Communication

Enantioselective Synthesis of (+)-Peganumine A

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Enantioselective Synthesis of (+)-Peganumine A

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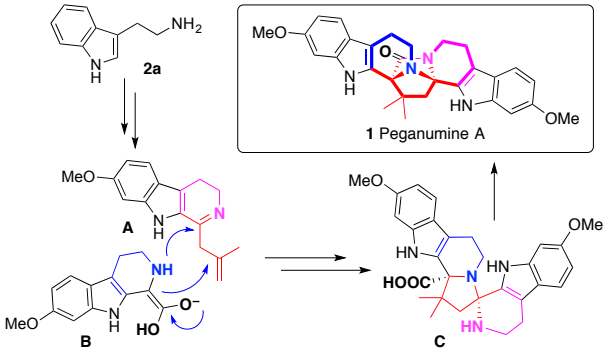
Supporting Information Placeholder

ABSTRACT: A gram-scale enantioselective total synthesis of (+)-peganumine A was accomplished in 7 steps from commercially available 6-methoxytryptamine. Key steps included a) A Liebeskind-Srogl cross coupling; b) A one-pot construction of the tetracyclic skeleton from an ω-isocyano-γ-oxoaldehyde via a sequence of an unprecedented C-C bond forming lactamization and a transannular condensation; c) A one-pot organocatalytic process merging two achiral building blocks into an octacyclic structure via a sequence of enantioselective Pictet-Spengler reaction followed by a transannular cyclization. This last reaction created two spirocycles and a 2,7-diazabicyclo[2.2.1]heptan-3-one unit with excellent control of both the absolute and relative stereochemistry of the two newly created quaternary stereocenters.

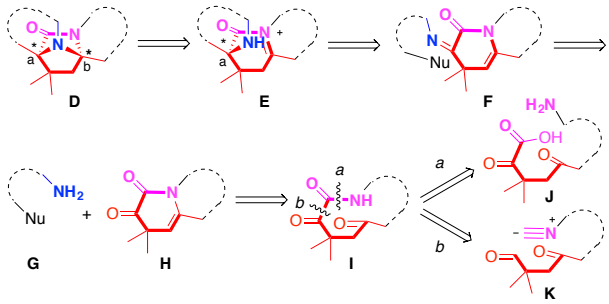
Peganumine A (**1**), a dimeric tetrahydro-β-carboline alkaloid, was isolated by Li, Hua and co-workers in 2014 from the seeds of *Peganum harmala* L.[1] Its structure including the absolute configuration was determined by spectroscopic data, X-ray crystallography, ECD calculation, and CD exciton chirality method. Its octacyclic architecture with a unique 3,9-diazatetracyclo-[6.5.2.$0^{1,9}$.$0^{3,8}$]pentadec-2-one scaffold was unprecedented. It displayed significant cytotoxic activity against MCF-7, PC-3, HepG2 cells and selective effect on HL-60 cells with an IC_{50} value of 5.8 μM. Biosynthetically, it was postulated that heteroannulation of the two C_1-substituted β-carbolines **A** and **B,** both derived from tryptamine (**2a**), could afford spirocycle **C** with concurrent generation of two quaternary stereocenters. Lactamization of the latter would then provide the natural product **1** (Scheme 1).[1]

The intriguing molecular architecture in conjunction with its significant bioactivity and extremely low isolation yield (3.5 mg from 15.4 kg of the seeds of *P. harmala* L.) prompted us to undertake the total synthesis of peganumine A (**1**). While the proposed biosynthesis is appealing, achieving the same [3+2] heteroannulation in the laboratory setting would be difficult if not impossible. Therefore, we set out to develop a disparate approach involving different strategic bond disconnections. The characteristic structural feature of **1** is the presence of a central 2,7-diazabicyclo[2.2.1]heptan-3-one unit that connects the two tetrahydro-β-carbolines *via* spirocyclizations (Scheme 2). Retro-synthetically, cleavage of one of the two C-N bonds of the aminal function in **D**, which was used to represent the generic structure of peganumine A, would generate an *N*-acyliminium salt **E** that would be in equilibrium with enamide **F**. Further bond disconnection of

Scheme 1. Peganumine A and Its Biosynthetic Hypothesis



Scheme 2. Strategic Bond Disconnections of the Core Structure of Peganumine A

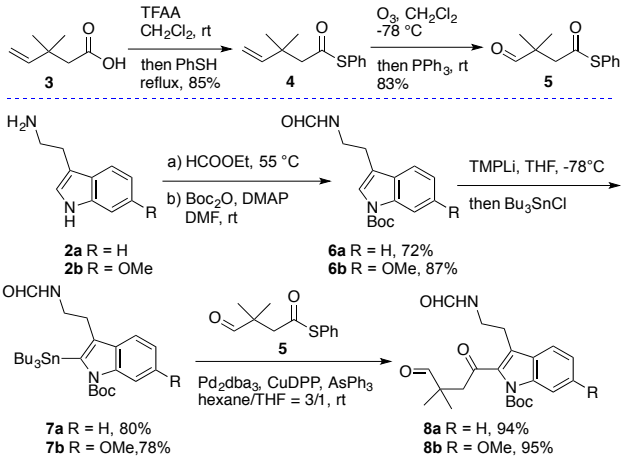


F would reveal an amine **G** containing a tethered nucleophile and a cyclic α-ketoamide **H**. In a forward sense, it was expected to obtain compound **D** in a one-pot manner from **G** and **H**. Since the absolute configuration of C_a generated in the Pictet-Spengler (PS) reaction will be completely translated into that of C_b, a catalytic enantioselective PS reaction[2] would allow us to convert achiral building blocks **G** and **H** to enantio-enriched final product **D**. Compound **H** could be obtained by transannular cyclization of δ-oxo-α-ketolactam **I**. Instead of the classic macrolactamization of an appropriately functionalized linear ω-amino-δ-oxo-α-ketoacid **J** (disconnection *a*) for the access to **I**, we envisaged to build the macrolactam via the formation of a C-C bond with concurrent formation of the α-hydroxylamide or α-ketoamide function and planned to use either the intramolecular Passerini reaction[3] or the Ugi reaction[4] of ω–isocyano-γ-oxoaldehyde **K** for this purpose (disconnection *b*). This last transformation was unknown in the forward sense, presenting therefore a

new opportunity to explore the synthetic potential of the isocyanide chemistry.

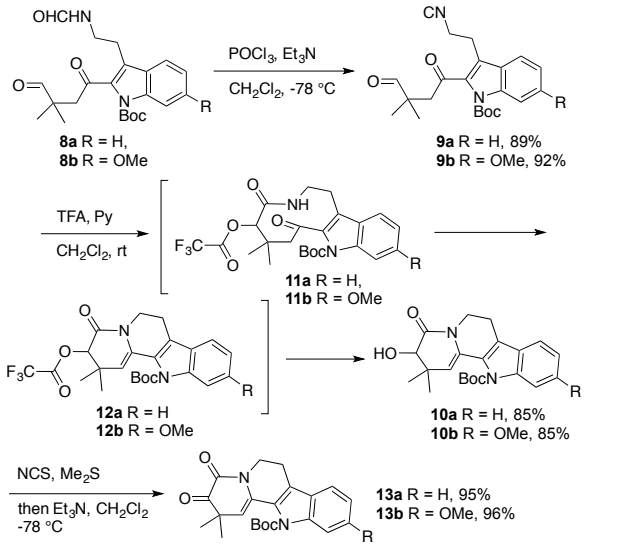
Our synthesis began with the preparation of C2 acylated tryptamine **8** (Scheme 3). Thioesterification of 3,3-dimethylpent-4-enoic acid (**3**) [5] afforded **4** (TFAA, PhSH, CH_2Cl_2, reflux, 85%) which, upon ozonolysis, was converted to *S*-phenyl 3,3-dimethyl-4-oxobutanethioate (**5**) in 83% yield. In parallel, chemoselective *N*-formylation of the primary aliphatic amine of tryptamine (**2a**, HCOOEt, 55 °C) followed by *N*-Boc protection of the indolic nitrogen (Boc_2O, DMAP, DMF, rt) afforded **6a** in 72% overall yield. C2-Lithiation followed by interception of the resulting vinyllithium with tributyltin chloride provided **7a** in 80% yield.[6] The Liebeskind-Srogl cross coupling[7] between **7a** and **5** turned out to be challenging. Under standard conditions [copper(I) thiophene-2-carboxylate (CuTC, Pd_2dba_3, PPh_3 or TFP, THF), [8] the major product isolated was **6a**. The competitive transmetallation of tin to copper is presumably responsible for the rapid protodestannylation of **7a** to **6a**.[9] A systematic survey of reaction parameters was subsequently carried out that allowed us to obtain the desired coupling product **8a** in 94% yield under optimized conditions [Pd_2dba_3 (0.1 equiv), $AsPh_3$ (0.1 equiv), copper(I) diphenylphosphinate (CuDPP, 1.2 equiv), hexane/THF = 3/1, *c* 0.067 M, rt]. We note that the effective concentration of Cu ion in the above solvent system is significantly reduced due to the low solubility of CuDPP in hexane, avoiding therefore the protodestannylation process. It is worthy noting that coupling of 2-indolylboronic acid with thioester **5** failed to produce the desired coupling product.

Scheme 3. Synthesis of C2 Acylated Tryptamine Derivatives

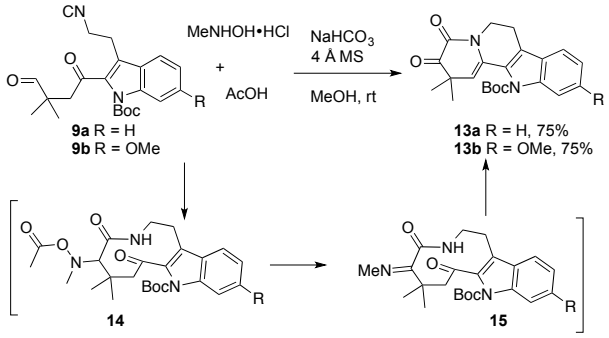


Dehydration of *N*-formamide **8a** ($POCl_3$, Et_3N, CH_2Cl_2, -78 °C) provided ω-isocyano-γ-oxoaldehyde **9a** in 89% yield (Scheme 4). Compound **9a** has to be purified by FCC on aluminum support as partial decomposition occurred on silica gel. Gratefully, Passerini 3-center-2-component reaction of **9a** with acetic acid in dichloromethane (*c* 0.01 M, 1.5 days) at rt followed by saponification of the resulting acetate afforded directly tetracycle **10a** in 83% overall yield (*cf* SI). Using TFA as acid input, the same reaction afforded directly **10a** (TFA, Py, CH_2Cl_2, rt, 5 days) after simple aqueous work-up in 85% yield, albeit with a longer reaction time.[10] It is reasonable to assume that the reaction went through the 10-membered macrolactam **11a**, which underwent spontaneous transannular cyclization to provide tetracycle **12a**. Hydrolysis of the latter furnished then the product **10a**. Attempts to detect the presence of intermediate **11a** or its hydrolyzed product in the crude reaction mixture were unsuccessful due probably to the fast transannular cyclization process. Corey-Kim oxidation[11] of **10a** afforded α-ketolactam **13a** in 94% yield. Swern oxidation[12] of **10a** provided **13a** in a slightly lower yield (87%). Following the same synthetic sequence detailed in Schemes 3 and 4, 6-methoxytryptamine (**2b**) was converted to **13b** in 48% overall yield.

Scheme 4. Passerini 3-Center-2-Component Reaction of ω-Isocyano-γ-oxoaldehyde with Carboxylic Acid: Synthesis of Tetracyclic α-Ketoamide 13



Scheme 5. One-pot Conversion of ω-Isocyano-γ-oxoaldehyde 9 to Tetracyclic α-Ketoamide 13 by an Internal Redox Process

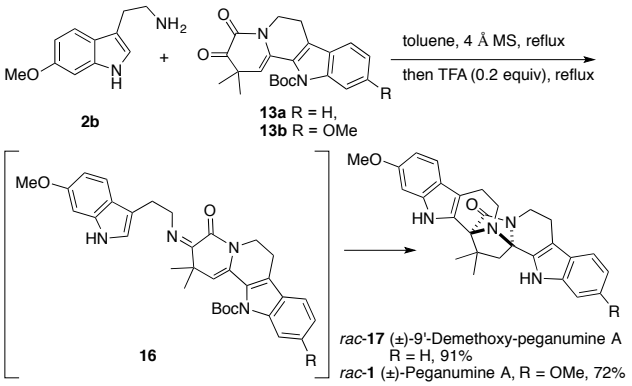


A one-pot synthesis of tetracycle **13** from **9** involving a formal intramolecular oxidative coupling of the ω-isocyano-γ-oxoaldehyde is shown in Scheme 5. Reaction of **9a** with *N*-methylhydroxylamine and acetic acid in MeOH (*c* 0.01 M) in the presence of 4 Å molecular sieves and $NaHCO_3$ afforded **13a** in 75% yield.[13] Compound **9b** (R = OMe) was converted to **13b** in a similar yield. In accordance with the previous mechanistic studies, we assumed that the initial Ugi 4-center-3-component reaction occurred smoothly to afford the adduct **14** which underwent β-elimination to afford the α-iminolactam **15**. Hydrolysis of the latter furnished then the observed product **13**. We stress that, against the common

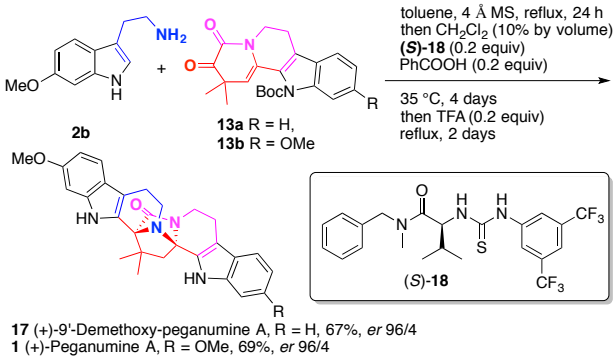
wisdom, the formation of 7-membered lactam resulting from the attack of the isocyano group onto the internal oxo function, a generally much faster process than that of 10-membered ring, was not observed. Note that the terminal aldehyde function is of neopentyl type and is therefore sterically hindered. To the best of our knowledge, ω-isocyano carbonyl compounds have never been used as bifunctional inputs neither in Passerini nor in Ugi type reactions.[14] We believe that these reactions might be useful additions to synthetic arsenal in light of the frequent occurrence of the α-ketoamide unit in bioactive macrocycles and drugs.[15]

With a reliable, multigram synthesis of tetracycle **13a** in hand, its condensation with 6-methoxytryptamine (**2b**) was next attempted.[16] Although the ketone carbonyl is electronically activated by the neighboring amide function, it is sterically hindered due to its neopentylic position. After extensive screening of reaction conditions, it was found that heating to reflux a toluene solution of **2b** and **13a** in the presence of 4 Å molecular sieves afforded cleanly imine **16**. Addition of a catalytic amount of TFA (0.2 equiv) to the reaction mixture (reflux, 5 days) provoked a sequence of domino cyclization and *N*-Boc deprotection (*vide supra*) to afford (±)-9'-demethoxy-peganumine A (*rac*-**17**) in 91% yield (Scheme 6). It is worthy noting that increasing the amount of TFA reduced significantly the yield of the final product. Gratefully, condensation of **2b** with **13b** under the identical conditions, afforded (±)-peganumine A (*rac*-**1**) in 72% isolated yield.

Scheme 6. Synthesis of (±)-Peganumine A

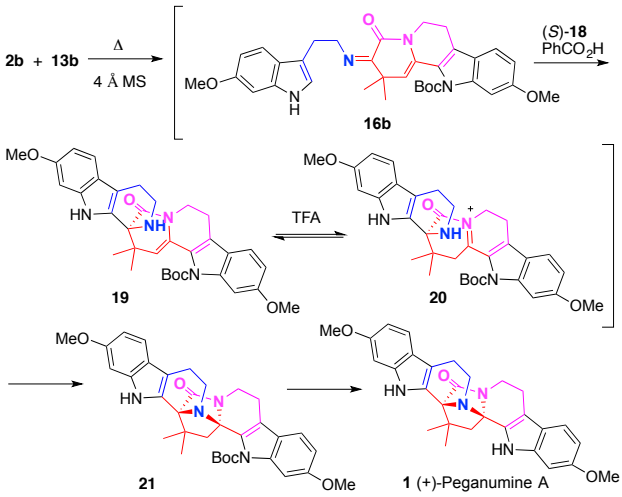


Scheme 7. Thiourea-catalyzed Enantioselective Synthesis of (+)-Peganumine A



The feasibility of our synthetic approach being approved, we next searched for conditions to accomplish a catalytic enantioselective synthesis of (+)-peganumine A. The reaction between **2b** and **13a** in the presence of chiral phosphoric acid (TRIP) indeed afforded 9'-demethoxy-peganumine A (**17**), albeit with low yield (7%) and enantioselectivity (*er* 64.5/35.5).[17] Using Jacobsen's chiral thiourea catalyst (*S*)-**18** was found to be more rewarding.[18] Since the thiourea of type **18** has not been applied to the Pictet-Spengler reaction of ketone, (*S*)-**18** was chosen arbitrarily as no empirical model could be followed to predict the stereochemical outcome. After survey of reaction parameters, the optimized conditions consisted of refluxing a toluene solution of **2b** and **13a** in the presence of 4 Å MS (24 h) followed by adding a solution of thiourea (*S*)-**18** (0.2 equiv) and PhCOOH (0.2 equiv) in CH_2Cl_2 (10% by volume). After being heated at 35 °C for 4 days, TFA (0.2 equiv) was added and the reaction mixture was refluxed for an additional 2 days to afford (+)-9'-demethoxy-peganumine A (**17**) in 67% yield with *er* of 96/4 (Scheme 7). Using PhCOOH as co-catalyst is of utmost importance for the enantioselectivity of the reaction since using AcOH instead of PhCOOH under otherwise identical conditions provided compound **17** (75% yield) with significantly reduced enantioselectivity (*er* 72/28). To our delight, condensation of **2b** with **13b** proceeded equally well to afford (+)-peganumine A (**1**) (69%, *er* 96/4) whose spectroscopic data are identical in all respects to those reported for the natural product.[19] Comparison of the sign and value of the $[\alpha]_D$ [synthetic: +6.2 (*c* 0.1, MeOH); [Lit][1]: +5.6 (*c* 0.15, MeOH)] allowed us to conclude that the natural enantiomer was produced using (*S*)-**18** as catalyst. Performing the reaction in a gram scale afforded the natural product with similar yield and enantioselectivity.

Scheme 8. Merging Two Achiral Building Blocks to (+)-Peganumine A: Reaction Pathway



The reaction pathway leading to (+)-peganumine A (**1**) is depicted in Scheme 8. Condensation of amine **2b** with α-ketoamide **13b** afforded imine **16b**, which underwent the enantioselective aza-Friedel-Crafts addition under the influence of the thiourea (*S*)-**18** and PhCOOH to provide the enantioenriched **19**. Upon addition of a catalytic amount of strong acid (TFA), enamine-imine tautomerization occurred to provide **20**, which, upon stereospecific transannular addition of the secondary amine to iminium, furnished octacycle **21**. Removal of *N*-Boc furnished then the natural product **1**. Monitoring the reaction progress using ^{1}H NMR spectroscopy

indicated that the *N*-Boc deprotection is the slowest step of the sequence. In this domino process, three chemical bonds were formed leading to the formation of two spirocycles and a diazabicyclo[2.2.1]heptan-3-one unit. Two quaternary stereocenters were created from two achiral building blocks with excellent control of both enantio- and diastereoselectivities.

In summary, the first asymmetric total synthesis of (+)-peganumine A (**1**) has been achieved featuring two novel multiple bond forming processes: a) A hydroxylamine-mediated intramolecular oxidative coupling of ω-isocyano aldehydes for the direct access to tetracycles with an α-ketoamide function. This lactamization process via C-C rather than C-N bond formation is unprecedented; b) A one-pot chiral thiourea/PhCOOH-catalyzed domino process merging two achiral building blocks into an octacyclic structure via a sequence of enantioselective Pictet-Spengler reaction followed by a TFA-catalyzed transannular cyclization. Overall (+)-peganumine A (**1**) was synthesized in 7 steps with 33% overall yield (*er* 96/4) from the commercially available 6-methoxytryptamine. The synthetic route, scalable and amenable for the analogues synthesis, paved the way for the SAR studies of this structurally novel natural product.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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(19) We found that (+)-peganumine A (**1**) is poorly soluble in most of the common organic solvents including methanol and DMSO.

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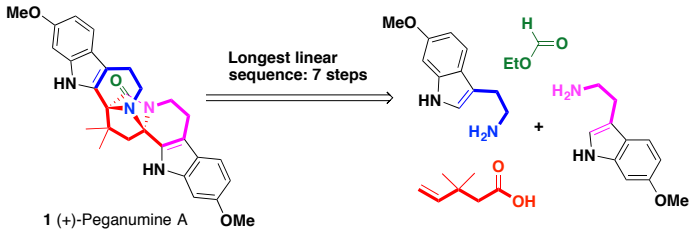

1 (+)-Peganumine A