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Progress Toward the Total Synthesis of (±)-Actinophyllic Acid

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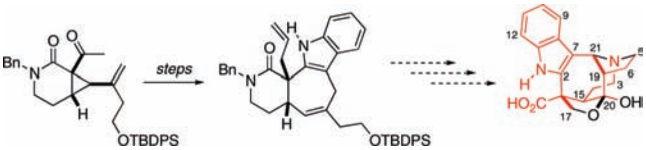
ABSTRACT



This paper describes ongoing progress toward the synthesis of the novel indole alkaloid actinophyllic acid via a synthetic strategy that allows for the installation of all C-atoms (highlighted in red) requisite for completion of a total synthesis.

Actinophyllic acid (**1**) was identified in 2005 by Carroll and co-workers during a program to screen natural products as potential therapeutic agents for the treatment of cardiovascular disorders.[1] Isolated from the leaves of the tree *Alstonia actinophylla*, **1** was reported to inhibit (IC$_{50}$ = 0.84 μM) carboxypeptidase U (CPU) during a coupled enzyme assay. The enzyme CPU is an endogenous inhibitor of fibrinolysis, the process that the body uses to clear fibrin clots, and suppression of fibrinolysis by CPU can lead to a variety of pathological consequences (i.e., acute myocardial infarction, pulmonary embolism, cerebral infarction, etc.).[2] It thus follows that compounds that inhibit the action of CPU, and thereby facilitate fibrin degradation, demonstrate potential as therapeutic agents for the treatment of cardiovascular disorders in which blood clots are implicated.

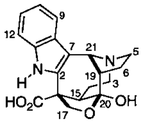


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Figure 1. Structure of actinophyllic acid.

Structurally, actinophyllic acid (**1**) comprises an impressive fusion of ring systems (Figure 1). The molecular framework represents an unprecedented 2,3,6,7,9,13c-hexahydro-1*H*-1,7,8-(methanetriyloxymethano)pyrrol[1′,2′:1,2]azocino-[4,3-*b*]indole-8(5*H*)-carboxylic acid architecture. While the carbon connectivity and relative stereochemistry of **1** were determined by extensive NMR analysis,[1] assignment of the absolute stereochemical configuration[3] was only recently made possible after the first total synthesis was disclosed by Overman and co-workers.[4] The imposing molecular architecture and activity of **1** provided the impetus for our synthetic efforts. Herein we report our ongoing progress toward the total synthesis of **1**.

Retrosynthetic simplification began with scission of the C21−N bond of **1** (Scheme 1). In the synthetic direction, cyclization of the pendant secondary amine is envisioned to involve the intermediacy of an indole−quinonemethide[5]

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(1) Carroll, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. *J. Org. Chem.* **2005**, *70*, 1096–1099.

(2) (a) Willemse, J. L.; Hendriks, D. F. *Front. Biosci.* **2007**, *12*, 1973–1987. (b) Schatteman, K.; Goossens, F.; Leurs, J.; Verkerk, R.; Scharpé, S.; Michiels, J. J.; Hendriks, D. *Clin. Appl. Thromb. Hemost.* **2001**, *7*, 93–101. (c) Luers, J.; Hendriks, D. *Thromb. Haemost.* **2005**, *94*, 471–487. (d) Polla, M. O.; Tottie, L.; Nordén, C.; Linschoten, M.; Müsil, M.; Trumpp-Kallmeyer, S.; Aurkurst, I. R.; Ringom, R.; Holm, K. H.; Neset, S. M.; Sandberg, M.; Thurmond, J.; Yu, P.; Hategan, G.; Anderson, H. *Biorg. Med. Chem.* **2004**, *12*, 1151–1175. (e) Cesarman-Maus, G.; Hajjar, K. A. *Br. J. Hamaetol.* **2005**, *129*, 307–321.

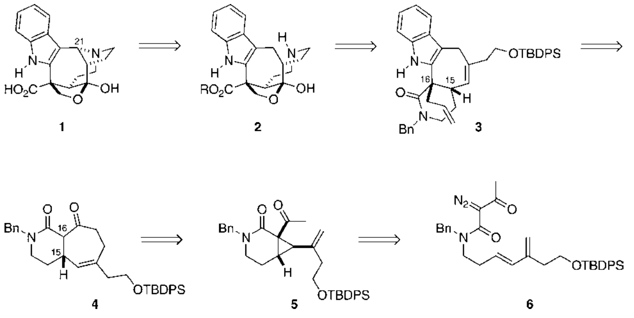
(3) Taniguchi, T.; Martin, C. L.; Monde, K.; Nakanishi, K.; Berova, N.; Overman, L. E. *J. Nat. Prod.* **2009**, *72*, 430–432.

(4) For an account of this elegant approach, see: Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569.

10.1021/ol901746c CCC: $40.75

species to furnish the completed core of **1**. Pentacycle **2** was expected to arise from indole lactam **3** wherein formation of the desired C16 quaternary center and indole ring system occur through sequential substrate-controlled alkylation and indolization reactions, respectively, applied to β-keto lactam **4**. Further antithetic simplification revealed that **4** could possibly evolve from a *cis*-divinylcyclopropane rearrangement of cyclopropyl lactam **5**, which in turn would arise via an intramolecular cyclopropanation of dienyl diazoacetoacetamide **6**.

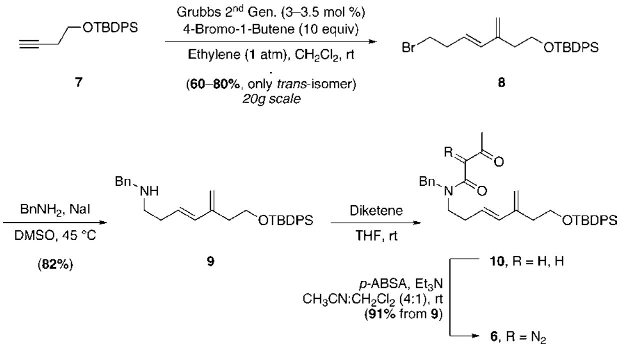
Scheme 1. Retrosynthetic Analysis to **1**



The synthesis commenced with the efficient and expedient preparation of dienyl diazoacetoacetamide **6**, a requisite precursor for constructing the [6,7]-fused β-keto lactam **5** (Scheme 2). Accordingly, homopropargylic silyl ether[6] **7** was treated with Grubbs' second-generation catalyst, 4-bromo-1-butene, and ethylene gas to furnish the bromo diene **8** via an enyne cross-metathesis reaction.[7−9] Displacement of the bromide with benzylamine (**8** → **9**),[10] followed by acetoacetamide formation using diketene (**9** → **10**) and a standard Regitz diazotransfer reaction using Et_3N and *p*-acetamidobenzenesulfonyl azide[11] (*p*-ABSA), afforded **6** in 75% yield over three steps.

Following the successful synthesis of **6**, the metal-catalyzed cyclopropanation reaction was investigated (Scheme 3).[12] To this end, ^1H NMR analysis of crude reaction mixtures produced upon reaction of **6** in the presence of various achiral rhodium- or copper-based catalysts clearly indicated the presence of complex mixtures that appeared to be comprised of C−H insertion products (**11** and **12**), in addition to the desired cyclopropanation product (**5**). After a survey of reaction parameters it was realized that copper(II) bis(salicylidene-*tert*-butylamine)[13] [$Cu(TBS)_2$] effectively promoted the cyclopropanation of **6**.[11,14] In the event, slow addition of **6** to a solution of 10 mol % $Cu(TBS)_2$ in 1,2-dichloroethane induced the formation of the desired 3-azabicyclo[4.1.0]heptan-2-one system (**5**) as a *single* diastereomer, albeit in 50−60% yield.[15]

Scheme 2. Preparation of Dienyl Diazoacetoacetamide **6**



To construct the [6,7]-fused bicyclic lactam **4**, ketone **5** was initially treated under soft enolization conditions (with TBSOTf and Et_3N) at −40 °C (Scheme 4).[16,17] The resultant enoxysilane (**13**) was thus poised to intercept the 1,1-disubstituted olefin in a divinylcyclopropane rearrangement. Accordingly, subsequent warming of enoxysilane **13** to ambient temperatures promoted the facile [3,3]-sigmatropic rearrangement (**13** → **14**), thereby unveiling **4** as a mixture of keto-/enol-tautomers.[18] The release of ring strain associated with a cyclopropane in conjunction with the *syn*-stereochemical predisposition of the enoxysilane and vinyl moiety facilitated the [3,3]-sigmatropic process.[17]

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[5] For examples of amine trapping of indole−quinonemethide species, see: (a) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N *J. Org. Chem.* **1992**, *57*, 70–78. (b) Ohshima, T.; Xu, Y.; Takita, R.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 9569–9588. (c) Ohori, K.; Shimizu, S.; Ohshima, T.; Shibasaki, M. *Chirality* **2000**, *12*, 400–403.

[6] Nicolaou, K. C.; Lizos, D. E.; Kim, D. W.; Schlawe, D.; de Noronha, R. G.; Longbottom, D. A.; Rodriquez, M.; Bucci, M.; Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460–4470.

[7] Lee, H. -Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855–1853.

[8] For a review on enyne cross-metathesis, see: Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

[9] Importantly, bromo diene **8** was produced in 60%−80% yield with exclusive *trans*-olefin selectivity under these reaction conditions.

[10] Amine displacement of homoallylic dienyl bromide was adapted from: Arnold, H.; Overman, L. E.; Sharp, M. J.; Witschel, M. C. *Org. Synth.* **1992**, *70*, 111–118.

[11] Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, D. *Synth. Commun.* **1987**, *17*, 1709–1716.

[12] For studies on the cyclopropanation of diazoacetamides, see: (a) Doyle, M. P.; Eismont, M. Y.; Protopopova, M. N.; Kwan, M. M. Y *Tetrahedron* **1994**, *50*, 1665–1674. (b) Doyle, M. P; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763–5775.

[13] For synthesis of $Cu(TBS)_2$, see: Charles, R. G. *J. Org. Chem.* **1957**, *22*, 677–679.

[14] Under these conditions only minimal quantities of side products were observed.

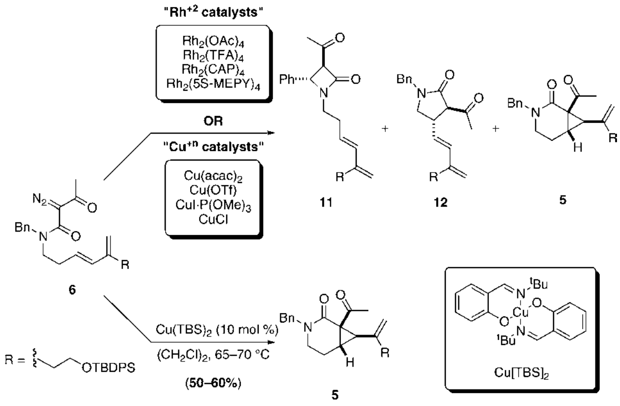
[15] These conditions remain unoptimized, and current efforts are focusing on both improving efficiency and utilizing chiral metal catalysts to induce asymmetry.

[16] (a) Simchen, G.; Kober, W. *Synthesis* **1976**, 259–261. (b) Kobayashi, M.; Masumoto, K.; Nakai, E.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 3005–3008.

[17] For a review on the use enoxysilane formation with silyl triflates, see: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1–26.

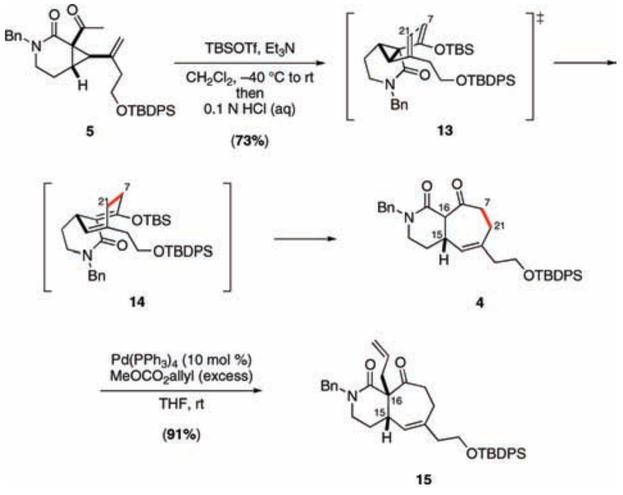
[18] For some examples of enoxysilane-mediated divinylcyclopropane rearrangement in the synthesis of functionalized cycloheptene rings, see: (a) Piers, E.; Burmeister, M. S.; Reissig, H.-U. *Can. J. Chem.* **1986**, *64*, 180–187. (b) Piers, E.; Jung, G. L. *Can. J. Chem.* **1987**, *65*, 1668–1675. (c) Piers, E.; Jung, G. L.; Ruediger, E. H. *Can. J. Chem.* **1987**, *65*, 670–682. (d) Hudlicky, T.; Nguyen, P. V. *J. Org. Chem.* **1992**, *57*, 1933–1935. (e) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.

Scheme 3. Metal-Catalyzed Reaction of **6**



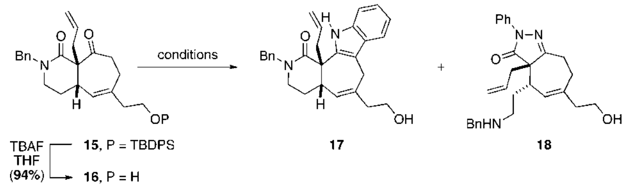
With the mixture of keto-/enol-**4** in hand, we next turned to installation of the hydroxymethyl moiety residing at the C16 quaternary center. Initial attempts to functionalize directly via an aldol reaction were met with limited success (not shown). As an alternative, **4** was subjected to a Tsuji–Trost allylation reaction using catalytic $Pd(PPh_3)_4$ and allyl methylcarbonate. Gratifyingly, this substrate-controlled allylation reaction provided the allylated β-keto amide **15** as essentially a *single* diastereomer.[19,20] At this stage, NOE studies on **15** failed to offer conclusive evidence for the relative stereochemical configuration of the newly generated C16 center; however, this issue was eventually resolved on a subsequent intermediate (vide infra).

Scheme 4. Elaboration of Cyclopropane **5**



Our attention next turned to examining protocols for the installation of the indole moiety. Removal of the silyl ether was achieved under standard conditions to afford alcohol **16**.[21] The indolization of **16** was realized via a Fischer indole synthesis (Table 1). Unfortunately, under conventional conditions only low to modest yields of the desired indole **17** were observed. Additionally, the formation of the undesired pyrazolone **18** was also detected as a major side product.

Table 1. One-Pot Fischer Indolization



entry	conditions	**17** (%)	**18** (%)	**16** (%)
1	$PhNHNH_2$·HCl (3.6 equiv) EtOH, reflux	10		
2	$PhNHNH_2$·HCl (1.2 equiv) EtOH, seal tube, 100 °C	28	37	20
3	$PhNHNH_2$·HCl (1.4 equiv) EtOH, 150 °C (microwave), 2 h	42	14	

To improve the yield of this pivotal transformation, we next attempted an alternative protocol for the installation of the indole moiety. Ultimately, addition of 10 mol % scandium(III) triflate [$Sc(OTf)_3$] to **15** in the presence of phenylhydrazine efficiently provided phenylhydrazone **19** as a *single* regioisomer (Scheme 5).[22−25] At this point, nOe studies on hydrazone **19** revealed the relative *syn*-stereochemical relationship between the C16 quaternary and the C15 positions (see red arrows in Scheme 5). Subsequent microwave irradiation of unpurified **19** in the presence of anhydrous $ZnCl_2$ at elevated temperature cleanly afforded the desired indole **3** in 64% yield (unoptimized) from ketone **15**. Importantly, **3** embodies all of the C-atoms required (highlighted in red in Scheme 5) for the completion of a total synthesis of **1**.

In summary, herein we have disclosed the efficient construction of **6** and its application in an intramolecular cyclopropanation reaction which, in turn, holds potential for an asymmetric synthesis via chiral metal catalysis. Subsequent facile *cis*-divinyl cyclopropane rearrangement of **5**

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(19) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809–4812.

(20) For a review of palladium-catalyzed allylic alkylations, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173–1192. (b) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361–4401.

(21) Initial attempts to employ phenylhydrazine hydrochloride in the Fischer indolization reaction of substrate **15** led to mixtures of products, which arose from non-deprotected and deprotection of the silyl ether.

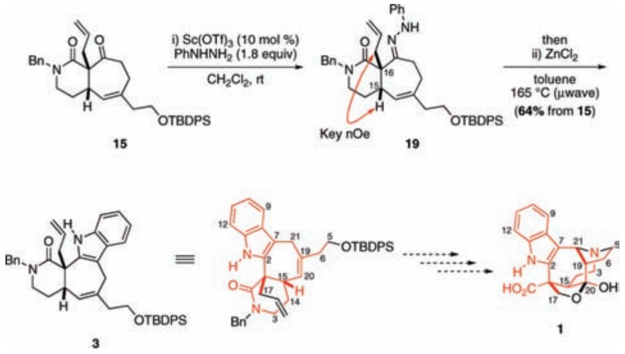
(22) Attempts to condense phenylhydrazine with ketone **15** under either neutral or protic acid conditions provided only low conversions to the desired hydrazone **19**.

(23) For examples of the use of $Sc(OTf)_3$ as a Lewis acid activator for aldehydes in the presence of hydrazines, see: (a) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436–5445. (b) Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* **2001**, 1140–1142.

(24) $Sc(OTf)_3$-catalyzed formation of hydrazone **19** proceeded quantitatively as judged by ^1H NMR analysis of the unpurified reaction mixture. Isolation yields of **19** typically ranged between 84%−97% yield.

(25) The configuration of hydrazone **19** (i.e., *E*-hydrazone vs. *Z*-hydrazone) could not be determined by NMR.

Scheme 5. Improved Construction of Indole Nucleus



provided access to the seven membered core of **1** and set the stage for subsequent incorporation of the C16 quaternary center and the indole nucleus. The former via a substrate-controlled Tsuji−Trost allylation and latter using a modified Fischer indolization reaction. Overall, this synthetic strategy allowed for the assembly of all the requisite carbon atoms in only eight steps.

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Supporting Information Available: Experimental procedures, compound characterization, ^{1}H NMR and ^{13}C NMR data for all compounds. 2D-NMR spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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