yield. Our synthesis exhibits several salient features: (i) chiral phosphine-catalyzed [3 + 2] annulation between an allenoate and an indole imine; (ii) CuI-catalyzed coupling between a 2-iodoindole and a ketoester to assemble a hexahydro-1*H*-azocino[4,3-*b*]indole system; (iii) intramolecular alkylative lactonization to form a tetrahydrooxocine ring; (iv) highly efficient pinacol coupling between a ketone and a lactone to form the caged scaffold of (−)-actinophyllic acid; and (v) regioselective removal of a tertiary alcohol by taking advantage of a vicinal hemiketal. Our strategy not only circumvented the difficulties typically associated with forming the correct stereochemistry around the pyrrolidine ring but also resulted in the first enantioselective total synthesis of (−)-actinophyllic acid in which the asymmetric synthesis employs the same starting materials as the racemic synthesis.[6] Detailed screening of the biological activity of (−)-actinophyllic acid is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00567.

Experimental details and data (PDF)
Crystallographic data for **16**(CIF)
Crystallographic data for **17** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) A weak base (e.g., K_2CO_3), a weak acid (e.g., *p*-TSA), or neutral conditions (e.g., $NaBH_3CN$ or PhSNa) could induce the epimerization.

(11) Both chiral phosphines are commercially available from Sigma-Aldrich. Phosphine A: catalog no. L512397; phosphine B: catalog no. L512478.

(12) After removing the crystalline racemic pyrroline **11**, we could enrich the ee of the mother liquid up to 94%.

(13) See the Supporting Information for further details regarding optimization of the conditions.

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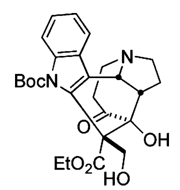
(21) More than 10 equiv of *t*-BuOH slowed down the reaction and necessitated the use of increased amounts of SmI_2, and <10 equiv of *t*-BuOH resulted in formation of the following rearrangement side product:



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