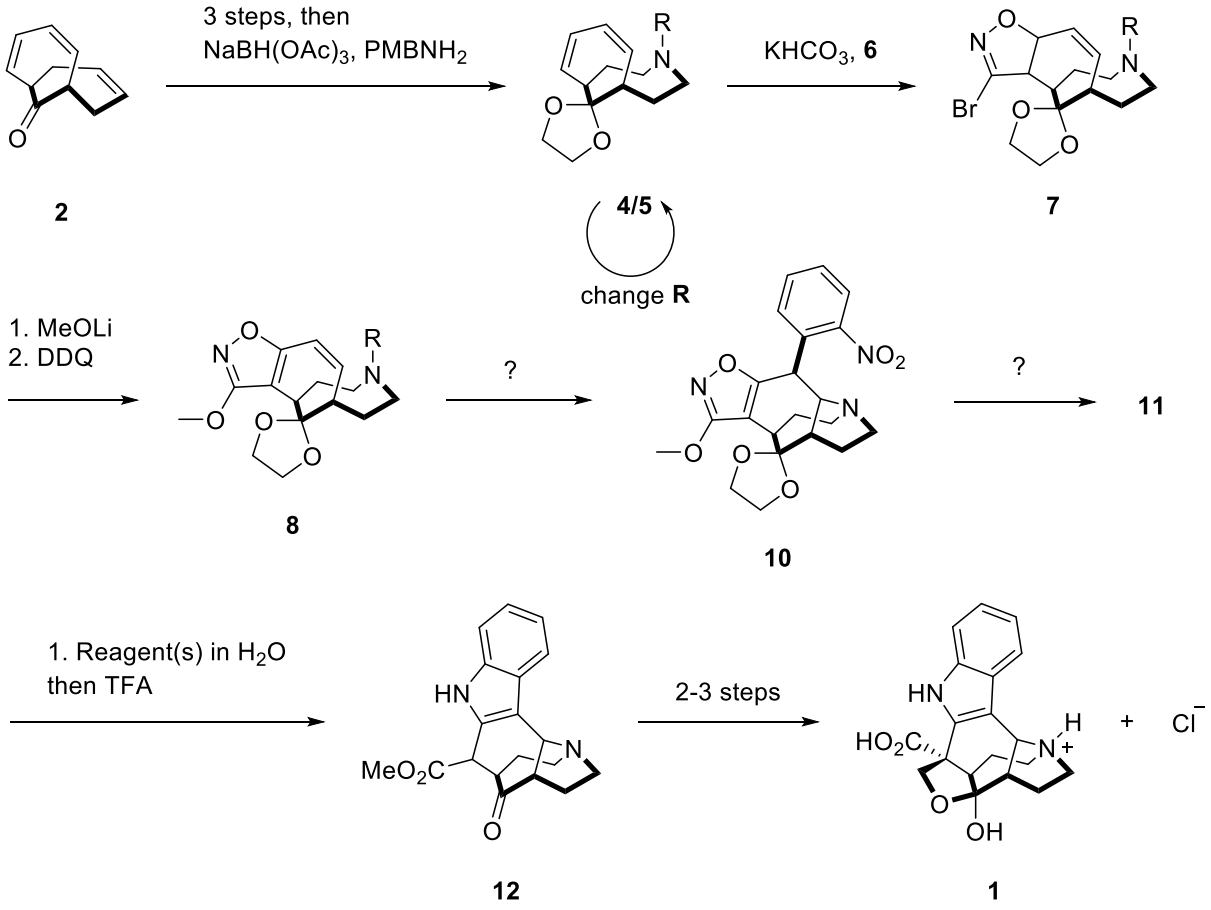
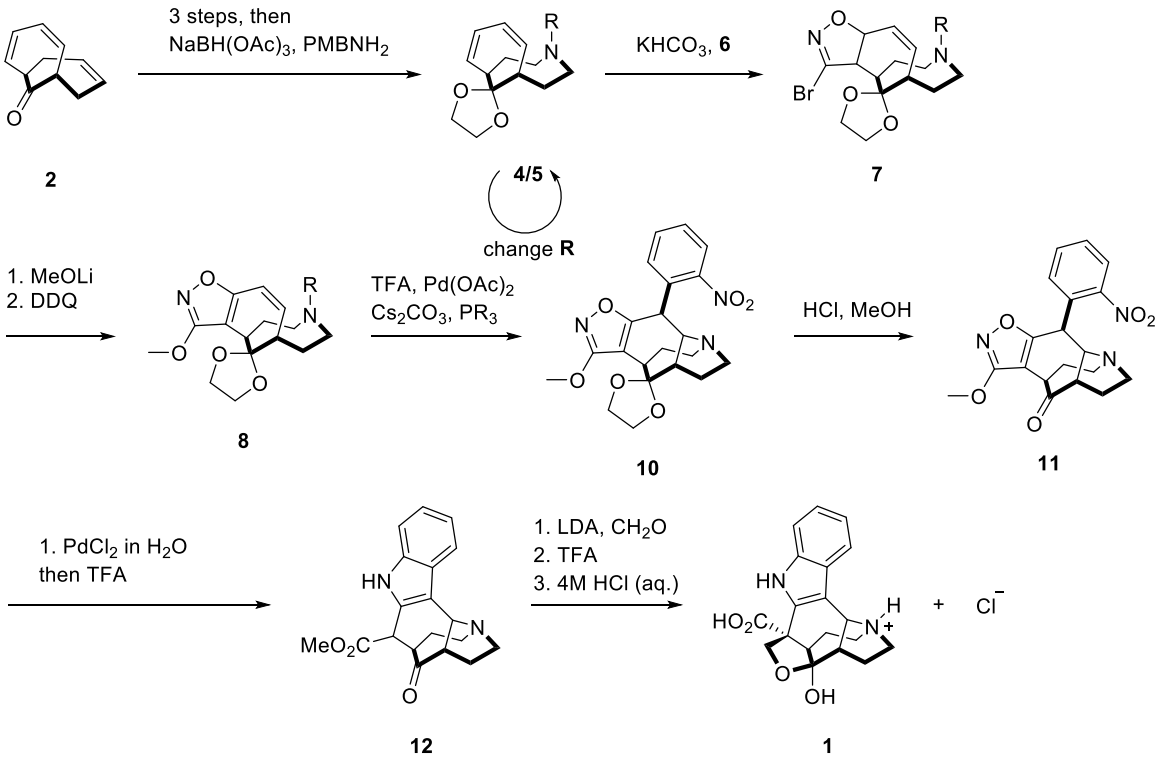


1.) Give the 3 steps remaining for the formation of **4/5** out of **2**. Explain possible diastereo/enantio-selectivity.
2.) What is reagent **6**? How are such reagents prepared?
3.) What connections do you have to make from **8** to **10**? The R-group is Teoc
4.) Give the (most obvious) intermediate **11**. Give the reagent(s) and the mechanism to transform **11** into **12**.
5.) Give the 2-3 steps missing to form the desired natural compound **1**



1.) Give the 3 steps remaining for the formation of **4/5** out of **2**. Explain possible diastereo/enantio-selectivity.

This is a trick question to realize that the SM is symmetrical.

a) the ketone is protected first

b) OsO_4 does not react with the conjugated system. The diol is installed exo for steric reasons.

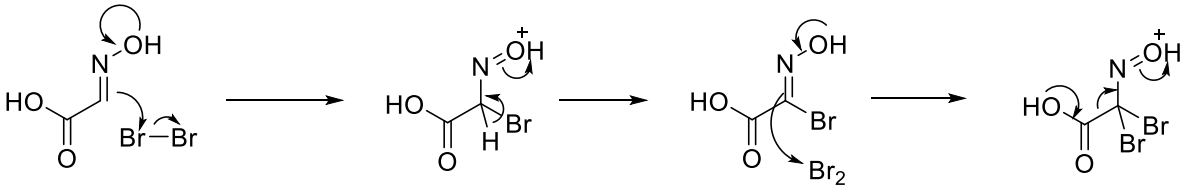
c) The diol is then oxidized/cleaved with $Pb(OAc)_3$

double reductive amination gives the desired product

2.) What is reagent **6**? How are such reagents prepared?

Dibromooxime, which is in-situ transformed into dibromonitrileoxide. The product is formed as a single diastereomer JACS, 2009, 131, 17066

The mechanism for the formation of 6 is probably as follows:

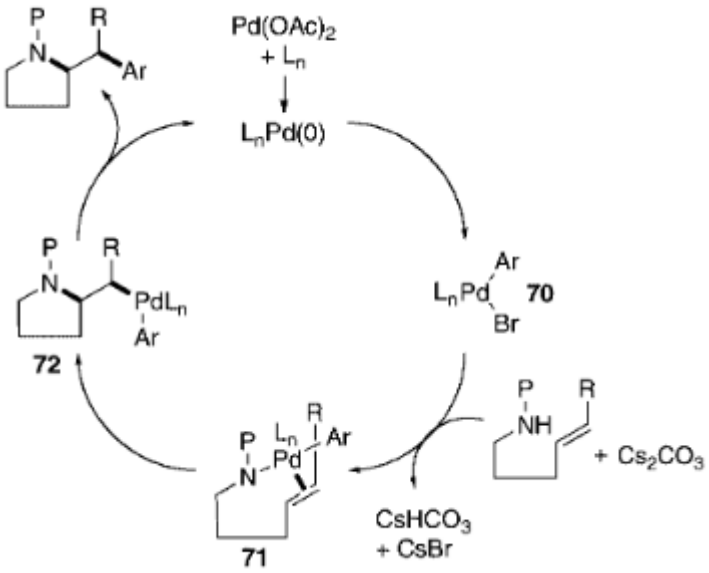


However, this would require at least two equivalents of bromine (two times a Br+ is reacted), but almost none of the procedures uses two equivalents (usually 1.5) – But the yield is usually lower than 50%...

3.) What connections do you have to make from **8** to **10**? The R-group is Teoc

a) deprotection to form the free amine

b) palladium catalysed amino-arylation (Wolfe), J. Org. Chem., 2008, 73, 885:



4.) Give the (most obvious) intermediate **11**. Give the reagent(s) and the mechanism to transform **11** into **12**.

See solution scheme

5.) Give the 2-3 steps missing to form the desired natural compound **1**

See solution scheme

Natural Products Synthesis

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Total Synthesis of Actinophyllic Acid

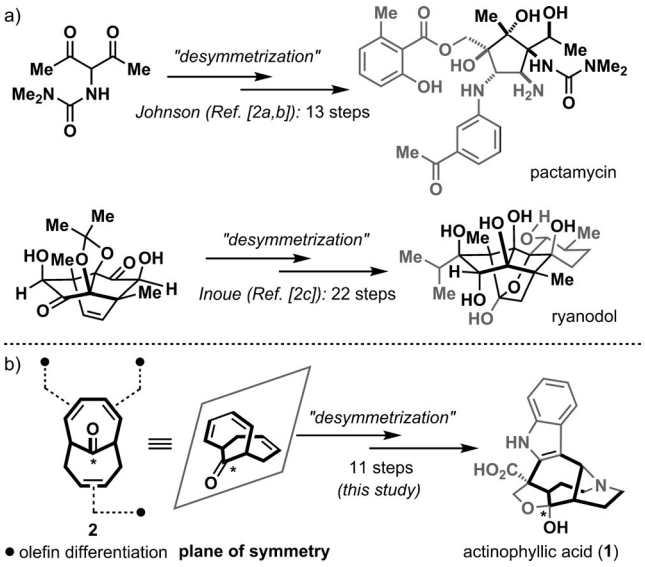
*Yu Yoshii, Hidetoshi Tokuyama, and David Y.-K. Chen**

Dedicated to Professor Yoshito Kishi on the occasion of his 80th birthday

Abstract: *Herein we report a total synthesis of the indolohydroazocine natural product actinophyllic acid. The target molecule was retrosynthetically deconvoluted to render a greatly simplified and symmetrical [4.4.1] bicyclic trienone, the desymmetrization of which was carefully examined under a variety of conditions, including oxidative, reductive, and transition-metal-catalyzed transformations. Ultimately, the successful synthetic strategy featured chemoselective catalytic dihydroxylation, desymmetrizing nitrile oxide dipolar cycloaddition, and palladium-catalyzed aminoarylation to sequentially modify the three olefins within the trienone, followed by a late-stage reductive cascade indolization and alkylation to complete the target molecule.*

Plane symmetry is a ubiquitous feature in the chemical sciences that has captivated our imaginations in terms of both its generation and function. By definition, a compound possessing plane symmetry harbors two identical structural domains with mirrored chemical reactivity, and a selective operation on one of its two identical structural domains renders an asymmetric product with a new identity and reactivity. This process, so-called desymmetrization, has profoundly impacted organic synthesis, from the widespread preparation of simple building blocks to highly elaborated molecular architectures.[1] The success of desymmetrization strategies relies heavily on the chemical method of choice and the timing of its implementation in the overall synthetic scheme. In the context of target-oriented total synthesis, impressive feats have been realized through the exquisite insight of the practitioners (Scheme 1 a).[2] Although the judicious application of desymmetrization-based synthetic strategies can be highly advantageous, more importantly, desymmetrization represents a generalized "thought process" on the basis of which a synthetic plan could be logically conceived.[1e]

The power of desymmetrization-based synthetic strategies in target-oriented synthesis is best appreciated when the target molecule does not possess any symmetry elements. Actinophyllic acid (**1**) readily fulfills this criterion, with its unique architecture adding to the scientific challenge (Scheme 1 b).[3] Moreover, it would be possible to measure the success of our proposed desymmetrization strategy against the benchmark set by the elegant and efficient syntheses of actinophyllic acid (**1**) by the Overman,[4a,b] Martin,[4f,h] and Kwon research groups.[4i] In accordance with the terminology used by Hanessian, deconvolution of the cagelike structure of actinophyllic acid (**1**) is by large a reflexive process.[5] After several generations of symmetry-driven retrosynthetic simplification, the [4.4.1] bicyclic trienone **2** was revealed as a plausible synthetic precursor.



Scheme 1. a) Selected recent examples of desymmetrization in target-oriented synthesis. b) Use of the [4.4.1] bicyclic trienone **2**, with a plane of symmetry, as a precursor to actinophyllic acid (**1**).

The simplicity of trienone **2** and its ready availability[6] were particularly attractive; however, its three olefinic residues had to be modified sequentially to fulfill the objective of desymmetrization. In this context, upon ketal protection of trienone **2** (ethylene glycol, *p*-TsOH·H_2O), we soon discovered that under carefully controlled reaction conditions, the isolated olefin could be selectively dihydroxylated (OsO_4, NMO, 78% yield over two steps) without affecting the conjugated diene (Scheme 2).[7] This latter process was followed by oxidative cleavage of the dihydroxylated carbocycle within **3** ($Pb(OAc)_4$) and subsequent reconstitution of the cyclic framework through double reductive amination of the intermediate dialdehyde with $PMBNH_2$ in 65% overall yield. As a precautionary maneuver, particularly in view of the likelihood of employing oxidative transforma-

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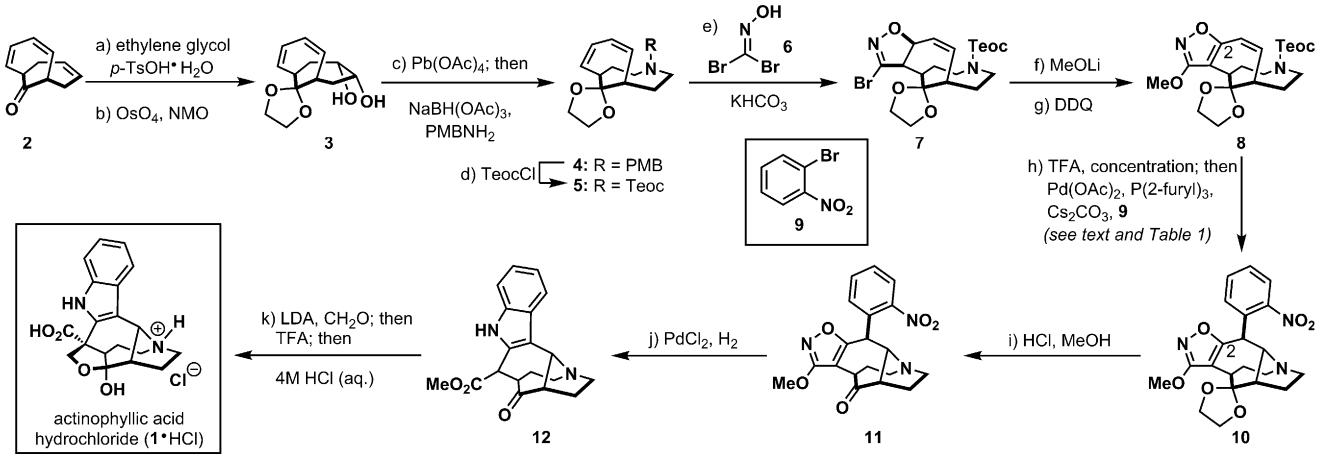


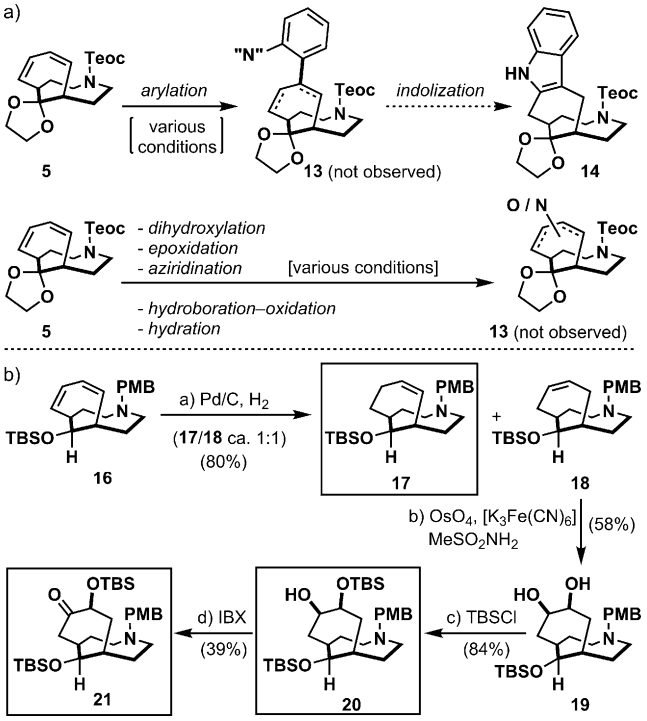
Scheme 2. Total synthesis of actinophyllic acid hydrochloride (**1**·HCl). Reagents and conditions: a) *p*-TsOH·H_2O (1.0 equiv), ethylene glycol, 23 °C, 3 h; b) OsO_4 (0.06 mol %), NMO (1.5 equiv), acetone, 23 °C, 72 h, 78 % for two steps; c) $Pb(OAc)_4$ (1.5 equiv), $NaHCO_3$ (2.8 equiv), benzene, 23 °C, 1 h; then MS4Å (1.3 wt equiv), $NaBH(OAc)_3$ (2.4 equiv), $PMBNH_2$ (1.7 equiv), 1,2-dichloroethane, 23 °C, 1.5 h; then $NaHCO_3$ (2.8 equiv), Boc_2O (1.8 equiv), 1,2-dichloroethane, 23 °C, 1 h, 65 %; d) TeocCl (1.3 equiv), CH_2Cl_2, 23 °C, 1 h, 89 %; e) **6** (2.2 equiv), $KHCO_3$ (3.3 equiv), ethyl acetate, 23 °C, 48 h, 68 %; f) LiOMe (1.0 M in MeOH, 20 equiv), MeOH, 50 °C, 72 h; g) DDQ (1.0 equiv), toluene, reflux, 16 h, 36 % for two steps; h) TFA/CH_2Cl_2 (1:10), 23 °C, 12 h; then **9** (3.0 equiv), Cs_2CO_3 (5.0 equiv), (2-furyl)$_3$P (1.6 equiv), $Pd(OAc)_2$ (0.8 equiv), THF, reflux, 4 h, 65 %; i) HCl (4.0 M aqueous)/MeOH (1:1), reflux, 48 h, 76 %; j) $PdCl_2$ (4.5 equiv), MeOH/H_2O/AcOH (8:2:1), H_2 (1 atm), 23 °C, 6 h; then TFA; k) LDA (4.3 equiv), THF, −78 °C, 0.5 h; then CH_2O (ca. 0.5 M in THF, 14 equiv), −78 °C, 5 min; then TFA (0.9 M in THF, 14 equiv), 23 °C; then HCl (4.0 M aqueous), 70 °C, 13 h, 15 % overall yield from **11**. Boc_2O = di-*tert*-butyl dicarbonate; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LDA = lithium diisopropylamide; NMO = *N*-methylmorpholine *N*-oxide; PMB = *para*-methoxybenzyl; Teoc = 2-(trimethylsilyl)ethylcarbonyl; TFA = trifluoroacetic acid; *p*-TsOH·H_2O = *para*-toluenesulfonic acid monohydrate.

tions or π-philic Lewis acidic reagents on the conjugated diene, *p*-methoxybenzyl amine **4** was readily converted into Teoc carbamate **5** (TeocCl) in 89 % yield.

With the bicyclic diene carbamate **5** in hand, the stage was set for the key desymmetrization event (Scheme 3). In view of the rich repertoire of alkene- or conjugated-diene-specific transformations, while keeping in mind the structure of the target molecule, the methods initially considered for the proposed desymmetrization were largely focused on transformations that would enable the installation of the indole moiety required for actinophyllic acid (**1**). In this context, several arylation protocols were examined but soon abandoned primarily owing to reactivity and selectivity issues (Scheme 3 a). Oxidative or redox-neutral transformations that involved either oxygenation or amination also proved largely ineffective. We were pleased to find, however, synthetically useful hydrogenation conditions that afforded a nearly equal mixture of alkenes **17** (the first desymmetrized intermediate obtained) and **18** in 80 % combined yield (Scheme 3 b).

Although the precise mechanism behind the formation of the migratory hydrogenation product **18** is unclear,[8] alkene **18** underwent catalytic dihydroxylation (OsO_4, $[K_3Fe(CN)_6]$, 58 % yield), and the resulting diol **19** could be desymmetrized by silylation (TBSCl, 84 % yield). Presumably, the steric pressure within TBS ether **20** prevented further silylation. Alcohol **20** could be oxidized (IBX) to provide ketone **21** as a synthetically more versatile intermediate. The success of the selective silylation has a broader implication in view of the recent advances in enantioselective desymmetrization silylation reactions,[9] thus suggesting potential access to optically active intermediates.

Next, we carefully analyzed the options to further elaborate intermediates **17**, **20**, and **21** towards actinophyllic acid (**1**), particularly in connection with the introduction of the requisite indole moiety. In this analysis, we soon realized that although several plausible synthetic pathways could be



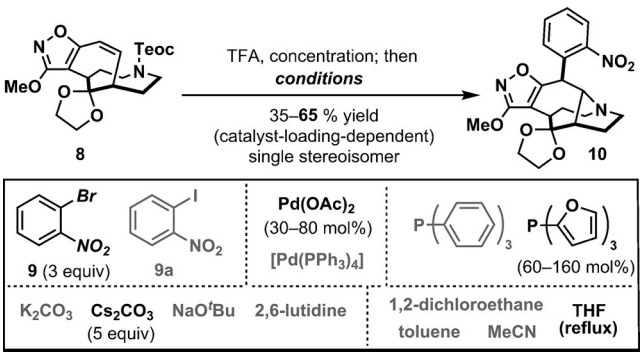
Scheme 3. a) Early exploration of the desymmetrization of diene **5**. b) Synthesis of unsymmetrical alkene **17**, bis(TBS ether) **20**, and ketone **21**. See the Supporting Information for details. IBX = 2-iodoxybenzoic acid; TBS = *tert*-butyldimethylsilyl.

devised on the basis of intermediates **17**, **20**, and **21**, the overall number of synthetic steps was likely to far exceed those required by the Overman,[4a,b] Martin,[4f,h] and Kwon groups.[4i] Therefore, an alternative desymmetrization solution had to be identified to ensure comparable overall efficiency.

Gratifyingly, our continued efforts in desymmetrization ultimately led to the discovery of a cycloaddition process that proved highly effective on diene **5** (Scheme 2). In this instance, the bromonitrile oxide generated in situ from dibromooxime **6** underwent regioselective [2+3] cycloaddition with diene **5** to afford isoxazoline **7** in 68% yield as a single stereoisomer.[10] The use of $KHCO_3$ was previously adopted by the Baran group,[10b] and the optimized procedure was routinely performed on a gram scale with excellent reproducibility. Bromoisoxazoline **7** further underwent methoxy substitution (MeOLi) and oxidation (DDQ) to afford isoxazole **8**, a masked β-ketoester with a concealed carboxylate group and the desired C2 (actinophyllic acid numbering) oxidation state for actinophyllic acid (**1**).

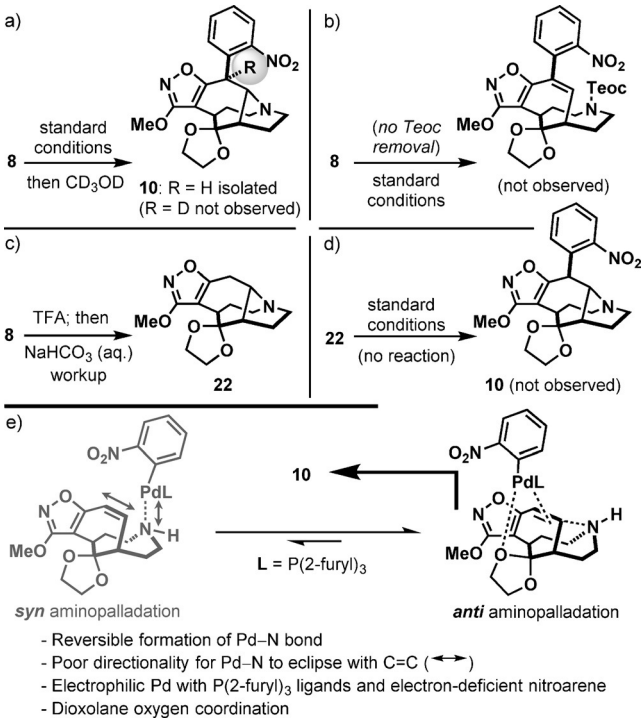
At this juncture, following the selective functionalization of two of the three olefins in triene **2**, the remaining alkene in **8** was poised to undergo an arylation reaction to render a substrate for late-stage indolization. Moreover, the proposed arylation could be made more appealing by synchronizing it with the formation of the adjacent pyrrolidine, a dual objective well-suited for the palladium-catalyzed aminoarylation reaction developed by Wolfe and co-workers.[11] Teoc carbamate **8** was first treated with TFA to unmask its secondary amine while leaving the acid-labile dioxolane intact, and the resulting amine·TFA salt was directly subjected to the aminoarylation conditions. The yield of aminoarylation product **10** varied depending on the reaction conditions (Scheme 4; see also the Supporting Information). The choice of aryl halide, phosphine ligand, base, and solvent were all examined. Although an increase in the catalyst loading had a positive effect on the reaction yield, we opted for a lower catalyst loading for economic reasons and routinely recycled the crude reaction mixture.

The stereochemical assignment of aminoarylation product **10** was established on the basis of extensive 2D NMR studies, and although inconsequential for our synthesis, the observed stereostructure was not in agreement with the generally



Scheme 4. Summary of the optimization of the aminoarylation. All reactions were performed under an Ar atmosphere (see the Supporting Information for details).

accepted mechanism postulated for the aminoarylation reaction.[11] We initially speculated that the originally formed aminoarylation product might have undergone epimerization, or that the arylation reaction might take place without the assistance of the amino group. However, deuteration and control experiments failed to support these speculations (Scheme 5a,b). Interestingly, cleavage of the Teoc



Scheme 5. Probing the stereochemical course of the aminoarylation reaction (see the Supporting Information for details).

carbamate, followed by workup with aqueous $NaHCO_3$, afforded cyclized pyrrolidine **22** (Scheme 5c), a compound that failed to undergo arylation under our standard reaction conditions (Scheme 5d). At the present, our working model for the observed stereochemical outcome is consistent with an *anti*-aminoarylation pathway instead of the originally anticipated *syn*-aminoarylation (Scheme 5e), in which the electrophilic palladium center together with the conformational constraint that prohibited proper Pd–N and C=C alignment would appear to favor *anti*-aminoarylation under reversible palladation conditions.[12] Furthermore, coordination of the palladium center with a dioxolane oxygen atom could also contribute to the observed stereochemical outcome.[13]

With nitroarene **10** in readiness for the planned indolization, the requirement to reduce its nitro group together with the rupture of the isoxazole moiety motivated us to execute both reductive events as a single operation, followed by spontaneous indolization (Scheme 2). This proposed cascade transformation proved nontrivial in practice. In particular, the isoxazole moiety was resilient towards a variety of reducing conditions examined. Ultimately, upon removal of the dioxolane moiety in **10** (HCl, MeOH), $PdCl_2$-catalyzed hydrogenation successfully afforded the targeted indole **12**.

The final conversion of indole **12** into actinophyllic acid (**1**) was realized through slight modification of the original procedure reported by Overman and co-workers,[4a,b] and after acidic hydrolysis (HCl) provided synthetic actinophyllic acid hydrochloride (**1**·HCl)[14] with spectroscopic properties in perfect agreement with those reported previously.[4]

In conclusion, a desymmetrization-based total synthesis of actinophyllic acid (**1**) has been realized. Insightful structural deconvolution of the target molecule uncovered a symmetrical [4.4.1] bicycle **2** as a possible readily accessible starting material. Sequential implementation of judiciously selected and carefully optimized catalytic dihydroxylation, nitrile oxide dipolar cycloaddition, and intramolecular aminoarylation effectively differentiated the three olefins within **2**, followed by reductive indolization and late-stage alkylation to complete the total synthesis. The expedient synthetic pathway showcases "strategy-based" design (desymmetrization) in contrast to the "reaction-based" approach of the Overman (aza-Cope Mannich), Martin (cationic cascade), and Kwon groups (phosphine-catalyzed [3+2]). Further demonstration and variation of desymmetrization-based target-oriented total synthesis are currently in progress in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · cycloaddition · desymmetrization · natural products · total synthesis

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along the reaction pathway. A more detailed theoretical study is currently in progress.
[14] The low yield of actinophyllic acid hydrochloride may be caused by the isolation and purification of this highly polar compound. LCMS analysis of the reaction progress and NMR analysis of the crude reaction mixture indicated that all reactions proceeded smoothly in the final transformations leading to actinophyllic acid hydrochloride.

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