Published in final edited form as:

J Am Chem Soc. 2018 July 18; 140(28): 8675–8680. doi:10.1021/jacs.8b01918.

Total Synthesis of the Norhasubanan Alkaloid Stephdiamine

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Abstract

Stephdiamine is an unusual alkaloid isolated from the vine *Stephania japonica*. It features a norhasubanan skeleton, and contains two adjacent α -tertiary amines, which renders it an attractive synthetic target. Here, we present the first total synthesis of stephdiamine, which hinges on an efficient cascade reaction to implement the aza[4.3.3]propellane core of the alkaloid. The α -aminolactone moiety in a highly hindered position was installed via Tollens reaction and Curtius rearrangement. Useful building blocks for the asymmetric synthesis of morphine and (nor)hasubanan alkaloids are introduced.

Graphic Table of Contents (TOC)

Morphine and hasubanan alkaloids have inspired synthetic chemists for decades. Following the pioneering work of Gates in 1952,^[1] more than 30 total and formal syntheses of morphine (**1**) have been published,^[2] some of them very recently.^[3] Many syntheses of hasubanonine (**2**) and its congeners have appeared in the literature since the isolation of the first hasubanan alkaloid was reported by Konto *et al.* in 1951.^[4] Therefore, it is surprising

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Supporting Information

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Experimental procedures, spectroscopic data and copies of NMR-spectra (PDF). CIF file for compounds **5** (CCDC 1823787), **6** (CCDC 1823794), (*rac*)-**8** (CCDC 1823788), (*R*)-**8** (CCDC 1823795), (*S*)-**8** (CCDC 1823796), **9** (CCDC 1823789), **11** (CCDC 1823792), **16** (CCDC 1823793), **17** (CCDC 1823791), **19** (CCDC 1823798), **21** (CCDC 1823801), **23** (CCDC 1823786), **S1** (CCDC 1823790), **S3** (CCDC 1823800), **S4** (CCDC 1823797), **S6** (CCDC 1823799) (CIF files are also available free from charge on <https://www.ccdc.cam.ac.uk/structures/>)(CIF)

The authors declare no competing financial interest.

that one of the most beautiful and challenging molecules in the series, *viz.* stephadiamine (**3**), has been virtually ignored by the synthetic community.

Stephadiamine (**3**) was isolated from the snake vine *Stephania japonica* in 1984 by Inubushi *et al.* and is the first example of a norhasubanan alkaloid, which feature a contracted C-ring.^[5] Although *S. japonica* is used in traditional Chinese medicine to treat asthma, fever and digestive disorders,^[6] the biological activity of stephadiamine (**3**) has yet to be established due to a paucity of material. Structurally, **3** features a unique pentacyclic skeleton arranged around an aza[4.3.3]propellane core. It bears a total of four stereocenters, including a benzylic quaternary carbon and two adjacent α -tertiary amines in a *cis*-1,2 relationship.^[7] One of these is part of an α -amino δ -lactone which contains the benzylic oxygen often found in hasubanan alkaloids.

Motivated by these unusual structural features and our general interest in hasubanan alkaloids,^[8] we set out to explore the synthesis of stephadiamine (**3**). Our initial strategy called for the installation of both α -tertiary amines and the [4.3.3]-azapropellane core through a late-stage *cis*-1,2-diamination (Scheme 1). The requisite diamination precursor of type **4**, a highly substituted cyclopentene carboxylate, could be traced back to conjugated ester **5** *via retro*-reductive aldol condensation. Ketone **5**, in turn, could be accessed from the known tetralone **6**.^[9] Tetralones with this substitution pattern are popular intermediates in the synthesis of hasubanan and morphinan alkaloids,^[10] but most reported preparations are lengthy, require expensive catalysts and starting materials, or are difficult to scale up.^[9]

We therefore set out to develop a one-pot procedure starting from the commercially available carboxylic acid **7**. Conversion of **7** to the corresponding acyl chloride, followed by treatment with AlCl₃ under an ethene atmosphere provided tetralone **6** in good overall yield and on a multigram scale (Scheme 3). Low temperatures were necessary in this reaction to prevent competing cyclization to the corresponding benzofuranone with participation of the adjacent methoxy group.^[11] Alkylation of **6** with bromo acetonitrile under Stork conditions,^[12] followed by conversion to the enol carbonate and decarboxylative Tsuji allylation yielded tetralone **8** as a racemate with the benzylic quaternary stereocenter in place.^[13] A subsequent cross metathesis with methyl acrylate then provided the conjugated ester **5** in excellent yield.^[14]

With ester **5** in hand, we investigated a reductive aldol reaction to form the five-membered ring.^[15] Despite intensive screening efforts, we were only able to obtain traces of the desired tertiary alcohol **10**. Instead, we isolated varying amounts of the lactone **9**, which is apparently formed by attack of a tertiary alcoholate onto the nitrile, followed by hydrolysis. The single crystal X-ray structure of **9** revealed a perfect *anti*-periplanar arrangement of the C,H-bond next to the methyl ester and a C,O-single bond in the lactone. Despite this, we were unable to promote an elimination to install the cyclopentene carboxylate. Therefore, we sought conditions that would allow us to isolate aldol product **10** with the nitrile intact (Scheme 3). Hydrogenation of **5** yielded saturated ester **11**. Upon exposure of **11** to sodium methoxide in methanol at 75 °C, we isolated two new products in excellent combined yield. To our pleasant surprise, these were identified as the pyrrolidinones **16** and its C7-epimer **17**, both of which contain the aza[4.3.3]propellane core of **3**.

Epimers **16** and **17** are obtained as a 10:1 mixture through a reaction cascade that presumably involves a transiently formed ester enolate **12**. Intramolecular aldol addition then affords alcohol **13**, which undergoes addition to the nitrile (**13**→**14**), elimination of the intermediary imidate (**14**→**15**), and conjugate re-addition through the nitrogen to yield the pyrrolidinones. This sequence of events resembles a cascade that was used by Inubushi and colleagues on their synthesis of cephamine.^[16] In our case, however, a different type of starting material is used and a different heterotricyclic system with an additional stereocenter is constructed in a remarkably efficient overall reaction.

At this point of our synthesis, completion of stephadiamine (**3**) formally required *N*-methylation, α -amination and closure of the lactone *via* benzylic functionalization. While the first task could be achieved by treating the diastereomeric mixture of lactams **16** and **17** with NaH and MeI, the latter two turned out to be exceedingly difficult due to the steric hindrance of the azapropellane system. We therefore decided to resort to chemistry that would employ a minimal base and a minimal electrophile: the Tollens reaction, *i.e.* an aldol reaction followed by a crossed Cannizzaro reaction.^[17] To this end, we first reduced the ester moiety to the corresponding aldehyde using DIBAL-H. Subsequent exposure to KOH and formaldehyde at elevated temperatures over two days then afforded diol **18**, which features a quaternary carbon in a sterically very congested position.

Next, we investigated the formation of the lactone moiety by differentiation of the two primary alcohols in **18**. After screening multiple oxidation and protection conditions, this could be accomplished by benzylic ether formation using DDQ and AcOH at elevated temperatures.^[18] With one hydroxymethyl group so isolated, we focused on the implementation of the second α -tertiary amine. To this end, the primary alcohol was converted to the carboxylic acid using Ley's conditions^[19] followed by a Pinnick-Lindgren oxidation.^[20] Formation of the acyl azide followed by Curtius rearrangement in the presence of benzyl alcohol then smoothly gave the Cbz-protected *cis*-1,2-diamine **19**.

At this stage, the completion of the synthesis would only require reduction of the lactam in **19**, oxidation of its tetrahydropyran to a lactone and deprotection of the primary amine. Although we were aware that chances were slim due to the presence of a benzylic C,H-bond and a very electron-rich aromatic ring, we first explored the oxidation under a variety of conditions (RuO₄, KMnO₄, CrO₃, DMDO, White-Chen catalyst). None of these led to an isolable product. We therefore decided to cleave the benzylic C,O bond *via* elimination, using excess BF₃·OEt₂ in acetic anhydride. This protocol furnished an oxazolidinone intermediate that was treated with Boc anhydride and then partially hydrolyzed to afford the Boc-protected amino alcohol **20**.^[21]

The completion of the synthesis required a very careful orchestration of redox reactions carried out on highly hindered and sensitive substrates. Ley oxidation of the primary alcohol in **20** to the corresponding aldehyde, followed by treatment with iodine in methanol yielded a methyl ester.^[22] Since this ester could not be hydrolyzed, we attempted the direct cyclization to lactone **21**. Acid-catalyzed lactonization and conventional halolactonization were unsuccessful. Using NBS in the presence of H₂O, however, we were able to install a bromohydrin that underwent rapid lactonization.^[23] The secondary bromide was removed

under radical conditions to obtain the pentacyclic lactone **21**, whose structure was confirmed by single X-ray analysis. In the final steps of the synthesis, the lactam moiety in **21** was reduced to the corresponding pyrrolidine using borane dimethyl sulfide complex.^[24] Careful deprotection of the primary amine then gave racemic stephadiamine (**3**). The analytical data of synthetic **3** were in complete agreement with the limited data available from the isolation paper.

To open a pathway toward an asymmetric synthesis of **3**, we investigated the formation of the quaternary stereocenter with transition metal catalyzed alkylations (Scheme 4).^[25] Treatment of the allylic carbonate **22** with a palladium (0) source in the presence of chiral *bis*-phosphine **24** gave (*R*)-**8** in 66% enantiomeric excess (see SI for details).^[26] After a single recrystallization we obtained an almost enantiomerically pure product, the absolute configuration of which could be established by X-ray crystallography. Conversely, by employing the asymmetric counteranion directed catalysis recently developed by List and co-workers,^[27] exposure of **23** to allyl methyl carbonate and a palladium (0) source in the presence of chiral phosphate diester **25** gave **8** in 93% ee.^[28]

In summary, we have achieved the first synthesis of the unusual alkaloid stephadiamine (**3**), in racemic form. Our synthesis is marked by a practical b-tetralone synthesis, the facile construction of the benzylic quaternary center through twofold alkylation, and a remarkably efficient cascade to forge the azapropellane core of **3**. The installation of the α -amino lactone moiety in a congested setting proved to be difficult but could eventually be achieved using a very small base (hydroxide anion) and a very small electrophile (formaldehyde). It also

required the careful orchestration of oxidation and reductions in densely functionalized molecules. Finally, we have mapped out a pathway for the asymmetric synthesis of stephadiamine, which was not followed through for economic reasons. Racemic compounds are also more likely to yield suitable crystals for single crystal X-ray crystallography, which we took ample advantage of in this study.^[29] The enantiomerically pure building blocks (**R**)-**8** and (**S**)-**8**, could serve as valuable intermediates in the synthesis of a variety of hasubanan and morphine alkaloids, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We would like to acknowledge Dr. Anastasia Hager and Dr. Dominik Hager for their contributions in the early stages of this project. The authors thank Dr. Hong-Dong Hao and Dr. Julius R. Reyes for experimental assistance, Dr. Scott Virgil and René Rahimoff for assistance with HPLC and Dr. Peter Mayer for X-ray structure analysis. Additionally, we acknowledge the Deutsche Telekom Foundation (Ph.D. fellowship to N.H.), the LMUMentoring program (fellowship N.H.), the Otto Bayer Scholarship (fellowship to N.H.) as well as the Deutsche Forschungsgemeinschaft (SFB 749 and CIPSM) for generous funding. B.M.S. thanks the NIH-NIGMS (R01GM080269) for partial financial support of this project. Dr. Felix Hartrampf and Dr. Julius R. Reyes are acknowledged for excellent support in the course of this project and with the preparation of this manuscript.

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Scheme 2. Synthesis of tetralone 8 and attempted aldol condensation.

^aReagents and conditions: (a) oxalyl chloride (1.2 eq.), DMF (cat.), CH₂Cl₂, 0 °C, 10 min, then r.t., 3 h; (b) AlCl₃ (6 eq.), ethene (1 atm), –32 °C, 6 h, 48% over 2 steps; (c) pyrrolidine (1.3 eq.), toluene, MgSO₄ 100 °C, 24 h, then BrCH₂CN (1.6 eq.), 100 °C, 28 h, 89%; (d) NaH (1.1 eq.), THF, 0 °C, 30 min, then allyl chloroformate (1.0 eq.), 0 °C, 1 h, 98%; (e) Pd₂(dba)₃ (2.5 mol%), PPh₃ (6.25 mol%), r.t., 12 h, 84%; (f) HG II (7 mol%), methyl acrylate (15 eq.), toluene, 48 h, 97%; Cu(OAc)₂·H₂O (0.5 eq.), *rac*-BINAP (0.5 eq.), TMDS (1 eq.), THF, 24 h → 1 M HCl, r.t., 1 h, 60%. BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl; dba = dibenzylideneacetone, HG II = Hoveyda Grubbs cat. 2nd generation, TMDS = 1,1,3,3-tetramethyldisiloxane

Scheme 3. Cascade reaction for the construction of the aza[4.3.3]propellane core.

^aReagents and conditions: (a) Pd-C (10wt%), H₂ (1 atm), EtOAc, r.t., 12 h, 97%; (b) NaOMe (1.2 eq.), MeOH, 75 °C, 24 h, 91% on 24 mmol scale, 99% on 3 mmol scale.

Scheme 4. Installation of the diamine and endgame.

^aReagents and conditions: (a) NaH (1.2 eq.), MeI (1.2 eq.), DMF, 30 °C, 14 h, 91%; (b) DIBAL-H (2.5 eq.), CH₂Cl₂, 78 °C, 3.5 h, 79%; (c) KOH (10 eq.), formaldehyde (10 eq.), MeOH, 50 °C, 48 h, 41% (d) DDQ (10 eq.), AcOH (10 eq.), 4 Å MS, DCE, 75 °C, 5 h, 92%; (e) TPAP (0.05 eq.), NMO (10 eq.), 4 Å MS, CH₂Cl₂, r.t., 1 h, 93%; (f) NaClO₂ (9.2 eq.), NaH₂PO₄ (9.2 eq.), 2-methyl-2-butene, *t*-BuOH/H₂O, r.t., 3 h, 96%; (g) DPPA (1.5 eq.), NEt₃ (3 eq.), toluene, r.t., 1 h, then 100 °C, 1 h, then BnOH (5 eq.), 100 h, 14 h, 84%; (h) BF₃·OEt₂ (30 eq.), Ac₂O, 0 °C to r.t., 6.5 h, 84%; (i) Boc₂O (2 eq.), NEt₃ (2 eq.), DMAP (0.1 eq.), THF, r.t., 17 h, 65%; (j) Cs₂CO₃ (0.5 eq.), MeOH, r.t., 12 h, 96%; (k) TPAP (0.02 eq.), NMO (4.5 eq.), 4 Å MS, CH₂Cl₂, r.t., 20 min, 80%; (l) I₂ (10 eq.), KOH (10 eq.), MeOH, r.t., 15 min, 94 %; (m), NBS (1.05 eq.), H₂O/THF, 0 °C, 90 min. then r.t., 90 min., 50%; (n) Bu₃SnH (10 eq.), AIBN (1 eq.), benzene, 90 °C, 3 h, 98%.; (o) DMS·BH₃ (10

eq.), THF, 0 °C to r.t., 20 h, then 0 °C, AcOH, 57%, 99% brsm; (p) TFA, DCM, 0 °C, 90 min, <90%. Cbz = carboxybenzyl, DIBALH = diisobutylaluminium hydride, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, MS = molecular sieves, TPAP = tetrapropylammonium perruthenate, NMO = *N*-Methylmorpholine *N*-oxide, DPPA = diphenylphosphoryl azide, Boc = *tert*-butyloxycarbonyl, DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, AIBN = α,α' -azoisobutyronitrile.