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Total Synthesis of (±)- and (−)-Actinophyllic Acid

Connor L. Martin, Larry E. Overman,* and Jason M. Rohde†

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025

Received January 14, 2010; E-mail: leoverma@uci.edu

Abstract: Development of efficient sequences for the total syntheses of (±)-actinophyllic acid (*rac*-**1**) and (−)-actinophyllic acid (**1**) are described. The central step in these syntheses is the aza-Cope/Mannich reaction, which constructs the previously unknown hexacyclic ring system of actinophyllic acid in one step from much simpler tetracyclic precursors. The tetracyclic hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ketone *rac*-**37** is assembled from *o*-nitrophenylacetic acid in four steps, with oxidative cyclization of a dienolate derivative of tricyclic precursor *rac*-**35** being the central step. In the first-generation synthesis, this intermediate is transformed in two steps to homoallyl amine *rac*-**43**, whose formaldiminium derivative undergoes efficient aza-Cope/Mannich reaction to give pentacyclic ketone *rac*-**44**. In four additional steps, this intermediate is advanced to (±)-actinophyllic acid. The synthesis is streamlined by elaborating ketone *rac*-**37** to β-hydroxyester intermediate *rac*-**53**, which is directly transformed to (±)-actinophyllic acid upon exposure to HCl and paraformaldehyde. This concise second-generation total synthesis of (±)-actinophyllic acid is realized in 22% overall yield from commercially available di-*tert*-butyl malonate and *o*-nitrophenylacetic acid by a sequence that proceeds by way of only six isolated intermediates. The first enantioselective total synthesis of (−)-actinophyllic acid (**1**) is accomplished by this direct sequence from tricyclic keto malonate (*S*)-**35**. Catalytic enantioselective reduction of α,β-unsaturated ketone **66** is the key step in the preparation of intermediate (*S*)-**35** from the commercially available Boc-amino acid **65**. Discussed also is the possibility that the aza-Cope/Mannich reaction might be involved in the biosynthesis of (−)-actinophyllic acid.

Introduction

Thrombotic diseases are a major cause of mortality and morbidity in the developed world. In healthy individuals, a complex network of enzymatic processes carefully regulates the balance between blood clotting and blood thinning.[1] Inhibition of activated thrombin-activatable fibrinolysis inhibitor (TAFIa), an unstable zinc-dependent carboxypeptidase, is a promising approach toward upregulating fibrinolysis, the process whereby small blood clots are removed from circulation.[2,3] In a screening program designed to discover natural product inhibitors of TAFIa, 40000 extracts from Australian plants and marine organisms were screened by Carroll and co-workers, initially leading to the identification of promising extracts from the tree *Alstonia actinophylla*, growing on the Cape York Peninsula, Far North Queensland.[4] Ultimately, a new indole alkaloid, (−)-actinophyllic acid (**1**, Figure 1), was identified from this source as a potent inhibitor in the coupled enzyme assay TAFIa/hippuricase ($IC_{50} = 0.84\ \mu M$).

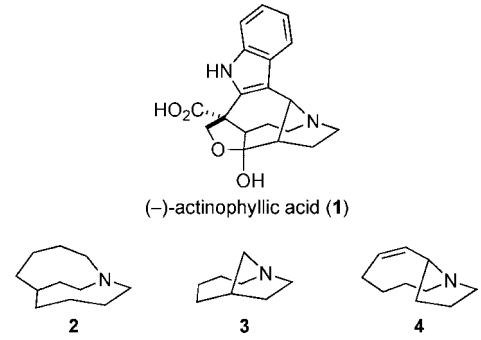


Figure 1. Structure of (−)-actinophyllic acid and its three unique fragments.

The carbon connectivity and relative configuration of actinophyllic acid (**1**) were determined largely by detailed NMR analysis.[4] The 2,3,6,7,9,13c-hexahydro-1*H*-1,7,8-(methanetriyloxymethano)pyrrolo[1′,2′:1,2]azocino[4,3-*b*]indole-8(5*H*)-carboxylic acid skeleton[5] of actinophyllic acid is unique among natural products. Moreover, the simpler 1-azabicyclo[4.4.2]dodecane (**2**), 1-azabicyclo[4.2.1]nonane (**3**), and octahydropyrrolo[1,2-*a*]azocine (**4**) fragments that define its structure are found in no other indole alkaloids. The absolute configuration depicted in structure **1** for (−)-actinophyllic acid was advanced on the basis of its proposed biogenesis from precondylocarpine via a novel

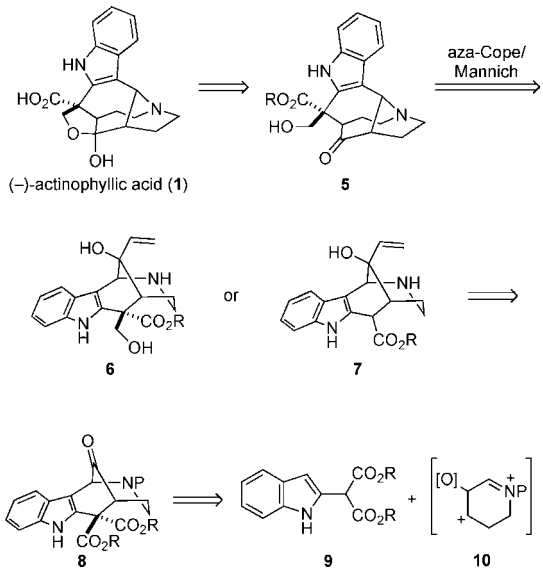
† Current address: Ironwood Pharmaceuticals, Inc., 320 Bent Street, Cambridge, MA 02141.

(1) Cesarman-Maus, G.; Hajjar, K. A. *Br. J. Hamaetol.* **2005**, *129*, 307–321.
(2) For reviews of the role of TAFIa in fibrinolysis, see: (a) Leurs, J.; Hendriks, D. *Thromb. Haemost.* **2005**, *94*, 471–487. (b) Willemse, J. L.; Hendriks, D. F. *Front. Biosci.* **2007**, *12*, 1973–1987. (c) For a review of small molecule inhibitors of TAFIa, see: (d) Bunnage, M. E.; Owen, D. R. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 480–486.
(3) Also known as carboxypeptidase U or plasma carboxypeptidase B.
(4) Carroll, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. *J. Org. Chem.* **2005**, *70*, 1096–1099.

(5) This ring system is named differently in *Chemical Abstracts*: 2,3,3a,4,8,12c-hexahydro-4-hydroxy-1,4,7-[1]propanyl[3]ylidene-1*H*-pyrrolo[2′,3′:6,7]oxocino[4,5-*b*]indole-7(6*H*)-carboxylic acid.

10.1021/ja100178u

Scheme 1. Retrosynthetic Analysis of Actinophyllic Acid



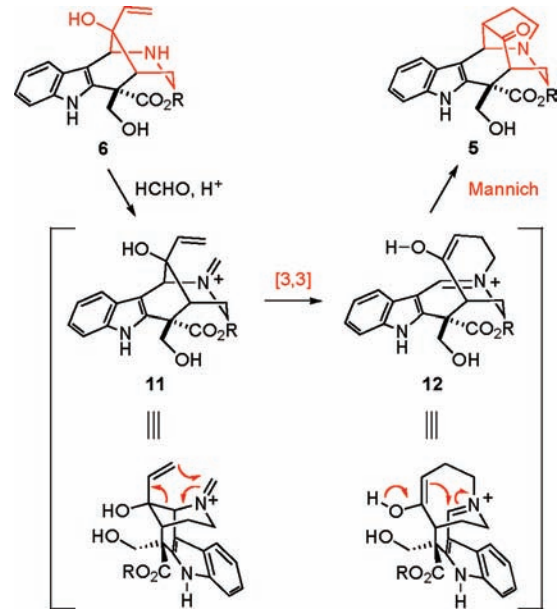
biogenetic pathway.[4] Rigorous definition of the absolute configuration of (−)-actinophyllic acid (**1**) by spectroscopic and computational methods[6] was realized only after this laboratory completed the first total synthesis of (±)-actinophyllic acid in 2008.[7]

We describe in this paper the development of an efficient strategy for assembling the ring system of actinophyllic acid, which culminated in the first total synthesis of this unique alkaloid. A simplification of the later stages of this sequence leading to an improved second-generation total synthesis of (±)-actinophyllic acid is also reported. In addition, the first enantioselective total synthesis of (−)-actinophyllic acid (**1**), which confirms the spectroscopic assignment of its absolute configuration, is disclosed.[8] The possibility that the aza-Cope/Mannich reaction is involved in the biosynthesis of natural products is considered and a potential biosynthetic route to actinophyllic acid is proposed.

Results and Discussion

Synthesis Plan. The retrosynthetic analysis that guided our efforts to prepare (−)-actinophyllic acid (**1**) is outlined in Scheme 1. Disconnecting the tetrahydrofuran ring at the hemiketal C−O bond reveals pentacyclic ketone **5**. This intermediate contains a 3-acylpyrrolidine unit, which suggests its potential formation by aza-Cope/Mannich rearrangement of formaldiminium ions derived from hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole precursors such as **6** or **7**.[9] Of these possibilities, the postulated transformation of intermediate **6** to **5** is particularly attractive as actinophyllic acid would result directly. If the relative configuration of the ester and hydroxymethyl side chains of precursor **6** could not be established in an efficient fashion, an alternate possibility would be to carry out

Scheme 2. Pivotal Aza-Cope/Mannich Rearrangement Step



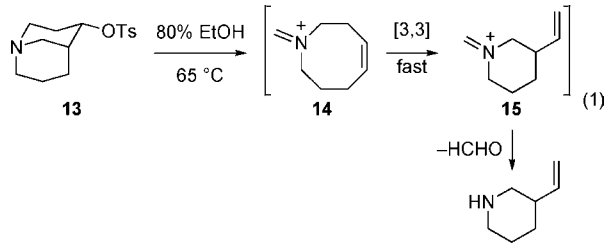
the aza-Cope/Mannich transformation with precursor **7**, and subsequently elaborate the product to intermediate **5** by reaction of an ester or acid enolate with formaldehyde. Disconnecting the allylic alcohol intermediates **6** and **7** identifies tetracyclic ketone **8** as an important subgoal of our synthesis plan.

The pivotal aza-Cope/Mannich rearrangement step of our projected synthesis plan is analyzed in more detail in Scheme 2. Although this reaction had not been employed previously to transform a 3-vinylpiperidine to a 1-azabicyclo[4.2.1]nonan-5-one (atoms highlighted in red in Scheme 2), the prospects for success appeared good. Molecular modeling of intermediates such as **11** showed that the overlap between the vinyl and iminium fragments, although far from ideal, was comparable to that of several other successful aza-Cope/Mannich processes.[9,10]

Moreover, there was evidence from early studies of Grob and co-workers that the proposed cationic aza-Cope rearrangement step, **11** → **12** (Scheme 2**)**, would likely take place readily.[11] Specifically, they had shown that solvolytic Grob-fragmentation of tosylate **13** generated largely 4-azocine iminium ion **14**, which was transformed rapidly to the 3-vinylpiperidine iminium ion **15** (eq 1). By the principle of microscopic reversibility, the reverse transformation, as postulated in the conversion of intermediate **11** to **12**, should be possible. That the equilibrium of the proposed iminium ion isomers likely lies on the side of the 3-vinylpiperidine isomer should be of no concern, as a stereoelectronically favorable intramolecular Mannich reaction would be expected to capture iminium ion isomer **12** in the postulated aza-Cope/Mannich transformation.

The hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system of intermediate **8** is a structural feature of several indole alkaloid families and the ring system of the uleine alkaloids.[12] As a result, a number of methods for assembling this tetracyclic

(6) Taniguchi, T.; Martin, C. L.; Monde, K.; Nakanishi, K.; Berova, N.; Overman, L. E. *J. Nat. Prod.* **2009**, *72*, 430–432.
(7) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569.
(8) For progress toward the total synthesis of actinophyllic acid by a different approach, see: Vaswani, R. G.; Day, J. J.; Wood, J. L. *Org. Lett.* **2009**, *11*, 4532–4535.
(9) (a) Overman, L. E.; Humphreys, P. G.; Welmaker, G. S. *Org. React.* **2010**, *75*, in press. (b) Overman, L. E. *Tetrahedron* **2009**, *65*, 6432–6446.
(10) Brüggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284–15285.
(11) Grob, C. A.; Kunz, W.; Marbet, P. R. *Tetrahedron Lett.* **1973**, *16*, 2613–2616.
(12) *The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; The Chemistry of Heterocyclic Compounds; Wiley: New York, 1983; Vol. 25, Part 4.

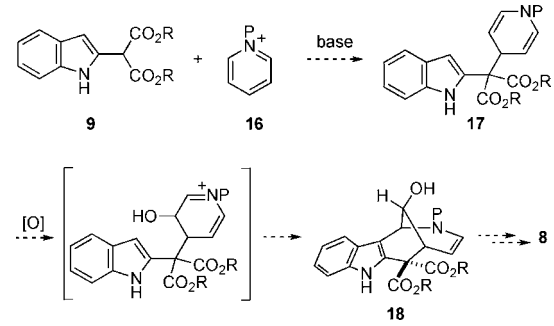


scaffold have been developed.[13,14] Particularly attractive to us was a new construction in which intermediate **8** would be assembled from two fragments of similar complexity: an indole-2-malonate (**9**) and a six-membered, azacyclic synthon having electrophilic sites for bond construction at C2 and C4.

Several aspects of the plan adumbrated in Scheme 1 warrant additional comment. The aza-Cope/Mannich disconnection is highly productive because this transformation, if successful in the synthetic direction, would construct the previously unknown hexacyclic ring system of actinophyllic acid in one step from a much simpler tetracyclic precursor. However, this strategy is not without significant risk. Besides deferring the pivotal aza-Cope/Mannich step to a late stage of the synthesis,[15] intermediate **8**, and later ones derived from this structure, contain a potentially labile gramine fragment that could result in unraveling of the piperidine ring. At the outset, we hoped that we could arrive at intermediate **8** by a sufficiently direct sequence that these key issues could be addressed relatively quickly in our experimental studies.

Total Synthesis of (±)-Actinophyllic Acid. Attempted Formation of the 2,5,6,7-Tetrahydro-1,5-methano-1*H*-azocino[4,3-*b*]-indole Ring System by Sequential Pyridinium Ion Alkylation/Pictet−Spengler-Type Cyclization. One of our early attempts to assemble the hydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system followed the general approach to this ring system developed by Bosch and co-workers.[16] We envisioned constructing tetracyclic ketone intermediate **8** by the sequence enunciated in Scheme 3. Intermediate **17** would arise from addition of the conjugate base of indole malonate **9** to C4 of pyridinium salt **16**.[17] Oxidation of one of the prochiral double bonds of the dihydropyridine fragment of this adduct could

Scheme 3. Initial Plan for Preparing a Tetracyclic Precursor from an Indole-2-malonate and a Pyridinium Salt



potentially promote intramolecular attack by the pendant indole with introduction of an oxygen substituent on the resulting one-carbon bridge of the product.

To pursue this potential construction of tetracyclic ketone **8**, dimethyl indole-2-malonate (**19**)[18,19] was deprotonated with 1.2 equiv of a variety of strong bases [LDA, NaHMDS, KHMDS or $BrMgN(i\text{-}Pr)_2$] in THF at temperatures between 0 and −78 °C,[20] and the resulting anion was allowed to react at −78 °C with the pyridinium salt generated in situ from the reaction of pyridine with 2,2,2-trichloroethyl chloroformate (Troc-Cl).[21] Product **20** resulting from the addition of the malonate side chain to C4 of the pyridinium salt was never observed. The major product produced in these reactions, adduct **21**, resulted from coupling at the 3-position of the indole malonate nucleophile. When the bromomagnesium salt of indole-2-malonate **19** was used, adduct **21** was formed in high yield (Scheme 4).

As an alternative approach, we investigated the reaction of a less-basic anion generated from α-keto malonate **22**[18] with several pyridinium salts, with the goal of forming the indole following the contruction of the azabicyclo[3.2.1]octane ring system (Scheme 5). The initial condensation was most efficient with the in situ generated *N*-triflylpyridinium triflate salt,[22] giving product **23** in excellent yield. However, attempted epoxidation of the *N*-sulfonylenamine functionality of adduct **23** with a variety of oxidants (DMDO, *m*-chloroperbenzoic acid,

(13) For representative examples of syntheses of the hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system, see: (a) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, *19*, 2738–2747. (b) Büchi, G.; Gould, S. J.; Näf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492–2501. (c) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683–3694. (d) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70–78. (e) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939–3951. (f) Micouin, L.; Diez, A.; Castells, J.; López, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1693–1696. (g) Blechert, S.; Knier, R.; Schroers, H.; Wirth, T. *Synthesis* **1995**, 592–604. (h) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765–766. (i) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158–3175. (j) Ergün, Y.; Patir, S.; Okay, G. *J. Heterocycl. Chem.* **2002**, *39*, 315–317. (k) Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534–3538. (l) Ishikura, M.; Takahashi, N.; Takahashi, H.; Yanada, K. *Heterocycles* **2005**, *66*, 45–50. (m) Uludag, N.; Hökelek, T.; Patir, S. *J. Heterocycl. Chem* **2006**, *43*, 585–591. (n) Bennasar, M.-L.; Roca, T.; García-Díaz, D. *J. Org. Chem.* **2008**, *73*, 9033–9039.

(14) For a review that covers the synthesis of uleine alkaloids, see: Alvarez, M.; Joule, J. A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 57, pp 247−258.

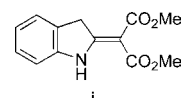
(15) Our motivations for pursuing such potentially high-risk strategies are discussed briefly in ref 9b.

(16) (a) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156–1168. (b) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587–596.

(17) For reviews, see: (a) Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789–824. (b) Comins, D. L.; Joseph, S. P. Alkaloid Synthesis Using 1-Acylpyridinium Salts as Intermediates. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI: Greenwich, CT, 1996; Vol. 2, pp 251−294.

(18) Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034–2041.

(19) Indole-2-malonate **19** contains variable amounts (8−94%) of the indolin-2-ylidene tautomer **i** depending upon the method employed to purify this intermediate. Purification by recrystallization gives the indole tautomer predominantly, whereas purification by column chromatography gives **i** as the major tautomer.[18] For simplicity, these structures are depicted only in their indole form. In cases where we have examined the issue, we have not observed differences in reaction outcome depending upon tautomer composition.



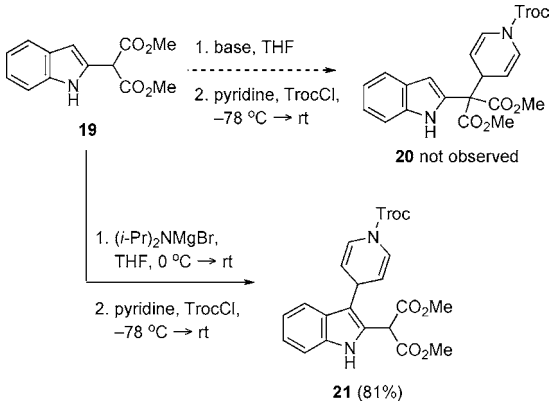
i

(20) In DMSO, the pK_a's of indole and dimethyl malonate are 21.0 and 15.9, respectively: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. (b) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.

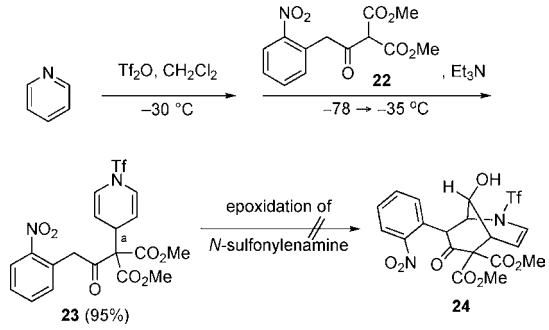
(21) Akiba, K.; Nishihara, Y.; Wada, M. *Tetrahedron Lett.* **1983**, *24*, 5269–5272.

(22) Corey, E. J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535–5537.

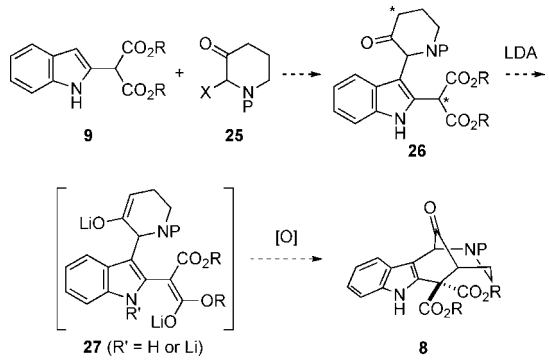
Scheme 4. Addition of Conjugate Bases of Indole-2-malonate **19** to a 1-Acyloxypyridinium Salt



Scheme 5. Addition of Tricarbonyl Intermediate **22** to a 1-(Trifluoromethanesulfonyl)pyridinium Salt



Scheme 6. Revised Plan for Preparing Ketone **8** by Intramolecular Oxidative Dienolate Coupling



Shi's dioxirane[23]) did not lead to the formation of tetracyclic product **24**. The major mode of reactivity observed under most of the conditions examined was fragmentation of bond *a* of adduct **23** to regenerate keto malonate **22**.

Formation of the Keto-Bridged Hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole Ring System by Intramolecular Oxidative Dienolate Coupling. The observation that anions derived from indole malonate **19** reacted with electrophiles at C3 of the indole suggested that the order of bond formation in the construction of hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ketone **8** be reversed (Scheme 6). In such a sequence, coupling of the indole malonate with a six-membered iminium electrophile, in the ideal case one derived from a precursor such as **25** that incorporates a carbonyl group at C3, would deliver adduct **26**. The hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system would then be fashioned by bond formation between the starred carbons of intermediate **26**. One possibility we envisioned for this bond construction was oxidative coupling of a dienolate intermediate such as **27**.

The formation of C−C bonds by oxidative coupling of enolates generated from ester, ketone, and carboxylate precursors has a long history.[24,25] Throughout the 1970s and 1980s, intramolecular oxidative couplings of dienolates to form three-, four-, five-, and six-membered rings were disclosed,[26] as was the intramolecular couplings of enolates derived from two different functional groups.[27] Nonetheless, this C−C bond-forming method has received only modest attention for the construction of more elaborate structures such as polyfunctional natural products.[28] Three impressive examples from the Paquette, Cohen, and Baran laboratories are summarized in Scheme 7.[29] Absent from existing precedent was the intramolecular coupling of malonate and ketone enolates, as well as a demonstration that an unprotected indole might survive such a sequence. Nonetheless, because of the potential brevity of the synthetic sequence postulated in Scheme 6, we were drawn to examine the prospect that tricarbonyl intermediates such as **26** could be transformed directly to 1,5-methanoazocino[4,3-*b*]indole ketone **8**.

The short sequence for assembling 1,5-methanoazocino[4,3-*b*]indole ketones **36** and **37** that ultimately resulted from these studies is summarized in Scheme 8. The synthesis begins with acylation of the methoxymagnesium salts of dimethyl (**28**) or di-*tert*-butyl malonate (**29**) with acid chloride **30**, to give keto malonates **22**[18] and **31** in good yields. On small scales, dimethyl intermediate **22** could be transformed to indole dimethyl malonate **19** in a yield of 62% by catalytic hydrogenation over $Pd(OH)_2/C$ in methanol.[18] However, over multiple runs we found the yields of indole malonates **19** and **32** to be irreproducible using this procedure. These reactions suffered from formation of variable amounts of *N*-hydroxyindole products, which underwent reduction of the N−O bond only slowly. Forcing conditions, such as elevated reaction temperatures or high catalyst loadings, did lead to reduction of the N−O bond; however, these conditions also promoted competitive reduction of the indole C2−C3 double bond. Difficulties in optimizing

(23) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.

(24) Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76–78.

(25) For a recent historical summary and leading references, see: (a) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S *J. Am. Chem. Soc.* **2007**, *129*, 12857–12869. (b) For a brief review, see: Csákÿ, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313–320.

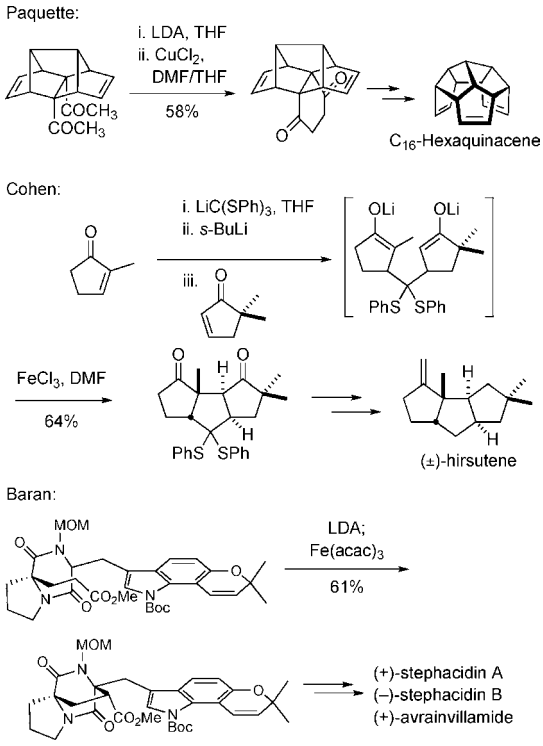
(26) (a) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487–1493. (b) Kobayashi, Y.; Taguchi, T.; Morikawa, T. *Tetrahedron Lett.* **1978**, *19*, 3555–3556. (c) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *Chem. Pharm. Bull.* **1980**, *28*, 262–267. (d) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125–1127. (e) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462–3464.

(27) (a) Kawabata, T.; Sumi, K.; Hiyama, T. *J. Am. Chem. Soc.* **1989**, *111*, 6843–6845. (b) Kawabata, T.; Minami, T.; Hiyama, T. *J. Org. Chem.* **1992**, *57*, 1864–1873.

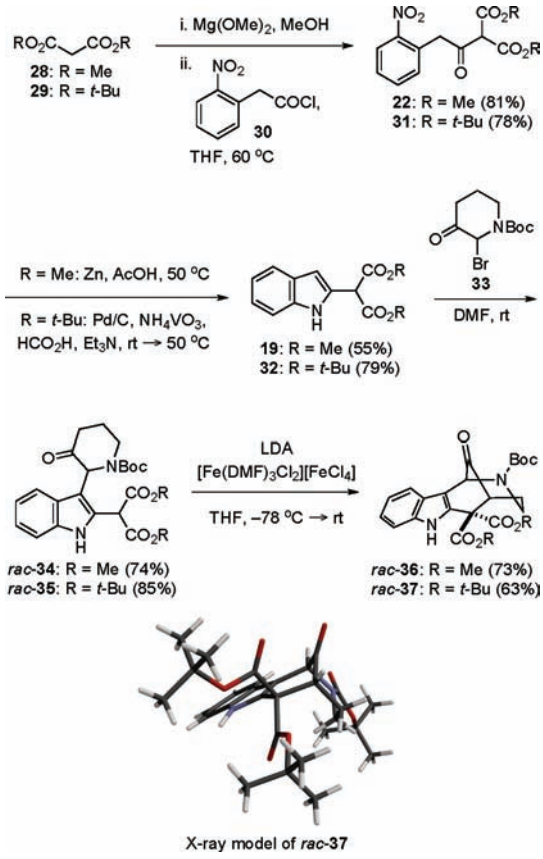
(28) For an early example, see Hendrickson, J. B.; Rees, R.; Göschke, R. *Proc. Chem. Soc.* **1962**, 383.

(29) (a) Paquette, L. A.; Snow, R. A.; Muthard, J. L.; Cynkowski, T. *J. Am. Chem. Soc.* **1978**, *100*, 1600–1602. (b) Ramig, K.; Kuzemko, M. A.; McNamara, K.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1968–1969. (c) Cohen, T.; McNamara, K.; Kuzemko, M. A.; Ramig, K.; Landi, J. J., Jr.; Dong, Y. *Tetrahedron* **1993**, *49*, 7931–7942. (d) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606–609. (e) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

Scheme 7. Selected Examples of Intramolecular Oxidative Enolate Couplings Used in Complex Molecule Syntheses



Scheme 8. Synthesis of Hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole Ketones **36** and **37**



the $Pd(OH)_2/C$ reduction prompted us to investigate alternative methods for reducing the nitro group of intermediates **22** and **31**. In the dimethyl series, simply carrying out the reaction with excess zinc in acetic acid at 50 °C delivered indole malonate **19** reliably in 48−55% yield.[30] However, this procedure was problematic in the di-*tert*-butyl ester series, particularly in large-scale runs wherein the reaction exotherm was difficult to control. In these cases, zinc and acetic acid reduction gave product **32** contaminated with various amounts of *tert*-butyl 2-indoleacetate. After examining several alternative procedures, we finally found that transfer hydrogenation over Pd/C in a 2:1 mixture of formic acid and triethylamine in the presence of catalytic amounts of ammonium metavanadate at 50 °C promoted reproducible transformation of keto malonate **31** to indole di-*tert*-butyl malonate **32** in 74−79% yield.[31] In the absence of NH_4VO_3, the reaction rapidly produced a mixture of the desired indole malonate **32** and the corresponding *N*-hydroxyindole, which was slow to undergo further reduction. Inclusion of a catalytic amount of NH_4VO_3 accelerated reduction of the hydroxyindole.[32]

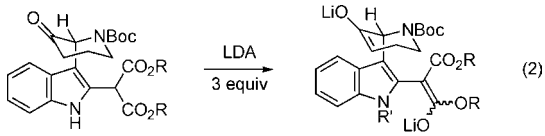
We next examined methods for joining indole malonate and piperidone fragments. We soon found that the desired transformation could be accomplished by simply allowing the indole to react at room temperature in *N*,*N*-dimethylformamide (DMF) with crude bromopiperidone **33**, a reactant readily generated by radical bromination of commercially available 1-*tert*-butoxycarbonyl-3-piperidone.[33] This condensation was carried out on multigram scale to provide indole piperidones *rac*-**34** and *rac*-**35** in 74% and 85% yield, respectively. Presumably the highly reactive *N*-acyloxy-*C*-acyliminium cation generated by ionization of bromide **33** is an intermediate in this coupling step.[34]

With convenient access to keto malonates *rac*-**34** and *rac*-**35** in hand, we turned to examine the intramolecular oxidative coupling of dienolates generated from these intermediates. In early studies carried out largely with dimethyl malonate precursor *rac*-**34**, we surveyed several bases including lithium diisopropylamide (LDA), lithium hexamethyldisilazide, and potassium hexamethyldisilazide, along with various metal oxidants including ferrocenium hexafluorophosphate, iron(III) chloride, iron(III) acetylacetonate, $[Fe(DMF)_3Cl_2][FeCl_4]$, Cu(II) 2-ethylhexanoate, and Cu(II) chloride. The best results were obtained with a combination of LDA and $[Fe(DMF)_3Cl_2][FeCl_4]$, a complex simply formed by combining $FeCl_3$ with DMF.[35] Deprotonation of indole piperidone *rac*-**34** or *rac*-**35** with 3.2 equiv of LDA in tetrahydrofuran (THF) at −78 °C followed by adding a THF solution of 3.5 equiv of $[Fe(DMF)_3Cl_2][FeCl_4]$ and allowing the reaction to warm to room temperature over 60−90 min provided crystalline tetracyclic ketones *rac*-**36** (68−73% yield) or *rac*-**37** (60−63% yield) on scales up to 10 g.

(30) The major byproduct under these conditions is 2-oxindole.
(31) This procedure is a modification of Heck's procedure for transfer hydrogenation with triethylammonium formate. For the original procedure, see: Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926–4931.
(32) For the use of NH_4VO_3 as a promotor in the catalytic hydrogenation of nitroarenes, see: Baumeister, P.; Blaser, H.-U.; Studer, M. *Catal. Lett.* **1997**, *49*, 219–222.
(33) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700–709.
(34) For the closest precedent of which we are aware, see: Whitlock, C. R.; Cava, M. P. *Tetrahedron Lett.* **1994**, *35*, 371–374.
(35) For the use of this oxidant in phenolic couplings, see: (a) Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc.* **1972**, *94*, 309–310. For the use of $FeCl_3$ in DMF for oxidative coupling of enolates, see, inter alia (b) Frazier, R. H.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408–5411. (c) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277–7283. (d) Poupart, M.-A.; Paquette, L. A. *Tetrahedron Lett.* **1988**, *29*, 269–272, and refs 29b and 29c.

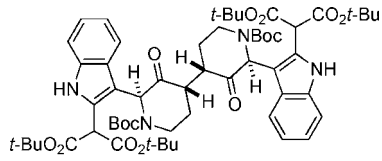
Single-crystal X-ray analysis of *rac*-**37** confirmed the 1,5-methanoazocino[3,4-*b*]indole structure of this product.[36a]

Although mechanistic details of this oxidative cyclization have not been examined thoroughly, several aspects merit mention. To avoid destabilizing $A^{1,3}$ interactions between the indole and *tert*-butoxycarbonyl (Boc) groups,[37] the piperidine ring of the piperidone indole malonate precursors should exist in a conformation, **38**, in which the indole moiety is axial, thus positioning the methine hydrogen adjacent to the indole orthogonal to the π-bond of the carbonyl group (eq 2). For this reason, we anticipated that regioselection in the deprotonation of the 3-piperidinone at the methylene carbon would be high. As the yields of the cyclized products *rac*-**36** and *rac*-**37** were reduced significantly if only 2.2 equiv of LDA were employed, it is possible that the indole of **38** is also converted to its conjugate lithium base.[38] However, it is also plausible that the third equivalent of LDA deprotonates the indole of the cyclized product as it forms.



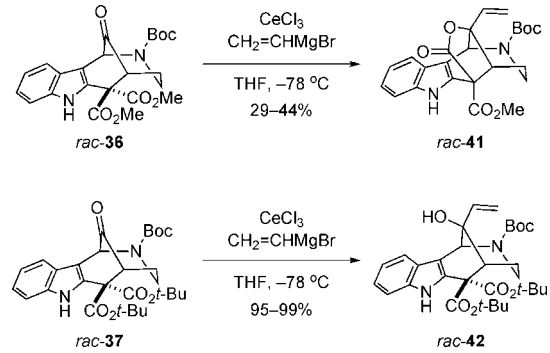
38 **39** (R′ = Li or H)

A major byproduct produced under the reaction conditions of the oxidative dienolate cyclization of precursor *rac*-**35** is a symmetrical homodimer resulting from coupling at the methylene carbon adjacent to the piperidone carbonyl group, *rac*-**40**. Although a solid, we have thus far been unable to obtain single crystals to allow its structure to be fully established. Nonetheless, its relative configuration can be assigned, because the same dimer is produced as a byproduct in the oxidative dienolate coupling of enantioenriched (*S*)-**35** (see below).[39] In the enantiomerically enriched series, the only symmetrical dimers that could result would have C_2-symmetry, of which two are possible. The C_2-symmetric dimer assigned as *rac*-**40** would result from dimerization of intermediate **39** from the face of the piperidone enolate opposite to the quasi-axial indole fragment. Fortunately, the yield of the dimer decreased as the oxidative coupling reaction was carried out at higher concentration.[40]



rac-**40**

Scheme 9. Vinylation of Ketones *rac*-**36** and *rac*-**37**



rac-**36** *rac*-**41** *rac*-**37** *rac*-**42**

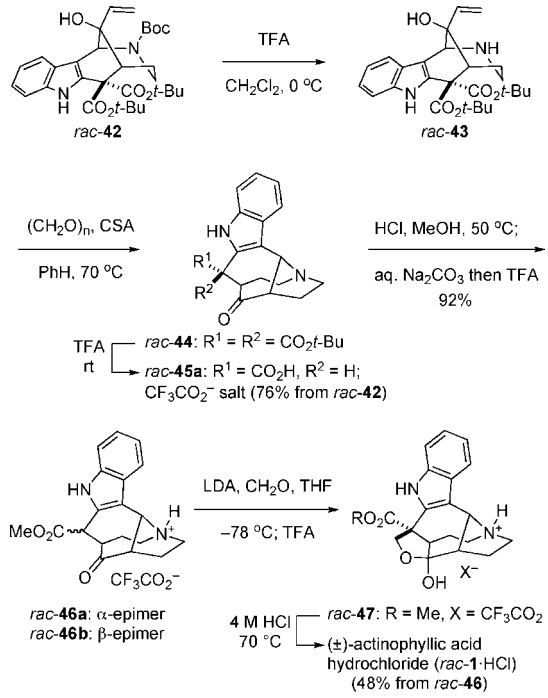
First-Generation Synthesis of (±)-Actinophyllic Acid (*rac*-1). The next step in advancing tetracyclic ketones *rac*-**36** and *rac*-**37** to (±)-actinophyllic acid was introduction of a vinyl group from the *Re* face of the carbonyl group (Scheme 9). It was anticipated that the proximal ester substituents, particularly in the *tert*-butyl ester series, would shield the *Si* faces of the ketones during addition of a vinyl nucleophile (see the X-ray model in Scheme 8). Vinyllithium and vinylmagnesium bromide did not add to ketones *rac*-**36** or *rac*-**37** at −78 °C in THF and produced complex product mixtures at higher temperatures. However, premixing these ketones with anhydrous cerium(III) chloride in THF, followed by addition of vinylmagnesium bromide at −78 °C, did bring about addition to the ketone carbonyl group.[41] In the dimethyl series, this reaction resulted in formation of lactone *rac*-**41** (IR 1790 cm^{-1}) in 29−44% yield, with 22−30% of the starting ketone recovered. Under the same conditions, di-*tert*-butyl ketone precursor *rac*-**37** was converted solely to allylic alcohol *rac*-**42** in nearly quantitative yield. Both the lactone and allylic alcohol products were viewed as viable intermediates in route to (±)-actinophyllic acid (*rac*-**1**). We chose to investigate elaboration of allylic alcohol *rac*-**42** first.

The first sequence developed to elaborate intermediate *rac*-**42** to (±)-actinophyllic acid (*rac*-**1**) is summarized in Scheme 10. Reaction of allylic alcohol *rac*-**42** with trifluoroacetic acid (TFA) at 0 °C selectively cleaved the Boc group to deliver, after aqueous base workup, amino alcohol *rac*-**43** in high yield. This intermediate was not purified but immediately allowed to react with 1 equiv of paraformaldehyde and a catalytic amount of camphorsulfonic acid (CSA) in benzene at 70 °C to promote aza-Cope/Mannich transformation to yield pentacyclic keto diester *rac*-**44**. Exposure of this crude product to neat TFA at room temperature gave the amino acid trifluoroacetate salt *rac*-**45a** as a single stereoisomer in 76% overall yield from *rac*-**42**. Fischer esterification of this amino acid, followed by counterion exchange delivered amino ester trifluoroacetate salt *rac*-**46** as a 2:1 mixture of α and β ester epimers in 92% yield. For characterization purposes, these methyl ester epimers could be separated by HPLC.[42]

The total synthesis (±)-actinophyllic acid (*rac*-**1**) was then completed in two additional steps. Deprotonation of the 2:1 mixture of α and β ester epimers *rac*-**46** with LDA at −78 °C, followed by addition of a THF solution of monomeric formal-

(36) Crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: (a) CCDC 701592; (b) CCDC 759087.
(37) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.
(38) Deuteration experiments showed that the malonate and α-methylene had been deprotonated. However, because of rapid exchange of the indole hydrogen under all the quenching conditions that we examined, no information about the fate of the indole hydrogen was obtained.
(39) This dimer is formed in 18% yield in cyclizations carried out at a substrate concentration of 0.08 M.
(40) (a) See the Supporting Information for more details. (b) Investigations into the mechanism of the oxidative cyclization of intermediate **35**, which hopefully will clarify the origin of this unexpected trend, are currently underway.
(41) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.
(42) The α-epimer, *rac*-**46a**, provided single crystals from methanol, allowing its constitution and relative configuration to be confirmed by X-ray analysis; however, diffraction data from these crystals was of insufficient quality to refine to high precision.

Scheme 10. Elaboration of Allylic Alcohol *rac*-**42** to (±)-Actinophyllic Acid Hydrochloride (*rac*-**1**·HCl)



dehyde,[43] gave largely one aldol adduct (diastereomer ratio, dr = 14−20:1), which was partially purified by reversed-phase chromatography to give (±)-actinophyllic acid methyl ester trifluoroacetate salt (*rac*-**47**).[44,45] Hydrolysis of this product with 4 M HCl and purification of the product by reversed-phase HPLC provided pure (±)-actinophyllic acid hydrochloride (*rac*-**1**·HCl) in 48% yield from amino ester *rac*-**46**.

The predominant formation of (±)-actinophyllic acid methyl ester from the aldol reaction of the lithium enolate of *rac*-**46** with formaldehyde is attributable to steric factors. As depicted in Figure 2, approach of formaldehyde from the *Re* (α) face of the enolate is hindered by the relatively bulky 2-carbon bridge (atoms *a* and *b*). In contrast, approach to the *Si* (*β*) face of the double bond is relatively free of obstruction, as the ketone bridge is small and tilted away from the π bond of the enolate.[46]

Purification of synthetic (±)-actinophyllic acid hydrochloride (*rac*-**1**·HCl) by HPLC, as reported for the natural product,[4] does not reproducibly give samples of (±)-actinophyllic acid (*rac*-**1)** that exhibit identical ^{1}H NMR spectra. Moreover, the ^{1}H NMR spectra in DMSO-d_6 of these samples does not precisely match those reported for natural **1** in this solvent. We ascribe these differences to samples of (±)-actinophyllic acid (*rac*-**1)** purified in this way containing variable small amounts of the conjugate acid. To confirm this supposition, incremental amounts of sodium methylsulfinylmethylide-d_5 were added to a sample of (±)-actinophyllic acid hydrochloride in DMSO-d_6, which resulted in substantial changes for several ^{1}H NMR resonances. When just less than 1 equiv of base was added, a ^{1}H NMR spectrum identical to that reported for natural **1** was obtained (see the Supporting Information). Unfortunately, a sample of natural actinophyllic acid is no longer available for direct comparison.[47a]

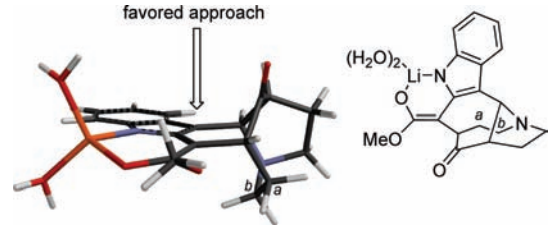
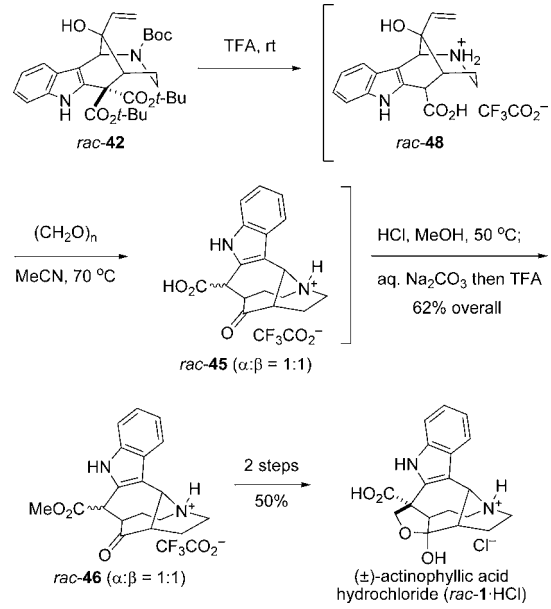


Figure 2. Rationale for stereoselection in the reaction between the ester enolate of *rac*-**46** and formaldehyde; for clarity, water molecules rather than THF are shown as ligands on lithium.

Scheme 11. Streamlined First-Generation Total Synthesis of (±)-Actinophyllic Acid



This first-generation total synthesis of (±)-actinophyllic acid hydrochloride (*rac*-**1**·HCl) could be streamlined by combining the four acid-catalyzed steps in the conversion of *rac*-**42** → *rac*-**46** into a single operation (Scheme 11). Reaction of allylic alcohol *rac*-**42** with neat trifluoroacetic acid at room temperature resulted in cleavage of the Boc group and the *tert*-butyl esters, promoting decarboxylation to provide amino acid salt *rac*-**48** as a single stereoisomer. Removal of trifluoroacetic acid in vacuo, dissolution of the crude residue in acetonitrile, addition of 1 equiv of paraformaldehyde, and heating at 70 °C for 3 h promoted aza-Cope/Mannich reorganization to the carboxylic

(43) (a) Schlosser, M.; Coffinet, D. *Synthesis* **1971**, 380–381. (b) We prepared monomeric formaldehyde by an improved procedure, see: Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

(44) These samples were contaminated with minor quantities of two inseparable byproducts (5−10% of each). We tentatively assign these compounds as the aldol product resulting from addition of formaldehyde from the α-face of the lithium ester enolate and an aldol product that incorporates an additional hydroxymethylene fragment attached to the nitrogen atom of the indole. These assignments were made on the basis of diagnostic peaks in the ^{1}H NMR spectra corresponding to hydroxymethylene fragments and on the basis of LRMS data.

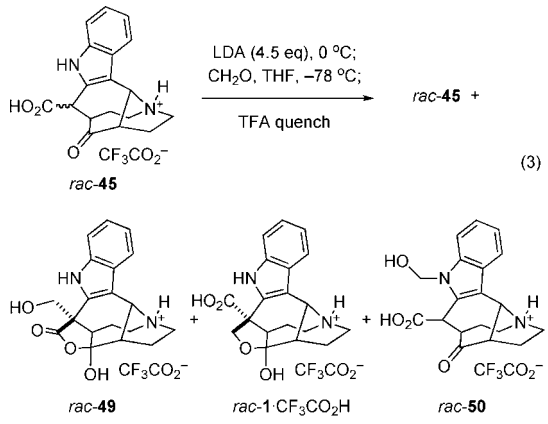
(45) Comparable yields for this transformation were obtained when the pure α-epimer, *rac*-**46a**, was used or when a 1:1 mixture of α and *β* epimers of *rac*-**46** was employed.

(46) The prediction would be the same if lithium was not chelated to the indole nitrogen.

(47) (a) The natural sample of actinophyllic acid (**1**) degraded sometime after its isolation and bioassay. (b) The concentration reported for the optical rotation of natural (−)-actinophyllic acid is incorrect in ref 4; it should be (0.05 M); the low reported rotation could be the result of the low solubility of this zwitterionic amino acid or that the natural sample started to degrade prior to analysis. Personal communications from Professor Tony Carroll, Griffith University, Gold Coast Campus, Australia.

acid salt *rac*-**45**.[48] Removal of acetonitrile in vacuo, followed by dissolution of the resulting residue in a 0.5 M methanolic solution of HCl and heating at 50 °C provided amino ester trifluoroacetate salt *rac*-**46** as a 1:1 mixture of α and β ester epimers in 62% overall yield. In this streamlined fashion, the first-generation total synthesis of actinophyllic acid was completed in 8% overall yield by a sequence that proceeds via only seven isolated intermediates.

In an attempt to shorten the synthesis even further, we examined the aldol reaction between carboxylic acid *rac*-**45** and formaldehyde in an attempt to generate (±)-actinophyllic acid (*rac*-**1**) directly from this precursor. In one such experiment, carboxylic acid trifluoroacetate salt *rac*-**45**, which is available in 73% yield from precursor *rac*-**42**, was deprotonated with 4.5 equiv of LDA at 0 °C in THF and after 30 min was cooled to −78 °C (eq 3). Addition of a THF solution of monomeric formaldehyde,[43] followed by quenching with trifluoroacetic acid before allowing the reaction to warm to room temperature, returned a mixture of the unreacted amino acid starting material, lactone *rac*-**49**, actinophyllic acid hydrotrifluoroacetate (*rac*-**1**·CF_3CO_2H), and *N*-hydroxymethylindole *rac*-**50** after reversed-phase C18 column chromatography. The relative configuration of aldol adduct *rac*-**49** was assigned on the basis of a diagnostic lactone carbonyl stretch at 1762 cm^{-1} and 2D NMR analysis. The unexpected reversal in diastereoselection in the aldol reaction of the carboxylic acid dianion compared to that of the corresponding methyl ester led us to abandon this shorter sequence.[49]

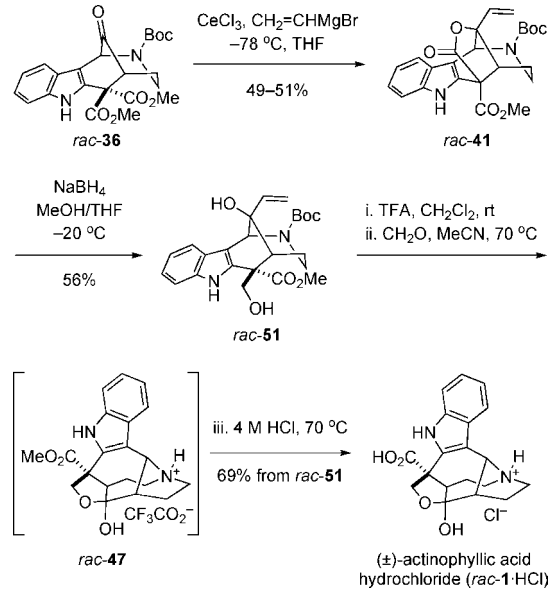


(3)

[*rac*-**45**:*rac*-**49**:*rac*-**1**·CF_3CO_2H:*rac*-**50** = 6.4:3.5:1.5:1.0]

Second-Generation Total Synthesis of (±)-Actinophyllic Acid (*rac*-1): An Improved Endgame. The total synthesis of (±)-actinophyllic acid (*rac*-**1**) summarized in Schemes 8−11 suffered from a low-yielding aldol−hydrolysis sequence (Scheme 10) used to transform aza-Cope/Mannich product *rac*-**46** to (±)-actinophyllic acid. Moreover, in this inaugural route the all-carbon quaternary center present in allylic alcohol intermediate *rac*-**42** is sacrificed by the decarboxylation−formaldehyde aldol sequence used to establish the relative configuration of the

Scheme 12. Synthesis of (±)-Actinophyllic Acid Hydrochloride via Lactone Intermediate *rac*-**41**



quaternary carbon stereocenter of (±)-actinophyllic acid. The formation of pentacyclic lactone *rac*-**41** from vinyl cerium addition to the keto dimethyl ester *rac*-**36** (Scheme 9) showed that it would be possible to differentiate the two ester substituents of the malonate fragment prior to the aza-Cope/Mannich step. Thus, we turned to examine the possibility of optimizing the generation of such pentacyclic lactone intermediates and subsequently transforming them to actinophyllic acid.

Successful elaboration of pentacyclic ketone *rac*-**36** via lactone intermediate *rac*-**41** to (±)-actinophyllic acid is summarized in Scheme 12. The formation of lactone intermediate *rac*-**41** was improved by employing 2.5 equiv of cerium(III) chloride and 3.5 equiv of vinylmagnesium bromide in the reaction with ketone dimethyl ester intermediate *rac*-**36**. Under these conditions, all of the starting ketone was consumed at −78 °C, with lactone *rac*-**41** being formed reproducibly in 49−51% yield.[50] Selective reduction of the lactone carbonyl of this intermediate with excess sodium borohydride in methanol/THF at −20 °C delivered hydroxy ester *rac*-**51** in 56% yield. Removal of the Boc group with TFA in dichloromethane at room temperature, followed by concentration in vacuo, dissolution of the residue in acetonitrile, and heating with 1 equiv of paraformaldehyde at 70 °C generated (±)-actinophyllic acid methyl ester hydrotrifluoroacetate (*rac*-**47**). This intermediate was not purified, but directly hydrolyzed with 4 M HCl to furnish (±)-actinophyllic acid hydrochloride (*rac*-**1**·HCl) in 69% yield.

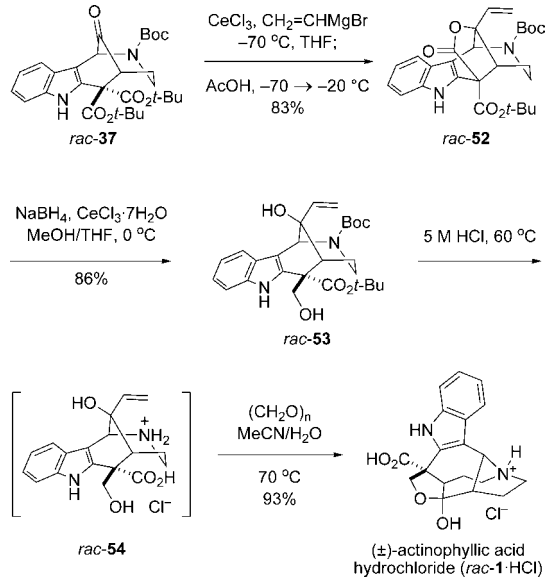
The sequence summarized in Scheme 12 showed that the primary alcohol side chain generated by chemoselective reduction of lactone *rac*-**41** presented no problem in the pivotal aza-Cope/Mannich transformation. This improved synthesis of (±)-actinophyllic acid would be further streamlined if a related sequence could be realized in the di-*tert*-butyl ester series because a global deprotection−aza-Cope/Mannich sequence could potentially directly deliver actinophyllic acid.

(48) The β-epimer, *rac*-**45b**, crystallized from an aqueous solution of this mixture of carboxylic acid epimers. The relative configuration of this sample was established by single-crystal X-ray analysis; crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: CCDC 752916.

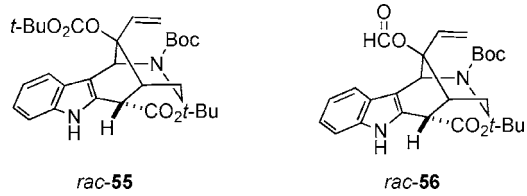
(49) Several other conditions that employed LiCl or TMEDA additives or potassium diisopropylamide as the base were also examined. In no case was actinophyllic acid the major product of this aldol reaction.

(50) (a) A complex mixture of byproducts was formed; products arising from competitive addition of the organometallic reagent to the methyl ester of the lactone product *rac*-**41** were isolated, but they did not account for the entire mass balance of the reaction. (b) In contrast to *rac*-**37**, complete consumption of keto diester *rac*-**36** was not possible when 2.5 equiv of vinylmagnesium bromide were used.

Scheme 13. Improved Endgame of the Concise Second-Generation Total Synthesis of (±)-Actinophyllic Acid

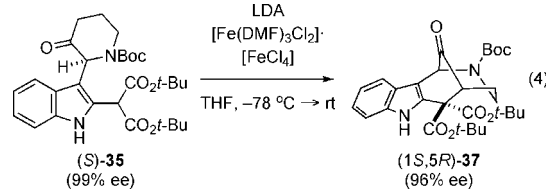


The optimized second-generation total synthesis of (±)-actinophyllic acid that resulted from these considerations is summarized in Scheme 13. The first obstacle to overcome was transformation of keto *tert*-butyl diester *rac*-**37** to lactone *rac*-**52**. After some experimentation, we found that this conversion could be realized in good yield by first allowing *rac*-**37** to react with 2.5 equiv of both cerium(III) chloride and vinylmagnesium bromide at −78 → −70 °C in THF. After the ketone was consumed, as judged by thin-layer chromatography, 1.5 equiv of acetic acid were added to quench the excess organometallic reagent; allowing the reaction to then warm to −20 °C promoted lactonization to give pentacyclic lactone *rac*-**52** in 83% yield.[51] The rate of vinylation was increased if 5 equiv of lithium chloride was added to the reaction mixture,[52] however carbonate *rac*-**55** was then a significant byproduct (*rac*-**52**:*rac*-**55** = 6:1). This byproduct was not observed when lithium chloride was absent. Lithium chloride likely activated the ester carbonyl and promoted elimination of the *tert*-butyl ester enolate from the tetrahedral intermediate formed upon cyclization. The propensity of lanthanides to interact only weakly with esters likely explains why byproduct *rac*-**55** was not formed in the absence of lithium chloride.[53]



In three additional steps, pentacyclic lactone *rac*-**52** was elaborated in high yield to (±)-actinophyllic acid. Chemoselective Luche reduction of lactone *rac*-**52** delivered hydroxy ester *rac*-**53** in 86% yield.[54] The use of cerium(III) chloride was crucial to obtain high yields in this transformation. Carrying out the reduction of the lactone with sodium borohydride in methanol/THF at 0 °C provided a 3.4:1.0 mixture of hydroxy ester *rac*-**53** and formate ester *rac*-**56** in 75% yield, whereas this formate byproduct was not formed under Luche conditions. Exposure of hydroxy ester *rac*-**53** to 5 N aqueous HCl at 60 °C removed the two protecting groups. Concentration of this reaction mixture, dissolution of the residue of *rac*-**54** in 5:1 acetonitrile/water, addition of 1.1 equiv of paraformaldehyde, and heating to 70 °C promoted aza-Cope/Mannich reaction to furnish (±)-actinophyllic acid hydrochloride (*rac*-**1**·HCl) in 93% yield.[55] This considerably improved second-generation total synthesis of (±)-actinophyllic acid was realized in 22% overall yield from commercially available di-*tert*-butyl malonate and *o*-nitrophenylacetic acid by a sequence that proceeds by way of only six isolated intermediates.

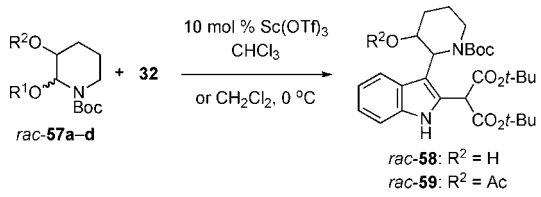
Enantioselective Total Synthesis of (−)-Actinophyllic Acid. As noted previously, there was no experimental evidence concerning the absolute configuration of (−)-actinophyllic acid (**1**) at the time our investigations in this area began. Contemporaneously with our collaboration with the Nakanishi group that established the absolute configuration of (−)-actinophyllic acid (**1**) by chiroptical methods,[6] we initiated efforts to ascertain its absolute configuration by enantioselective total synthesis. The first chiral intermediate in our synthetic route to actinophyllic acid is indole piperidone **35** (Scheme 8). Before beginning to prepare this intermediate enantioselectively, we wished to confirm that it would not be racemized under the basic conditions of the ensuing oxidative dienolate coupling step. To pursue this issue, the enantiomers of *rac*-**35** were separated by enantioselective HPLC. As illustrated in eq 4, conversion of these enantiomers to hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ketone **37** was accompanied by little, if any, racemization.[56]



Success has been registered recently in several laboratories in accomplishing some bimolecular nucleophilic additions to *N*-acyliminium ions in catalytic asymmetric fashion.[57] As a result, we examined briefly the possibility of preparing (*S*)-**35** directly by coupling of 1-(*tert*-butoxycarbonyl)-2-methoxy-3-piperidone (the methoxy analogue of **33**) with indole malonate **32** in the presence of several Bronsted acid catalysts derived from (*R*)-1,1′-bi(2-naphthol).[58] Thus far, our efforts in this area have not led to a satisfactory enantioselective synthesis of intermediate (*S*)-**35** (see the Supporting Information for details).

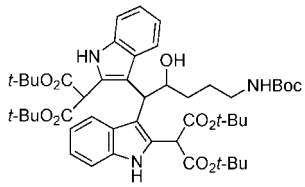
(51) This partial quench resulted in slightly improved yields, but it is not crucial.
(52) Dunn, T. B.; Ellis, J. M.; Kofink, C, C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658–5661.
(53) (a) For a review of the complexation of lanthanides with various functional groups, see: Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553–588, and references cited therein.
(54) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227. For Luche reduction of a lactone having a β ester substituent, see: (b) Kusama, H.; Mori, T.; Mitani, I.; Kashima, H.; Kuwajima, I. *Tetrahedron Lett.* **1997**, *38*, 4129–4132.
(55) Because of the limited solubility of hydrochloride salt *rac*-**54** in acetonitrile, the solvent was a mixture of acetonitrile and water.
(56) The absolute configurations of the structures depicted in eq 4 were established later in our studies.
(57) For some representative examples, see: Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743.

Scheme 14. Diastereoselective Heteroarylation of Piperidine Diol Derivatives



entry	piperidine	R^1	R^2	solvent	yield of *rac*-**58** or *rac*-**59**	trans:cis
1	*rac*-**57a**	H	H	$CHCl_3$[a]	40%[b]	5:1
2	*rac*-**57b**	CH_3	H	CH_2Cl_2	26%[b]	5:1
3	*rac*-**57c**	CH_2CF_3	H	CH_2Cl_2	29%[b]	5:1
4	*rac*-**57d**	Ac	Ac	CH_2Cl_2	74%[c]	20:1

[a] Piperidine *rac*-**57a** is sparingly soluble in CH_2Cl_2. [b] Yield of pure trans isomer. [c] Yield of a mixture of cis and trans isomers.



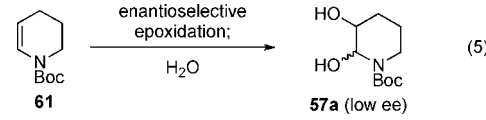
60

As a result, we turned to develop a diasteroselective construction of this key intermediate.

The obvious approach was to replace piperidone intermediate **33** with an appropriate piperidine electrophile bearing an alcohol substituent (or alcohol derivative) at C3 that would direct bond formation at C2. Prospects for success in such an endeavor appeared promising, as Kobayashi and co-workers had reported high trans diasteroselectivity in Lewis acid-catalyzed reactions of 2-acetoxy-3-acyloxy(or 3-alkoxy)-1-(benzyloxycarbonyl)piperidine with β-substituted enoxysilanes and silyl ketene acetals.[59]

Salient results of our initial examination of the coupling of indole malonate **32** with related precursors in the *N*-Boc piperidine series are summarized in Scheme 14. Kobayashi's conditions were effective in promoting the desired transformation, as combining piperidine diol *rac*-**57a**[60] and indole **32** in chloroform with a catalytic amount of scandium(III) triflate at 0 °C provided indole piperidine *rac*-**58** in 40% yield, as a 5:1 mixture of trans and cis stereoisomers. Byproduct **60** arising from the reaction of piperidine *rac*-**57a** with two equiv of the indole nucleophile was isolated in 9% yield. Similar reaction of the 2-methoxy derivative *rac*-**57b** led to a decreased yield of adduct *rac*-**58** (trans/cis = 5:1) and an increased yield (35%) of byproduct **60**. The piperidine ring-opening pathway was not significantly suppressed by employing an electron-withdrawing 2,2,2-trifluoroethoxy substituent at C2, as the reaction of piperidine *rac*-**57c** with indole **32** gave a product distribution similar to that of piperidine derivative *rac*-**57b**. In contrast, diacetoxypiperidine *rac*-**57d**[60c] condensed with indole malonate **32** in good yield to deliver indole piperidine *rac*-**59** as a 20:1 mixture of inseparable trans and cis stereoisomers.[61] In this case, no products arising from ring opening of the piperidine were detected.

With conditions for diastereoselective heteroarylation in hand, we sought to develop an efficient enantioselective synthesis of the 3*R* isomer of diacetoxypiperidine **57d**.[62] Initial work focused on sequential enantioselective epoxidation−hydrolysis of commercially available tetrahydropyridine **61** (eq 5).[63] Shi epoxidation was unselective and provided the diol product as a mixture of epimers, each in 7% ee.[64,65] Two conditions were examined for enantioselective epoxidation with Jacobsen's catalyst:[66] use of aqueous sodium hypochlorite as the stoichiometric oxidant[67] and the low temperature procedure that employs *m*-chloroperbenzoic acid as the stoichiometric oxidant.[68] The low temperature procedure was more successful; however, enantioselectivity was still modest (59−60% ee for both diol diastereomers).[65]



(5)

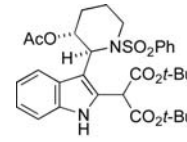
Proline-catalyzed α-oxidation[69] of Boc-protected amino aldehyde **62**[70] proved highly enantioselective, providing alkoxyamine **63** as a single stereoisomer in 98% ee (eq 6). However, under the best conditions we identified the yield was low, likely

(58) (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805. (b) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292–293. (c) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553–2556. (d) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354–6355.

(59) (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989–990.

(60) (a) Piperidine derivatives **57** were prepared from commercially available 1-(*tert*-butoxycarbonyl)-1,4,5,6-tetrahydropyridine using procedures similar to those employed by Kobayashi to prepare the related compounds in the benzyloxycarbonyl series; see the Supporting Information for details.[59] (b) Neat samples of diol **57a** decomposed shortly after being concentrated but could be stored for months in solution at −20 °C. (c) In contrast to the report of Kobayashi and coworkers,[59] we found diacetate **57d** to be sufficiently stable to be a viable synthetic intermediate.

(61) The trans configuration of indole piperidine **59** was determined by X-ray analysis of *N*-sulfonyl derivative **ii**.



ii

(62) (3*S*)-1-(Benzyloxycarbonyl)-2,3-diacetoxypiperidine has been prepared enantioselectively by Kobayashi and co-workers in six steps from a commercially available precursor.[59a]

(63) Sharpless asymmetric dihydroxylation of this alkene is reported to give the *cis*-diol product in only 40% ee. See: Sukemoto, S.; Oshige, M.; Sato, M.; Mimura, K.; Nishioka, H.; Abe, H.; Harayama, T.; Takeuchi, Y. *Synthesis* **2008**, 3081–3087.

(64) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293–296.

(65) Enantiomeric excesses were determined by enantioselective HPLC analysis of the dibenzoate derivative.

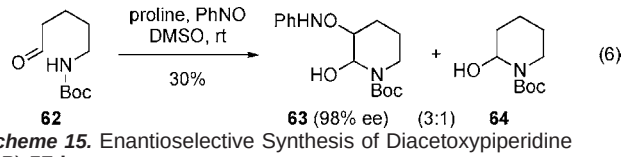
(66) Larrow, J. F.; Jacobsen, E. N. *Org. Synth.* **1998**, *75*, 1–11.

(67) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.

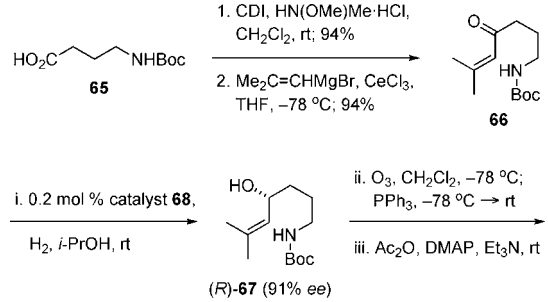
(68) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333–9334.

(69) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.

(70) Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem.* **1985**, *28*, 317–323.



Scheme 15. Enantioselective Synthesis of Diacetoxypiperidine (3*R*)-**57d**

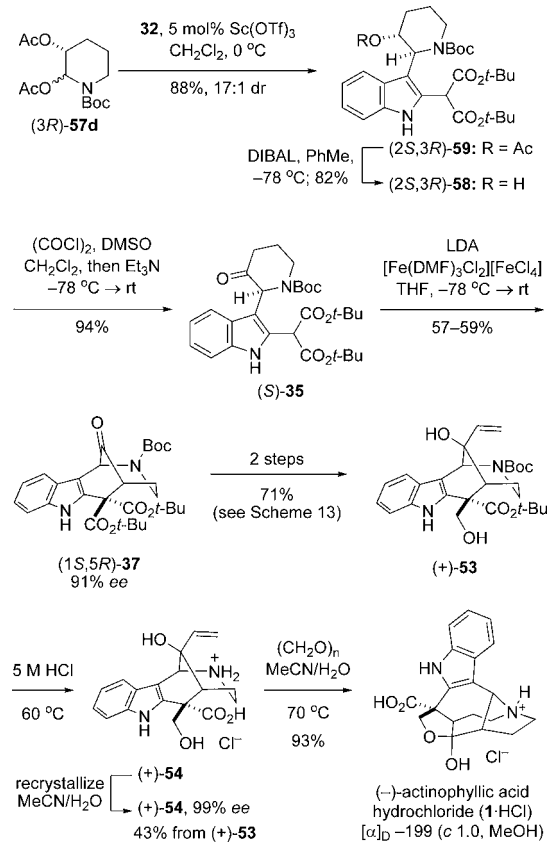


reflecting the facile cyclization of aldehyde **62** to hydroxypiperidine **64**.[71]

We eventually discovered that diacetoxypiperidine (3*R*)-**57d** could be prepared by the convenient sequence shown in Scheme 15. Commercially available amino acid **65** was initially converted to its Weinreb amide,[72] which underwent cerium(III) chloride-mediated vinylation to furnish enone **66** in 88% yield over the two steps.[73] In a sequence carried out without purification of intermediates, α,β-unsaturated ketone **66** was hydrogenated using Noyori's catalyst **68**[74] in 2-propanol to give allylic alcohol (*R*)-**67** in 91% ee.[75,76] Concentration of this reaction mixture, dissolution of the residue with dichloromethane, ozonolysis at −78 °C, quenching with triphenylphosphine, and finally addition of acetic anhydride, triethylamine, and a catalytic amount of 4-dimethylaminopyridine (DMAP) at room temperature gave diacetoxypiperidine (3*R*)-**57d** in 73% yield from enone **66**.

The elaboration of diacetoxypiperidine (3*R*)-**57d** to (−)-actinophyllic acid is summarized in Scheme 16. Piperidine electrophile (3*R*)-**57d** was added to a stirring mixture of 1.3 equiv of indole malonate **32** and 5 mol % of scandium(III) triflate in dichloromethane at 0 °C to give adduct (2*S*,3*R*)-**59** in 88% yield (dr = 17:1) on a multigram scale. Deacetylation of this product with diisobutylaluminum hydride (DIBAL) in toluene at −78 °C delivered, after column chromatography, the

Scheme 16. Total Synthesis of (−)-Actinophyllic Acid Hydrochloride (**1**·HCl)



pure *trans*-alcohol (2*S*,3*R*)-**58** in 82% yield.[77] Attempts to cleave the acetyl group of (2*S*,3*R*)-**59** with sodium or potassium methoxide in methanol resulted in competitive transesterification of the *tert*-butyl esters. Swern oxidation of alcohol (2*S*,3*R*)-**58** furnished indole piperidone (*S*)-**35**,[78] which underwent intramolecular oxidative dienolate coupling to provide ketone (1*S*,5*R*)-**37** in 57−59% yield and 91% ee. Whereas the corresponding racemate could be recrystallized from toluene, this enantioenriched ketone could not be purified in this fashion. Instead, tetracyclic ketone (1*S*,5*R*)-**37** was purified by column chromatography followed by trituration with diethyl ether; this change in the purification procedure likely accounts for the slightly lower yield realized in the enantioenriched series. Elaboration of (1*S*,5*R*)-**37** as described in Scheme 13 furnished (−)-actinophyllic acid hydrochloride (**1**·HCl) in high yield. Reversed-phase HPLC of **1**·HCl afforded the zwitterion, which was crystallized from methanol to provide single crystals of a methanol and water solvate, allowing the first X-ray analysis of (−)-actinophyllic acid (**1**) to be accomplished (Figure 3).[36b] The optical rotation of an analytical specimen of synthetic **1** (>99% ee) showed $[\alpha]_D$ −199 (*c* 0.67, MeOH). A nearly identical rotation was observed for the hydrochloride salt **1**·HCl. The optical rotation of **1** at the sodium D line did not compare well to the reported rotation of $[\alpha]_D$ −29 (*c* 0.001, MeOH).[4,47b] The total synthesis of enantioenriched (−)-actinophyllic acid

(71) Aldehyde **62** cyclizes upon silica gel chromatography or upon storage for a few days as a solution in benzene at 25 °C to give 2-hydroxy-1-(*tert*-butoxycarbonyl)piperidine (**64**).
(72) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
(73) The use of a non-basic organometallic reagent was essential to suppress lactam formation.
(74) (a) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509. (b) Careful control of reaction time was necessary to avoid over-hydrogenation.
(75) The *R* absolute configuration of allylic alcohol **67** was determined by Mosher ester analysis: (a) Dale, J. A.; Mosher, H. S *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451–2458.
(76) Enantiomeric excess was determined by enantioselective HPLC analysis of the benzoate derivative.
(77) To isolate **58** in good yield, it was essential to use a NaF workup; see: Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186–4194.
(78) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. (b) It was essential to remove triethylamine prior to concentration of the crude reaction mixture to prevent deterioration of the enantiopurity of this product.

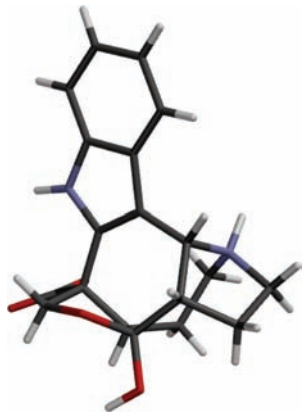
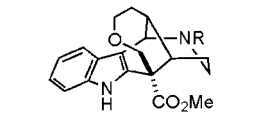


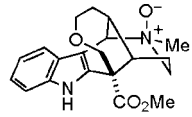
Figure 3. X-ray model of (−)-actinophyllic acid. The asymmetric unit has two molecules each of actinophyllic acid, methanol, and water; for clarity, only one molecule of actinophyllic acid is shown.

1·HCl summarized in Scheme 15 proceeds by way of nine isolated intermediates and was accomplished in 18% overall yield (91% ee); enantiopure **1**·HCl (>99% ee) was accessed in 8% yield.[79]

Potential Biosynthetic Relevance of the Aza-Cope/Mannich Reaction. The aza-Cope/Mannich reaction has proven to be a remarkably robust reaction that has been employed to construct a wide variety of pyrrolidine-containing ring systems.[9] This cascade reaction typically takes place in high yields under extremely mild reaction conditions, often at or near room temperature and at neutral pH. It is these features, along with the wide occurrence of pyrrolidine-containing natural products, that has led us over the years to wonder whether the aza-Cope/Mannich reaction is utilized in natural product biosynthesis. Our demonstration that (−)-actinophyllic acid (**1**) is formed in high yield in one step from a much simpler tetracyclic precursor (+)-**54** by an aza-Cope/Mannich reaction (see Scheme 16) surely raises this question in the current context.



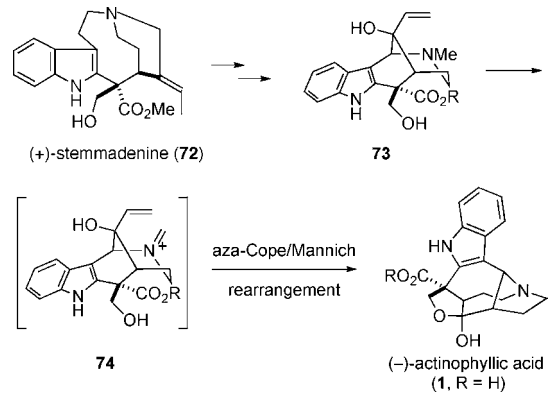
(−)-undulifoline (**69**, R = Me)
(−)-alstilobanine C (**70**, R = H)



(−)-alstilobanine B (**71**)

The possibility that the biogenesis of (−)-actinophyllic acid (**1**) involves an aza-Cope/Mannich reaction is hightened by the isolation from *Alstonia* plant species indigineous to Malaysia of the indole alkaloids (−)-undulifoline (**69**)[80] and (−)-alstilobanines C (**70**) and B (**71**)[81] that contain a uleine alkaloid ring system and the complete carbon scaffold found in synthetic aza-Cope/Mannich precursor (+)-**54**. A biosynthetic sequence,[82−84] potentially beginning with (+)-stemmadenine (**72**),[85,86] that delivers alkaloids **69**−**71** could plausibly lead to an intermediate such as tetracyclic diol **73** (Scheme 17). Oxidative transformation of this intermediate to formaldiminium ion **74** would give rise to (−)-actinophyllic acid (**1**) by an aza-Cope/Mannich sequence.

Scheme 17. Plausible Biosynthesis of (−)-Actinophyllic Acid (**1**) from an Intermediate Having a Uleine Aklaloid Skeleton by an Aza-Cope/Mannich Reaction



Conclusion

The first total syntheses of (±)-actinophyllic acid (*rac*-**1**) and (−)-actinophyllic acid (**1**) have been accomplished by short and efficient synthetic routes. (±)-Actinophyllic acid was prepared in 22% overall yield from commercially available di-*tert*-butyl malonate and *o*-nitrophenylacetic acid by a sequence that proceeds by way of only six isolated intermediates. The enantioselective total synthesis of (−)-actinophyllic acid (**1**) proceeds by way of nine isolated intermediates to deliver enantioenriched (−)-actinophyllic acid **1** (91% ee) in 18% overall yield or enantiopure **1** (>99% ee) in 8% overall yield.[79] In these syntheses, no protecting groups are introduced, and in the notably concise synthesis of *rac*-**1**, nearly all steps form skeletal bonds of actinophyllic acid.

A number of steps in the synthetic sequence are noteworthy. The aza-Cope/Mannich reaction allows the previously unknown hexacyclic ring system of actinophyllic acid to be constructed in one step from much simpler tetracyclic precursors. These total syntheses entail the first use of this powerful cascade reaction for forming medium azacyclic rings and 1-azabicyclic ring systems. An oxidative intramolecular dienolate cyclization is the pivotal step in an efficient construction of the commonly occurring 2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system found in the uleine alkaloids. This step represents the first intramolecular coupling of malonate and ketone enolates, as well as the first demonstration that an unprotected indole can survive such a coupling reaction.

(79) The yield of enantiopure (−)-**1** undoubtedly can be increased, as no attempt was made to optimize the recrystallization of intermediate (+)-**54**.
(80) Massiot, G; Boumendjel, A.; Nuzillard, J.-M.; Richard, B.; Le Men-Olivier, L.; David, B.; Hadi, H. A. *Phytochemistry* **1992**, *31*, 1078–1079.
(81) Koyama, K.; Hirasawa, Y.; Zaima, K.; Hoe, T. C.; Chan, K.-L.; Morita, H. *Bioorg. Med. Chem.* **2008**, *16*, 6483–6488.
(82) At the experimental level, little is known about the biosynthesis of monoterpene indole alkaloids that lack the normal tryptophan side chain and have only one-carbon linking the β-carbon of the indole and the basic nitrogen,[83] particularly for natural products having the uleine skeleton.[84]
(83) (a) Kutney, J. P.; Nelson, V. R.; Wigfield, D. C. *J. Am. Chem. Soc.* **1969**, *91*, 4278–4279. (b) Kutney, J. P.; Nelson, V. R.; Wigfield, D. C. *J. Am. Chem. Soc.* **1969**, *91*, 4279–4280.
(84) For reviews, see: (a) Kutney, J. P. *Heterocycles* **1976**, *4*, 429–451. (b) Herbert, R. B. Structural and Biosynthetic Relationships. In *The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; The Chemistry of Heterocyclic Compounds; Wiley: New York, 1983; Vol. 25, Part 4, Chapter I, pp 13−14.
(85) The laboratory formation of the "*nor*" alkaloid vallesamine from stemmadenine by a Polonovski fragmentation[86] is the basis of most biosynthetic proposals for the synthesis of uleine-type alkaloids.[81,84b]
(86) (a) Scott, A, I.; Yeh, C.-L.; Greenslade, D. *J. Chem. Soc., Chem. Commun.* **1978**, 947–948. (b) Ahond, A.; Cavé, A.; Kan-Fan, C.; Langlois, Y.; Potier, P. *Chem. Commun.* **1970**, 517.

Tetracyclic intermediates **36** and **37** produced in this way could well serve as precursors of other families of indole alkaloids.

In conclusion, the efficient construction of actinophyllic acid by an aza-Cope/Mannich reaction suggests the possibility that nature utilizes this powerful cascade reaction in natural product biosynthesis.

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Supporting Information Available: Experimental details and copies of ^{1}H and ^{13}C NMR spectra of new compounds; CIF files for compounds (−)-**1**, *rac*-**45b**, and **ii**. This material is available free of charge via the Internet at http://pubs.acs.org.

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