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Stereospecific Approach to the Synthesis of Ring-A Oxygenated *Sarpagine* Indole Alkaloids. Total Synthesis of the Dimeric Indole Alkaloid *P*-(+)-Dispegatrine and Six Other Monomeric Indole Alkaloids

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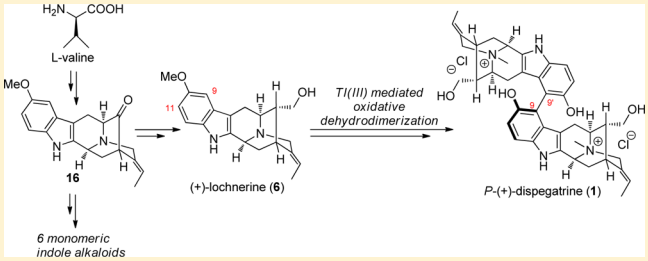
Supporting Information

ABSTRACT: The first regio- and stereocontrolled total synthesis of the bisphenolic, bisquaternary alkaloid (+)-dispegatrine (**1**) has been accomplished in an overall yield of 8.3% (12 reaction vessels) from 5-methoxy-D-tryptophan ethyl ester (**17**). A crucial late-stage thallium(III) mediated intermolecular oxidative dehydrodimerization was employed in the formation of the C9−C9′ biaryl axis in **1**. The complete stereocontrol observed in this key biaryl coupling step is due to the asymmetric induction by the natural *sarpagine* configuration of the monomer lochnerine (**6**) and was confirmed by both the Suzuki and the oxidative dehydrodimerization model studies on the tetrahydro β-carboline (**35**). The axial chirality of the lochnerine dimer (**40**) and in turn dispegatrine (**1**) was established by X-ray crystallography and was determined to be *P*(S). Additionally, the first total synthesis of the monomeric indole alkaloids (+)-spegatrine (**2**), (+)-10-methoxyvellosimine (**5**), (+)-lochnerine (**6**), lochvinerine (**7**), (+)-sarpagine (**8**), and (+)-lochneram (**11**) were also achieved via the common pentacyclic intermediate **16**.



INTRODUCTION

The *sarpagine-macroline* group is one of the largest groups of structurally related indole alkaloids isolated principally from the *Apocynaceae* plant family.[1] More than 150 members of this group have been isolated to date, many of which exhibit interesting pharmacological activities.[1,2] Among them, bisindoles are of special significance because they exhibit more potent bioactivity than their monomeric counterparts.[3] However, a vast majority of these alkaloids have been poorly evaluated due to paucity of material available for biological testing. The *sarpagine-macroline* bases are biogenetically related[4] to the clinically important *ajmaline* alkaloids,[5] and common to these three classes is the azabicyclo[3.3.1]nonane core, as illustrated in Figure 1.

In continuation of their efforts at the biology-oriented synthesis (BIOS)[6] of natural product derived probes, Waldmann et al. targeted the *sarpagine-macroline* indole alkaloids which led to the cycloocta[*b*]indole core (**I**) as a starting point for library design.[7] More than a hundred tetracyclic analogues of this core, synthesized by a stereoselective solid-phase synthesis, were investigated for their inhibitory activity in enzymatic assays with various tyrosine phosphatases. The screen yielded an unprecedented class of potent inhibitors of Mycobacterium protein tyrosine phosphatase B (MptpB) with IC_{50} values in low micromolar range (the most potent MptpB inhibitor of the library has an IC_{50} value of 4.71 ± 1.14 μM). The MptpB inhibitory activity of **I** seemed to be greatly influenced by the '*S*' stereochemistry at C-6 and C-10 and by the presence of a β-ketoester moiety (see Figure 1). The N_b-benzyl group in **I**, containing 1) an oxygen atom either within the aromatic ring system or as a phenol substituent and 2) with *m*,*p*-disubstituted electron withdrawing groups, was important to potent MptpB inhibition. MptpA and MptpB secreted by the causative organism of tuberculosis, *Mycobacterium tuberculosis*, are known to selectively dephosphorylate human host proteins involved in interferon-γ signaling pathways thereby preventing the initiation of host defense mechanisms.[8] The tetracyclic core (**I**) of the *sarpagine* alkaloids thus may be considered as a promising target for the development of new drug candidates against tuberculosis.

The dried roots and leaves of *Rauwolfia verticillata* (Lour.) or *Lou Fu Mu* have been used in Chinese folk medicines for thousands of years as tranquilizers and more recently in the treatment of hypertension and hyperthyroidism.[9] Illustrated in Figure 2 is (+)-dispegatrine (**1**),[10] a bisquaternary, bisphenolic *sarpagine* alkaloid isolated from the water-soluble fraction of the root of *R. verticillata* (Lour.) Baill var. *hainanensis Tsiang* along with the monomer (+)-spegatrine (**2**).[11] Bisphenolic, bisquaternary indole alkaloids are very rare.[12] Of the 300 or so dimeric indole alkaloids isolated to date, the homodimer **1** and blumeanine[13] (not shown) are the only two dimers belonging

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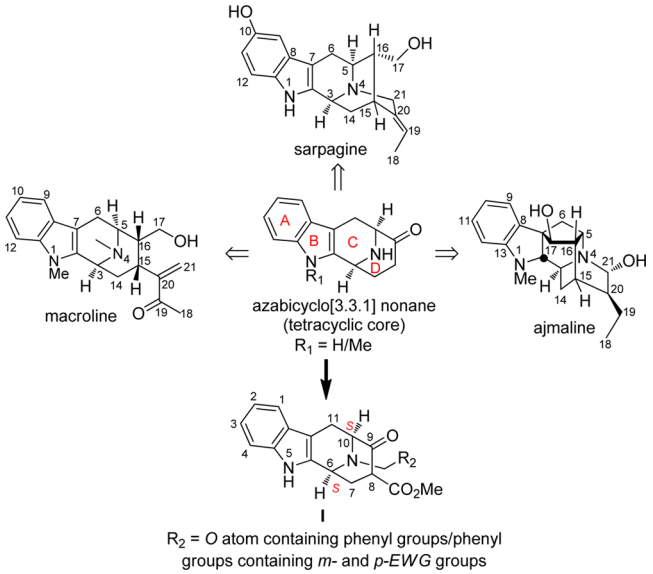

Figure 1. SAR of the cycloocta[*b*]indole framework (**I**) of the *sarpagine-macroline* and *ajmaline* related indole alkaloids active against MptpB.[7] EWG: electron withdrawing group.

to this class of alkaloids. Although dispegatrine (**1**) and its corresponding monomer spegatrine (**2**) exhibit promising hypotensive activity, the affinities and activities of the dimer **1** on both α1 and α2 adrenergic receptors was about an order of magnitude greater than that of the monomer **2**.[3e] The quaternary alkaloids verticillatine (**3**)[14] and macrospegatrine (**4**)[15] illustrated in Figure 2 are also known to exhibit promising antihypertensive activity.[16]

A number of biogenetically related ring-A oxygenated monomeric alkaloids such as (+)-10-methoxyvellosimine (**5**),[17] (+)-lochnerine (**6**),[18] (+)-sarpagine (**7**),[19] *O*-acetylsarpagine (**8**),[20] lochvinerine (**9**),[21] (+)-episarpagine (**10**),[20] (+)-lochneram (**11**),[18c,22] and (+)-lochnerine N_b-oxide (**12**)[23] have also been reported (Figure 2). Lochnerine (**6**), which itself has no antitumor activity, when combined with vincristine or daunorubicin (not shown) at subcytotoxic concentrations induced complete inhibition of the vincristine-resistant P388 leukemic cells in vitro.[24] Additionally, **6** is known to exhibit promising vasorelaxant actvity.[25] Most recently, **6** and **7** were found to be present in some of the new *macroline-sarpagine* bisindoles (**13**−**15**, Figure 2) isolated from *Alstonia angustifolia* by Kam et al.[26] The promising bioactivity of some of the members of these ring-A oxygenated group of indole alkaloids combined with their complex architecture made them very attractive targets.

The total synthesis of *P*-(+)-dispegatrine (**1**) and four other monomeric indole alkaloids was recently reported via a general approach for the synthesis of ring-A oxygenated *sarpagine* alkaloids.[27] Such a doubly convergent route could also be employed for the potential synthesis of the complex bisindoles **4**, **13**−**15**; the biological activities of which have not yet been fully investigated. In this report, the full details of the development of this general route including the first total synthesis of alkaloids **9** and **11** are reported.

RESULTS AND DISCUSSION

Although dispegatrine (**1**) was isolated as a single atropodiastereomer and its structure established on the basis of spectroscopic analysis (^{1}H NMR, ^{13}C NMR, and mass spectrum comparison to monomer **2**),[10] the apparent axial chirality at the C9−C9′ biaryl axis in **1** was not determined.

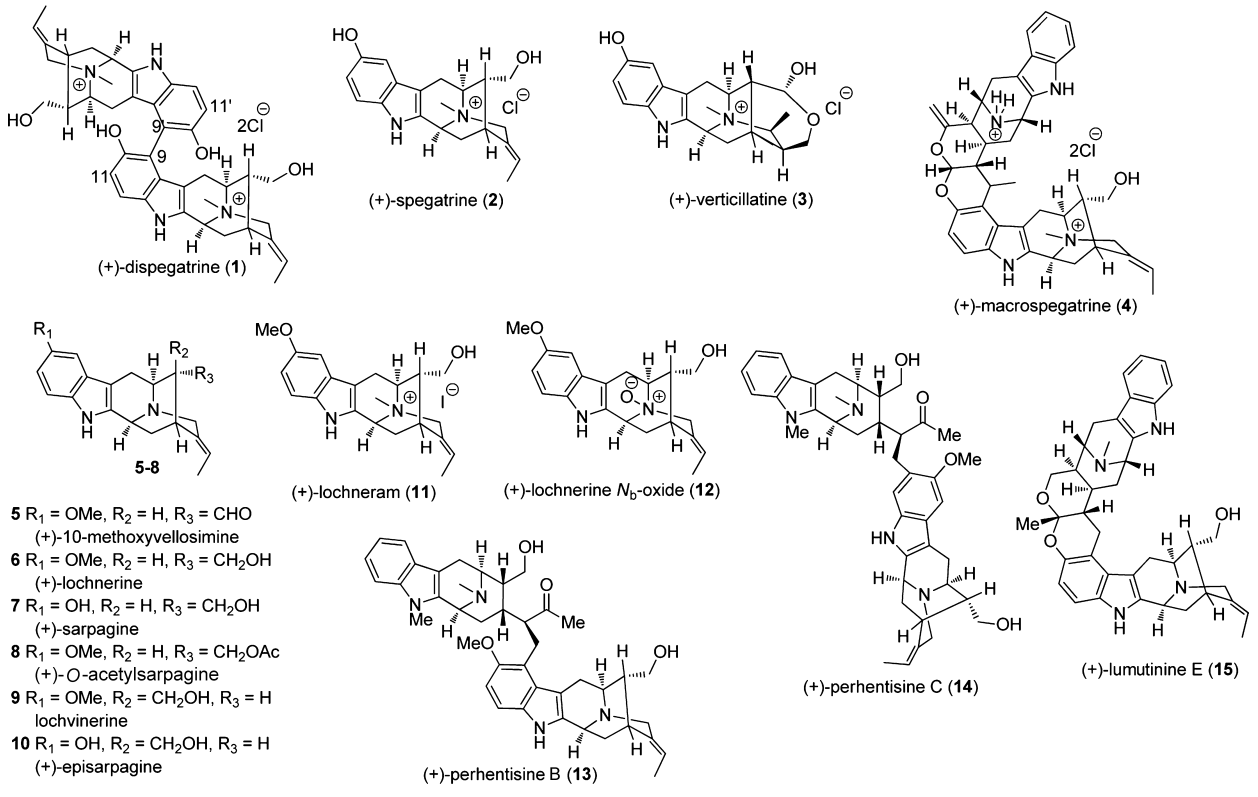

Figure 2. Ring-A oxygenated *sarpagine* (**1**−**12**) indole alkaloids and *macroline-sarpagine* (**4**, **13**−**15**) bisindole alkaloids.

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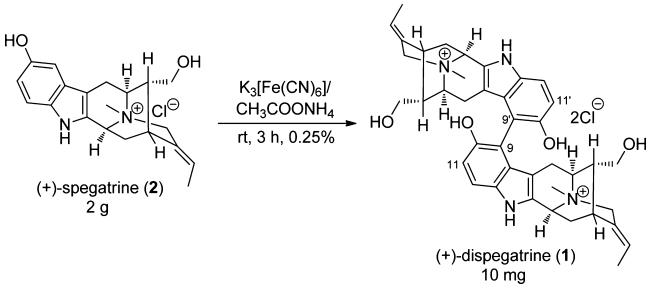
The isolation chemists also reported a semisynthesis of **1** in an almost negligible yield of 0.25% (Scheme 1), obtained by an

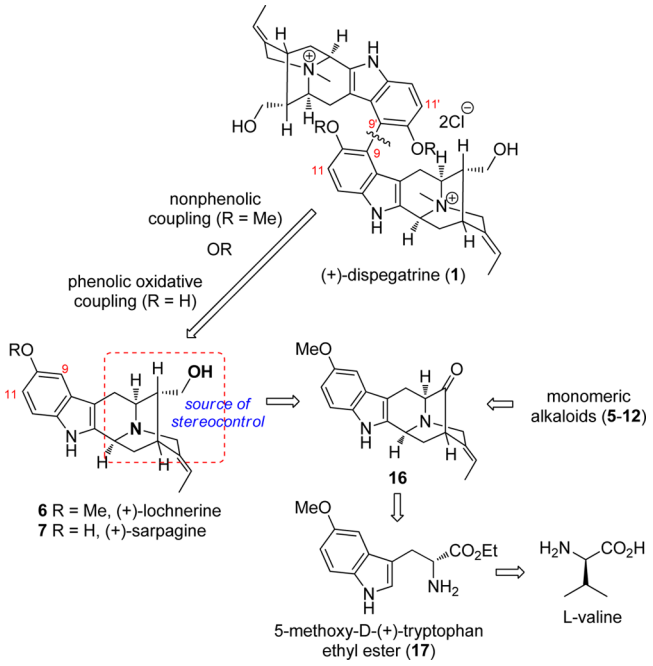
Scheme 1. Partial Biomimetic Synthesis of (+)-Dispegatrine (1) by Yu et al.[10]



oxidative phenolic dehydrodimerization of **2** in aqueous ammonium acetate with $K_3Fe(CN)_6$.[10] Since only one atropodiastereomer was reportedly formed, it can be assumed that the complete atropselectivity observed in this coupling is a result of internal asymmetric induction by the natural *sarpagine* configuration of the monomer **2**.

The retrosynthetic strategy was based on these reports (Scheme 2). A potentially biomimetic intermolecular biaryl

Scheme 2. Retrosynthetic Analysis

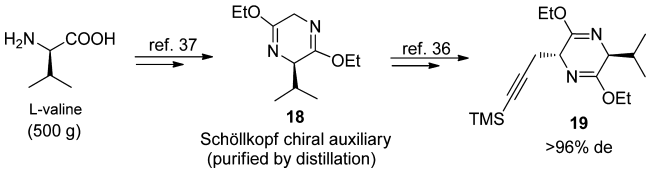


coupling could be employed to construct the C9−C9′ bond in **1** via a nonphenolic coupling of **6** or by a phenolic oxidative coupling of **7** or **2**. In contrast to the extremely low yield of phenolic coupling of **2**,[10] a nonphenolic Scholl type oxidative coupling of the methoxy analogue lochnerine (**6**) could be employed to this end.[27] By performing such a late stage biaryl coupling, one could not only avoid the potential formation of atropodiastereomeric intermediates throughout the synthesis but also take advantage of the existing chiral centers in the *sarpagine* unit **6** for maximum stereoinduction. The 5-methoxy-D-(+)-tryptophan ethyl ester **17** could be employed as the starting material and the chiral transfer agent for the synthesis of the key pentacyclic framework **16** of the *sarpagine* alkaloids via the asymmetric Pictet-Spengler,[28] which on further functionalization would result in the total synthesis of the target alkaloids.

Enantiospecific Synthesis of the 5-Methoxy-D-(+)-Tryptophan Ethyl Ester (17). Although a number of synthetic routes to substituted tryptophans exist, principally asymmetric hydrogenation,[29] enzymatic synthesis,[30] and more recently Negishi coupling,[31] attempts to execute these in a practical sense in the laboratory met with only limited success. Eventually, two approaches, the regiospecific bromination[32] and the Larock heteroannulation previously employed[33] for the synthesis of 5-methoxy-D-tryptophan both utilizing the Schöllkopf chiral auxiliary **18**, were reinvestigated.

The palladium-catalyzed heteroannulation of internal alkynes with *o*-iodoanilines developed by Larock et al.[34] has been successfully employed in this research group for the synthesis of optically active 6- and 7-methoxy tryptophans on a multihundred gram scale which in turn have resulted in the total synthesis of a number of alkoxy substituted *sarpagine* indole alkaloids[35] via the asymmetric Pictet-Spengler reaction. Attempts to employ the Larock heteroannulation for the synthesis of **17** under similar conditions, however, resulted in lower yields.[32b,33] With the success reported in the synthesis of 4-methoxytryptophan[36] via use of the TMS substituted propargylic chiral auxiliary **19** (Scheme 3), it was decided to

Scheme 3. Synthesis of the Propargyl-Substituted Schöllkopf Chiral Auxiliary 19



first test the effect of this alkyne on the regioselectivity of the Larock heteroannulation. If successful, it would provide a shorter and more efficient synthesis of 5-methoxytryptophan **17**. Since both regiospecific bromination and Larock heteroannulation employed the Schöllkopf chiral auxiliary, large scale preparation (500 g) of the Schöllkopf chiral auxiliary **18** from L-valine and glycine, based on the earlier procedure,[37] was undertaken. The TMS protected chiral auxiliary **19** was then prepared according to the modified procedure by Ma et al.[36] in 96−100% de (Scheme 3).

Larock Heteroannulation. In order to proceed with the Larock heteroannulation, Boc protected *o*-iodoaniline **20** was first synthesized based on a published procedure.[38] The amino group in *p*-anisidine was protected with a Boc group followed by a Snieckus ortho lithiation[39] with 2.2 equivalents of *tert*-butyllithium at −78 °C. Quenching the reaction with diiodoethane afforded the desired Boc protected iodo aniline **20** in 86% yield. With the TMS-substituted alkyne **19** and the iodoaniline **20** in hand, the annulation was carried out according to the recently developed conditions of Ma et al.[36] Gratifyingly, the starting aniline **20** was consumed entirely on continued stirring for 36 h, and the N_a-H protected indoles **21a** and **21b** were obtained in a combined yield of 81% (Scheme 4). Hydrolysis of the Schöllkopf chiral auxiliary in **21a** (separated by chromatographic separation) with aqueous 2 N HCl in THF, accompanied by concomitant loss of the silyl group,

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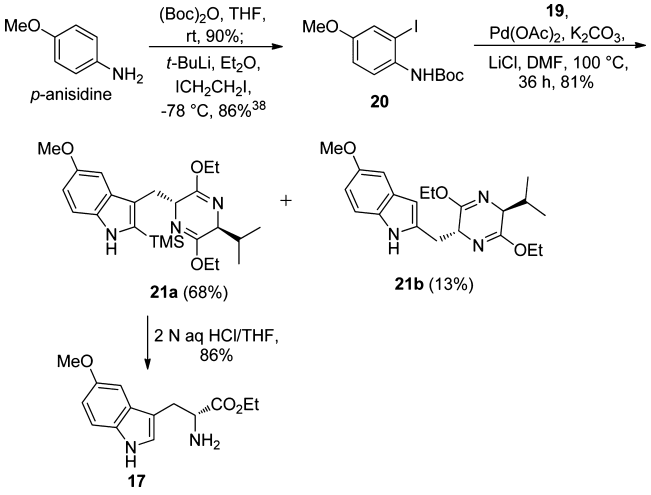
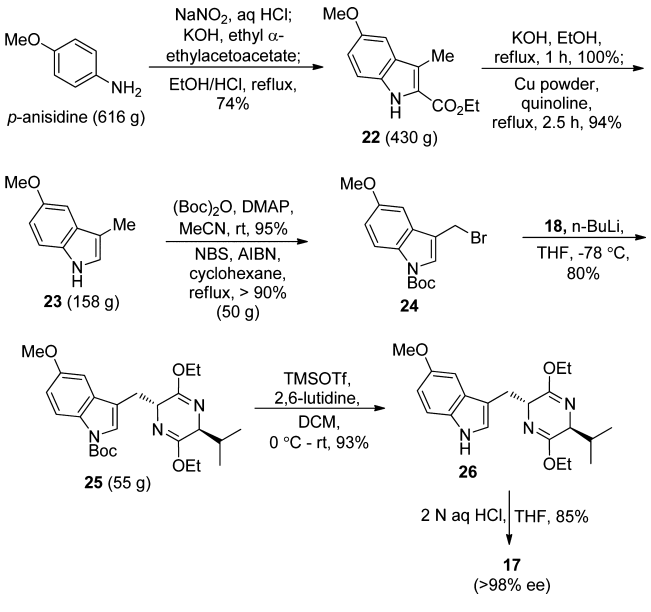
Scheme 4. Larock Heteroannulation for the Synthesis of 5-Methoxy-D-tryptophan Ethyl Ester (17)



provided the optically active 5-methoxy-D-tryptophan ethyl ester (**17**) in a single step in 86% yield. From a practical point of view, this approach to the synthesis of **17** was disappointing. In spite of replacement of the bulkier TES-substituted alkyne by the TMS alkyne **19**, the regioselectivity of this method did not improve. For this reason the earlier regiospecific bromination route[32] for the preparation of **17** was employed. The success of this sequence rested on the ability to scale up the first few steps to multihundred gram levels.

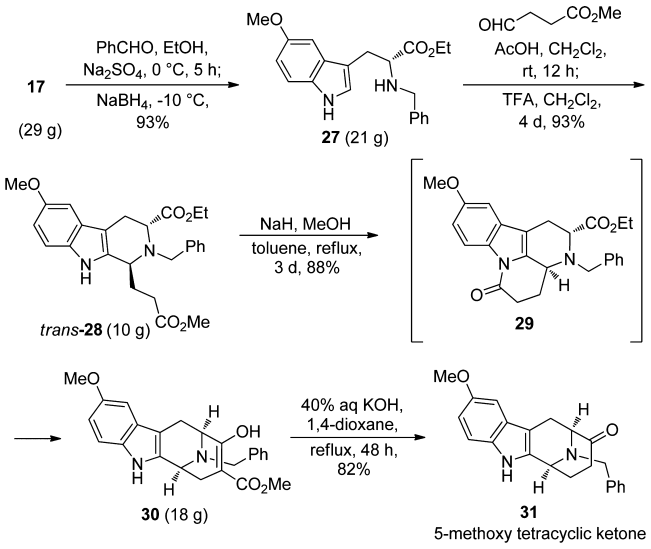
The commercially available 3-methyl-5-methoxyindole (**23**) was prepared on a 616 g scale via the Japp-Klingmann/Fischer indole protocol developed by Abramovitch and Shapiro[40,41] in two steps from *p*-anisidine (Scheme 5). Boc protection of the indole N_a-H function in **23**, followed by allylic bromination,[32,42] furnished the crude bromide **24** in greater than 90% yield, which was directly alkylated with the anion of the Schöllkopf chiral auxiliary (**18**) at −78 °C to provide the protected D-tryptophan analogue **25** in 80% yield. Earlier, the Boc group was removed in refluxing xylenes for 7 days;[32] however, the milder TMSOTf/2,6-lutidine system[43] was found to be much more effective. Deprotection of the Boc group in **25** was achieved on a 55 g scale at 0 °C in 12 h to furnish the Schöllkopf analog **26** in 93% yield. Hydrolysis of **26** under aqueous acidic conditions provided the desired optically active N_a-H-5-methoxy-D-tryptophan ethyl ester (**17**) in 85% yield in greater than 98% ee.

Scheme 5. Improved Regiospecfic Bromination Route for the Synthesis of 5-Methoxy Tryptophan Ethyl Ester (17) on a Large Scale



Synthesis of the 5-Methoxypentacyclic Ketone 16. Analogous to the parent system, the transformation of tryptophan **17** into the desired *trans*-diester **28** (Scheme 6) should follow the well-documented *trans* transfer of chirality in the asymmetric Pictet-Spengler reaction[44] in a straightforward fashion; however, this was not the case. The electron-rich character of the 5-methoxy indole in **17** facilitated the undesired Pictet-Spengler reaction (with the benzaldehyde imine) as observed for the N_a-methyl series;[32a] moreover, the 5-methoxyindole system **27** was not stable in TFA/CH_2Cl_2 to effect a one pot Pictet-Spengler cyclization (from **17**). Consequently, modifications were made analogous to the work of Zhao et al.[32] to achieve optimum yield and very high diastereoselectivity in the Pictet-Spengler cyclization. As illustrated in Scheme 6, tryptophan **17**, on treatment with benzaldehyde at room temperature, followed by sodium borohydride reduction (at −10 °C) afforded the corresponding N_b-benzyltryptophan ethyl ester **27** in 93% yield. If the reaction was carried out at room temperature as in the parent system, a 1:1 mixture of **27** and the undesired Pictet-Spengler product 1-phenyl tetrahydro *β*-carboline (not shown) were observed as reported earlier by Zhao et al.[32] Pictet-Spengler reaction of tryptophan derivative **27** with methyl 3-formylpropanoate, in AcOH/CH_2Cl_2 afforded a mixture of *trans*- and *cis*-diesters in nearly quantitative yield. If TFA was employed in this step decomposition of much of the N_b-benzyl tryptophan **27** was observed. After completion of the Pictet-Spengler reaction, one equivalent of TFA was then added to epimerize all of the *cis* isomer into the desired *trans*-diester **28** in 93% yield. Dieckmann cyclization of **28** was followed by a base mediated hydrolysis/decarboxylation sequence to provide the optically pure tetracyclic ketone **31** (Scheme 6). Based on the work of

Scheme 6. Synthesis of the 5-Methoxytetracyclic Ketone 31



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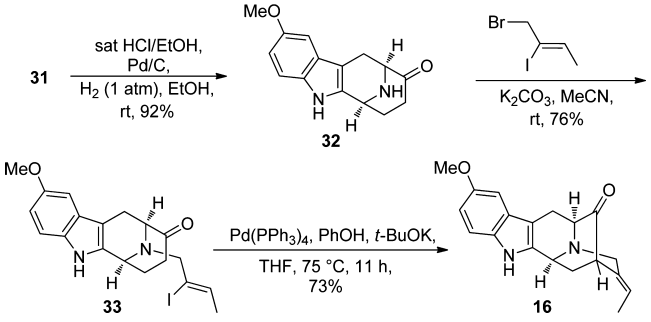
Wang,[45] in the presence of a large excess of sodium methoxide the δ-lactam **29** was initially formed, which on continued reflux for an extended period of time (72 h), provided the Dieckmann product **30** in 88% yield (see Scheme 6). The key to success in the Dieckmann cyclization is the controlled stirring rate and temperature for 3 days. A base induced decarboxylation worked smoothly to provide the tetracyclic ketone **31** in 82% yield.

Catalytic debenzylation of **31**, under acidic conditions, furnished the 10-methoxy N_b-H tetracyclic ketone **32** in 92% yield (Scheme 7). N_b-alkylation of the secondary amine **32** with

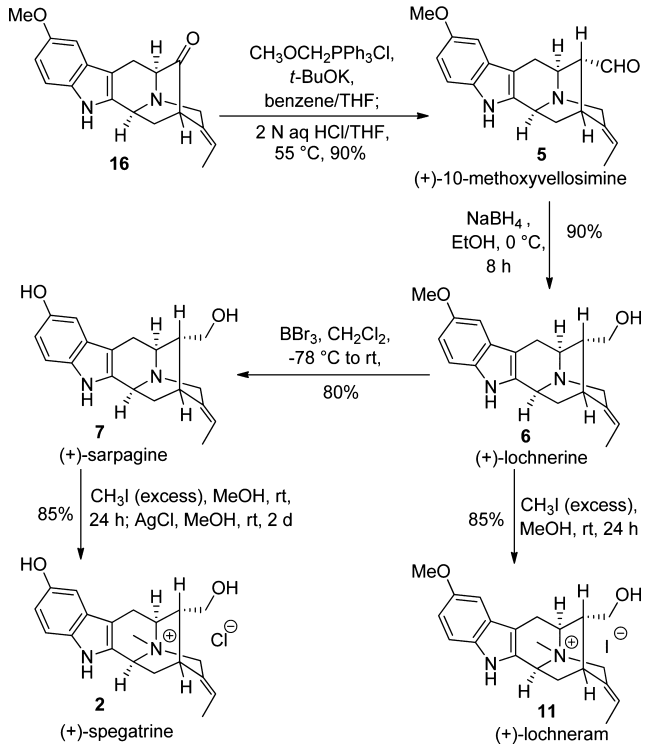
Scheme 7. Synthesis of the 5-Methoxypentacyclic Ketone 16



(Z)-1-bromo-2-iodo-2-butene[46] in dry THF/K_2CO_3/reflux[32,45] furnished the desired product **33**, but the reaction was very sluggish and led to the formation of a considerable amount of baseline impurities. Since substitution by amines on bromides was clearly an S_N2 type process and it is well-known that the nucleophilic strength is dependent on the solvent employed in the S_N2 reaction, it was decided to increase the nucleophilicity of the amine **32** by employing a more polar aprotic solvent. Dry acetonitrile proved to be the most suitable solvent for this process as the reaction went to completion at room temperature to give **33** in 76% yield. Attempts to increase the yield by adding excess (Z)-1-bromo-2-iodo-butene were not successful. Initial attempts at executing the key enolate mediated palladium-catalyzed cyclization of ketone **33** under the modified conditions[47] furnished the desired pentacyclic ketone **16**, albeit in lower yields (50%). The lower yields could be due to a combination of the stronger base (*t*-BuONa) and the electron-rich aromatic system in **33**, which led to a faster E2 elimination and formation of the unwanted acetylene by-product (not shown) before the oxidative addition of the vinyl iodide took place. This problem was circumvented by subjecting the vinyl iodide **33** to the much milder conditions [PhOK/$Pd(PPh_3)_4$] of Bonjoch et al.[48] to furnish the desired pentacyclic ketone **16** in 73% yield.

The Regiospecific, Stereospecific Total Synthesis of (+)-Spegatrine (2), (+)-10-Methoxyvellosimine (5), (+)-Lochnerine (6), (+)-Sarpagine (7), Lochvinerine (9), and (+)-Lochneram (11). With the key *E*-ethylidene intermediate **16** in hand, conversion into the desired α-aldehyde present in (+)-10-methoxyvellosimine (**5**) was accomplished by a Wittig-hydrolysis-epimerization sequence (Scheme 8). The one carbon homologation process was achieved by a Wittig reaction, followed by acidic hydrolysis of the corresponding two steroisomeric enol methyl ethers (not shown), to afford the theromodynamically stable α-aldehyde in **5** in 90% yield. The aldehyde function of **5** was then reduced with sodium borohydride to provide (+)-lochnerine (**6**). As illustrated in Scheme 8, demethylation of (+)-lochnerine (**6**)

Scheme 8. Completion of the Total Synthesis of (+)-Spegatrine (2), (+)-10-Methoxyvellosimine (5), (+)-Lochnerine (6), (+)-Sarpagine (7), and (+)-Lochneram (11)



was achieved with 5 equivalents of BBr_3 in dry CH_2Cl_2 at −78 °C for 1 h, after which the solution was allowed to warm to room temperature and stirred for an additional 4 h. Following work up, (+)-sarpagine (**7**) was obtained in 80% yield. Subsequent quaternization of the N_b-nitrogen function in **7** with excess methyl iodide provided the N_b-methiodide salt, which on stirring with silver chloride in ethanol[49] furnished (+)-spegatrine chloride (**2**). Lochnerine (**6**) on N_b-methylation under similar conditions provided (+)-lochneram (**11**) in 85% yield. The spectral data for the synthetic **2**, **5**−**7**, and **11** were in good agreement with that reported for the natural products[1a] and resulted in the first total synthesis of these alkaloids.

In order to synthesize the β-alcohol at C-16 in lochvinerine (**9**), the chemoselective hydroboration developed earlier[50] was employed. The Wittig reaction of the ketone **16** was then carried out with triphenylphosphonium bromide in benzene in the presence of potassium *t*-butoxide to afford the diene **34** in 92% yield (Scheme 9). Analogous to earlier reports, 9-BBN was chosen as the hydroborating agent to facilitate attack from the less hindered face of the C16−C17 double bond relative to the C19−C20 site.[50] Lochvinerine (**9**) was obtained as the only detectable diastereomer after the hydroboration-oxidation sequence. The proton NMR spectrum of **9** was in agreement with that of the natural product[21] although some difference was observed in chemical shifts of the reported and observed values of protons. This was mainly due to the presence of methanol in the synthetic sample. The synthetic sample retained methanol even after drying the compound under high vacuum for extended periods of time.

Direct/Intermolecular Biaryl Coupling. The biaryl core is an important subunit found in a large number of natural products such as alkaloids, coumarins, flavonoids, lignanes,

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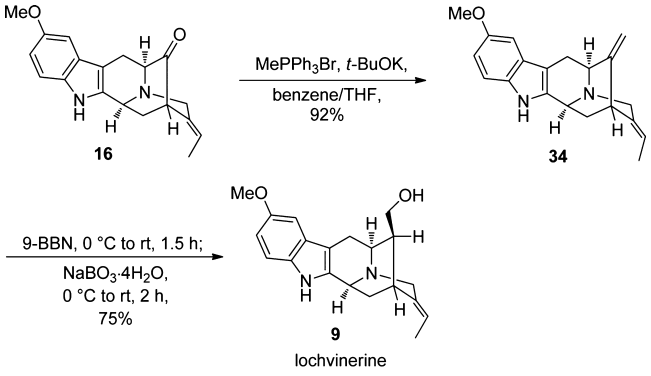
Scheme 9. Completion of the Total Synthesis of Lochvinerine (9)



polyketides, tannins, and terpenes. In particular, axially chiral biaryls are important as chiral ligands in asymmetric synthesis. Because of their interesting biological activity and complex architecture, natural and unnatural biaryls are considered as attractive synthetic targets.[51] For this reason considerable efforts have been made in recent decades for the efficient asymmetric synthesis of biaryls both in the intramolecular and the intermolecular mode.[51,52] Particularly noteworthy is the review by Bringmann et al.[51a] which focuses on enantioselective methods employed for the total synthesis of complex biaryl natural products.

Within the area of intermolecular biaryl synthesis, the two most common approaches employed are: (1) oxidative coupling[53] and (2) reductive coupling such as Ullmann,[52,54] Suzuki,[52,55] Stille[52,56] or C- H activation,[52,57] etc. Oxidative phenolic coupling is a powerful and economical method for the synthesis of biaryl compounds and is especially suited to natural product synthesis since many of the biosynthetic routes to biaryls involve such a coupling.[58] Although considerable progress has been made in carrying out the intramolecular oxidative couplings, in the absence of activating groups, the position of the newly formed C−C bond is determined by the electronic and steric preferences of the substrate and can lead to regioisomeric reaction products in complex substrates especially in the intermolecular mode.[52c,53c] The coupling mechanism is believed to involve either one two-electron or two one-electron oxidations to form an aryl−aryl coupled dimer through the *ortho* and/or *para* positions.[52c,59] In the case of phenols bearing no *ortho*- and *para*-substituents, the *ortho*−*ortho*, *ortho*−*para*, and *para*−*para* coupling reactions occur, giving rise to often unseparable mixtures. In some cases competing and/or subsequent oxidation to form quinones occurs, either from the coupled product or from the original substrate. Thus it is not always predictable which of the possible products will be formed predominantly, consequently, thorough optimization of the oxidizing agent/reaction conditions is required for successful transformations.

The Lewis-acid catalyzed direct oxidative nonphenolic coupling of two unfunctionalized arenes or the Scholl reaction[60] is one of the oldest C−C bond forming reactions and has been extensively used for the intramolecular oxidative dehydrodimerization of branched phenylene precursors to the corresponding polycyclic aromatic hydrocarbons (PAHs) such as triphenylenes, hexa-peri-hexabenzocoronenes (HBCs), etc.[61] and for the synthesis of hexaalkoxytriphenylenes.[62] Various strong acids (Brønsted acids/Lewis acids) and metal salts are generally used in combination with an oxidant (O_2, $KMnO_4$).[60] Variants of the reaction include oxidants such as: $FeCl_3$,[63] $CuCl_2$, or $Cu(OTf)_2$ with $AlCl_3$,[64] $Tl(O_2CCF_3)_3/BF_3{\cdot}OEt_2$,[65] $Pb(OAc)_4/BF_3{\cdot}OEt_2$,[66] $MoCl_5$,[67] $SbCl_5$,[68] and $(CF_3CO_2)_2I^{III}C_6H_5$ [phenyliodine(III) bis(trifluoroacetate): PIFA]/$BF_3{\cdot}OEt_2$.[69] Electrochemical oxidations of electron-rich aryl compounds have been reported but are not commonly used.[70] Based on the observations of King et al.[71] the outcome of the Scholl reaction of substituted substrates follows the directing group effects observed in electrophilic aromatic substitution. Alkoxy and alkyl groups are effective *o*,*p*-directors, whereas deactivating *m*-directors (e.g., NO_2) suppress the reaction rate. A variety of electron-rich substrates such as alkyl/alkoxy substituted aryl compounds have been successfully dimerized using the above-mentioned combinations. While a majority of these C−C bond forming reactions are reported in the intramolecular mode, very few cases are reported in the intermolecular mode, albeit in substrates with simpler systems, or in substrates with substitution patterns such as to prevent side reactions.

Among the reductive coupling processes, the Suzuki reaction is the most widely used method often affording good to high yields of the coupled products with predictable regioselectivity.[55] However, the advantages of employing preactivated aryl components can be offset by the requirement for their independent preparation, especially where multiple synthetic steps are required. Also since no standard procedures are available, each new catalyst and substrate requires time-consuming optimization of the particular reaction conditions.

Reductive Coupling-Model Reaction. As per the retrosynthetic plan, both oxidative (phenolic and Scholl-type) or reductive cross coupling could be employed to form the C9−C9′ bond in **1**. Although biomimetic oxidative phenolic coupling still stands as a practical method for the synthesis of many biaryls, the negligible yield obtained during the oxidative phenolic coupling of **2** by Lin et al.[10] made it the weakest method of choice. In order to avoid the potential problems associated with phenolic oxidative couplings it was thus decided to employ a nonphenolic coupling reaction for the construction of the biaryl axis in **1**. A nonphenolic oxidative coupling of the *sarpagine* alkaloid (+)-lochnerine (**6**), which contains all the chiral information required, could be attempted to this end. The quaternary alkaloid lochneram (**11**) could also serve the same purpose but could affect the isolation/purification process due to its polar nature. The nonphenolic coupling could either be a reductive cross-coupling or a Scholl type direct oxidative coupling.

Taking into consideration the pros and cons of both types of coupling reactions, it was decided to first study the biaryl coupling on a more robust model indole substrate. By doing so one would be able to compare the results of both reactions on the same substrate and then select the best method for coupling the *sarpagine* alkaloid **6**. It would also give one a chance to study the effect of oxidative dimerization conditions on the more sensitive 5-methoxy sarpagine substrate **6**, especially due to lack of literature precedent for such transformations. Additionally, the supposition that the natural *sarpagine* framework was indispensable for complete asymmetric induction in the formation of the biaryl axis could also be assessed. Tetrahydro *β*-carboline **35**, the N_a-methyl analogue of **28**,[32] was chosen as the model substrate for this purpose. In order to perform any type of reductive coupling reaction (such as the Ullmann, Suzuki, Stille, etc.) on **35**, it was necessary to first synthesize the corresponding aryl halide coupling partner.

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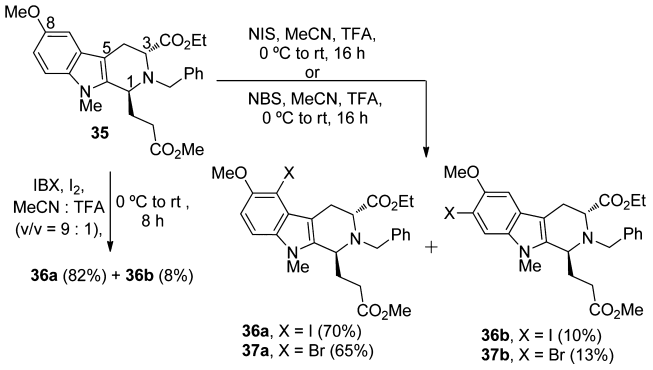
Synthesis of the Aryl Halide Coupling Partners 36a/37a. Due to the moderate reactivity of iodine, electrophilic iodination of aromatic compounds requires the use of an appropriate oxidant for efficient transformation. Numerous methods employing iodonium donating agents have been developed over the years; many of which employ harsh reaction conditions and longer reaction times.[72] Initially, a milder method for iodination with N-iodosuccinimide (NIS) and catalytic TFA, reported by Colobert et al.,[73] was employed for iodination of the model substrate **35**. Although the reaction proceeded at room temperature in acetonitirile, longer reaction times (16 h) were required for complete conversion of **35**, and the regiosiosmers **36a** and **36b** were obtained in a combined yield of 80% (Scheme 10). For synthesis of the corresponding aryl bromide, an NBS/TFA system provided the optimum yield of the desired product **37a**. Recently Moorthy et al.[74] reported an expedient protocol for iodination of a variety of electron-rich and electron-poor aromatic compounds using an IBX-I_2 redox couple. The high yields and very short reaction times were attributed to the rapid generation of 4 equivalents of iodonium ions per equivalent of IBX, thereby increasing the rate of the reaction even for electron-poor substrates. As illustrated in Scheme 10, iodination of the model substrate **35** under these conditions resulted in a much faster (8 h) and a cleaner reaction, with the desired product **36a** formed in 82% yield. The regiochemistry of iodination in **36a** was also confirmed by X-ray analysis (see SI).

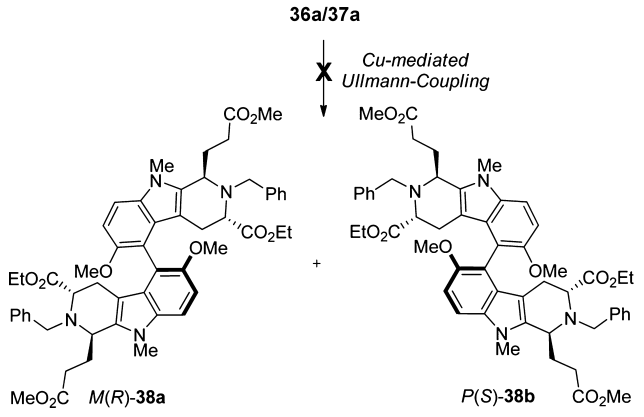
Scheme 10. Electrophilic Halogenation of 35



Attempted Ullman Coupling Reaction. With the appropriate aromatic halides **36a** and **37a** in hand, the Ullmann reductive coupling[54] to form the C7−C7′ bond was first investigated. Similar to other reductive coupling processes, various protocols of the Ullmann-type coupling have been developed; however, very few are suitable for atropselective synthesis of biaryls mainly due to the harsh conditions (multihour reactions at temperatures >100 °C) required to obtain high yields of the desired biaryl. Such harsher conditions could lead to racemization of the biaryls and are thus not useful.[55e] Illustrated in Table 1 are the various attempts to perform the Cu-mediated Ullmann coupling reaction of **36a** and **37a**. In spite of using up to 8 equivalents of activated Cu-powder at very high temperatures, either no conversion or complete decomposition of the starting materials **36a** and **37a** was observed (Table 1, entries 3−5). A copper(I)-thiophene-2-carboxylate (CuTC) protocol developed by Liebskind et al.[75] was also tested on both the aryl iodide **36a** and bromide **37a** (Table 1, entries 2 and 6) but failed to provide the desired product. After the failure of the Ullmann reaction to dimerize the model substrate **36a**/**37a**, the Suzuki reductive coupling process[55] was next attempted. To accomplish this, the aryl boronate ester coupling partner from the corresponding aryl halide had to be prepared.

Synthesis of the Aryl Boronic Ester Coupling Partner. The palladium-catalyzed cross coupling reaction of $(Bpin)_2$ with haloarenes developed by Miyaura et al.[55d,e] provides a direct procedure for the synthesis of aryl boronic esters from aryl halides. Application of these borylation conditions in the

Table 1. Attempted Copper-Mediated Ullmann Coupling Reaction of 36a and 37a[a]



entry	reaction conditions	results
1.	Cu powder (2.5 equiv),[54b] DMF, 100 °C, 12 h	SM only
2.	CuTC (3.0 equiv), *N*-methyl 2-pyrrolidine, 70 °C, 72 h	SM only
3.	activated Cu powder (8 equiv), DMF, reflux, 72 h	SM only
4.	activated Cu powder (8 equiv), *N*-methyl 2-pyrrolidine, sealed tube, sand bath, 140 °C, 26 h	SM only
5.	activated Cu powder (8 equiv), *N*-methyl 2-pyrrolidine, sealed tube, sand bath, 140 °C, 72 h	decomposition
6.	CuTC (8 equiv), *N*-methyl 2-pyrrolidine, sealed tube, sand bath, 140 °C, 26−72 h	decomposition

[a]CuTC: copper(I)-thiophene-2-carboxylate; SM: starting materials **36a** or **37a**.

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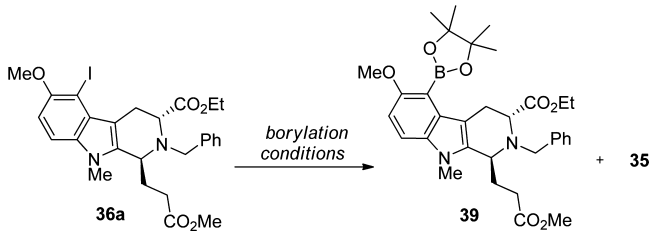
Table 2. Synthesis of the Aryl Boronic Ester Coupling Partner 39



	boron source[a]	Pd source	ligand[b]	base[c]	solvent	temp (time)	results[d]
1	$(Bpin)_2$ (4 equiv)	$Pd(dppf)Cl_2$ (10 mol %)	-	KOAc	DMSO	100 °C (10 h)	**39** (55%) + **35** (30%)
2	$(Bpin)_2$ (4 equiv)	$Pd(PPh_3)_4$ (10 mol %)	-	KOAc	DMSO	80 °C (15 h)	**36a** + **39** + **35**[e]
3	HBpin (3 equiv)	$Pd(MeCN)_2Cl_2$ (5 mol %)	DCPB (20 mol %)	Et_3N	dioxane	110 °C (3 h)	**36a** + **39**[e]
4	HBpin (3 equiv)	$Pd(MeCN)_2Cl_2$ (10 mol %)	DCPB (40 mol %)	Et_3N	dioxane	110 °C (3 h)	**36a** +**39**[e]
5	HBpin (3 equiv)	$Pd(MeCN)_2Cl_2$ (5 mol %)	XPhos (20 mol %)	Et_3N	dioxane	100 °C (3 h)	**36a** + **39** + **35**[e]
6	HBpin (3 equiv)	$Pd(OAc)_2$ (5 mol %)	DPEPhos (10 mol %)	Et_3N	dioxane	100 °C (3 h)	**39** (78%) + **35** (15%)
7	HBpin (3 equiv)	$Pd(OAc)_2$ (5 mol %)	DCPB (20 mol %)	Et_3N	dioxane	110 °C (3 h)	**39** (80%) + **35** (10%)
8	HBpin (3 equiv)	$Pd(OAc)_2$ (5 mol %)	DCPB (20 mol %)	Et_3N	dioxane	100 °C (3 h)	**39** (93%) + **35** (3%)

[a]$(Bpin)_2$: bis(pinacolato) diboron; HBpin: pinacol borane. [b]DCPB: 2-(dicyclohexylphosphanyl)biphenyl; DPEPhos: bis(2-phenylphosphinophenyl)ether; XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [c]3 equiv of base was employed. [d]Isolated yields. [e]Not separated.

Table 3. Suzuki-Miyaura Coupling (SMC)

36a or **37a** + **39** $\xrightarrow{\text{SMC}}$ *M*(*R*)-**38a** + *P*(*S*)-**38b**

	ArX	Pd source[a,b]	ligand[c,d]	base[e,f]	solvent[g]	temp (°C)/ time (h)	results
1	**36a**	$Pd(OAc)_2$	DCPB	K_3PO_4	dioxane:H_2O	100/24	**35** + **36a**
2	**37a**	$Pd(OAc)_2$	DCPB	K_3PO_4	dioxane:H_2O	100/24	**35** + **37a**
3	**36a**	$Pd(OAc)_2$	DCPB	CsF	dioxane	100/24	**35** + **36a**
4	**36a**	$Pd(OAc)_2$	XPhos	K_3PO_4	Tol:H_2O	100/24	**35** + **36a**
5	**36a**	$Pd(OAc)_2$	DavePhos	K_3PO_4	Tol:H_2O	100/24	**35** + **36a**
6	**36a**	$Pd(OAc)_2$	SPhos	K_3PO_4	Tol:H_2O	100/24	**35** + **36a**
7	**36a**	$Pd(OAc)_2$	SPhos	K_3PO_4	THF:H_2O	50/24	**38a** (20%) + **38b** (10%) + **35** (15%) + **36a** (13%)
8	**36a**	$Pd(OAc)_2$	SPhos	K_3PO_4	THF:H_2O	50/48	**38a** (37%) + **38b** (18%) + **35** (20%)
9	**36a**	$Pd_2(dba)_3$	SPhos	K_3PO_4	THF:H_2O	50/48	**38a** (38%) + **38b** (19%) + **35** (20%)

[a]5 mol % of $Pd(OAc)_2$. [b]2.5 mol % of $Pd_2(dba)_3$. [c]Ligands: DCPB: 2-(dicyclohexylphosphanyl)biphenyl; XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; DavePhos: 2-dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl; SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. [d]20 mol % of ligand. [e]2 equiv of K_3PO_4. [f]8 equiv of CsF. [g]Solvent:H_2O/10:1.

system under study here furnished the desired aryl boronate **39** in 55% yield, accompanied by a large amount of the hydrodehalogenation species **35** (Table 2, entry1). Performing the reaction at a lower temperature with $Pd(PPh_3)_4$ as the catalyst did decrease the amount of the byproduct **35** but also left some starting material (**36a**) unreacted (as observed on TLC). Based on the initial findings of Masuda et al.[76] and reports by Buchwald et al.[77] and Baudoin et al.,[78] it was found that a palladium-catalyzed coupling of pinacolborane with aryl halides in the presence of a tertiary amine as a base, especially Et_3N, prevented the pinacolborane from acting as a hydride donor and thus avoided formation of the undesirable Ar−H byproduct (**35** in this case). As illustrated in Table 2 (entries 3−8), a careful optimization of the reaction by varying the palladium source and the ligand finally led to a combination of $Pd(OAc)_2$ with the more electron-rich and bulkier ligand 2-(dicyclohexylphosphanyl)biphenyl (DCPB) to provide 93% yield of the arylboronate **39** (Table 2, entry 8).

Suzuki −Miyaura Coupling (SMC). With the appropriate aromatic halides (**36a** and **37a**) and aryl boronate ester **39** in hand, the Suzuki coupling reaction of these diortho substituted coupling partners was next attempted. The synthesis of hindered biaryls via the Suzuki reaction, especially of substrates containing large *ortho* substituents, and/or *ortho*, *ortho*′ substituents has been shown to be a challenging task.[73,77] The difficulty in such transformations can be increased in cases where the substrate has electron-donating groups thereby slowing down the oxidative-addition process. More recently the bulky and electron-rich, monodentate dialkylbiarylphosphine ligands, synthesized by Buchwald et al.,[77] were shown to improve the efficiency of such couplings. The superior activity of the catalysts derived from the biarylphosphine ligands was attributed to a combination of electronic and steric properties that enhanced the rates of oxidative addition, transmetalation, and reductive elimination steps in the catalytic cycle.

Outlined in Table 3 are the different catalytic systems that were employed to carry out the Suzuki-coupling reactions of the aryl halides **36a** and **37a** with the boronate ester **39**. Based on the various synthetic applications[79] a general reaction system of $Pd(OAc)_2$/dialkylbiarylphosphine ligand in a 1:4 ratio was employed with different solvents and bases (Table 3). Initial couplings with 20 mol % of the DCPB, XPhos, and DavePhos ligands, in the presence of a milder base (K_3PO_4), resulted in mixtures of hydrodehalogenation byproduct **35** and unreacted starting material **36a**/**37a** (Table 3, entries 1−5). Employment of the more efficient, electron-rich and bulkier

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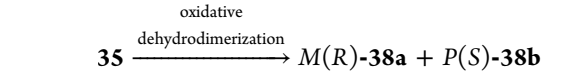
Table 4. Oxidative Dehydrodimerization of the Model Substrate 35



	oxidant (equiv)	Lewis acid (equiv)	temp (time)	solvent	results	
					% yield	*M*:*P*
1	PIFA (0.6)	$BF_3{\cdot}Et_2O$ (2.5 equiv)	0 °C − rt (2 h)	DCM	nd	nd
2	PIFA (1.02)	$BF_3{\cdot}Et_2O$ (4 equiv)	0 °C − rt (8 h)	DCM	11	3:2
3	PIFA (1.02)	$BF_3{\cdot}Et_2O$ (4 equiv)	−40 °C − rt (1.5 h)	DCM	20	3:2
4	PIFA (0.8)	$BF_3{\cdot}Et_2O$ (3 equiv)	−40 °C (0.5 h)	DCM	30	4:1
5	PIFA (0.8)	$BF_3{\cdot}Et_2O$ (3 equiv)	−78 °C (0.5 h)	DCM	25[a]	4:1
6	PIDA (0.8)	$BF_3{\cdot}Et_2O$ (3 equiv)	−40 °C (2.5 h)	DCM	nd	nd
7	$Tl(OCOCF_3)_3$ (0.8)	$BF_3{\cdot}Et_2O$ (3 equiv)	rt (15 min)	MeCN	nd	nd
8	$Tl(OCOCF_3)_3$ (0.8)	$BF_3{\cdot}Et_2O$ (3 equiv)	−40 °C (20 min)	MeCN	38	2:3
9	$Tl(OCOCF_3)_3$ (0.5)	$BF_3{\cdot}Et_2O$ (2.5 equiv)	−78 °C (40 min)	MeCN	30	3:7
10	$Tl(OCOCH_3)_3$ (0.7)	$BF_3{\cdot}Et_2O$ (3 equiv)	−40 °C (1.25 h)	MeCN	67[a]	3:7

[a]The yield is based on recovered starting material **35**. % yield is based on isolation of both the diasteromers. nd: not determined. PIFA: phenyliodine(III) bis(trifluoroacetate); PIDA: phenyliodine(III) diacetate.

SPhos[79] ligand also yielded similar results (Table 3, entry 6). It was possible that a combination of basic reaction conditions at higher temperature was responsible for the extensive hydrodehalogenation. In order to circumvent this it was decided to employ THF as the cosolvent. The low boiling point and higher dielectric constant of THF provided a more homogeneous reaction medium at a lower temperature. This change reduced the excessive hydrodehalogenation taking place, and a combined yield of 30% was obtained in favor of the *M*(*R*)-atropodiastereomer (Table 3, entry 7). Stirring the reaction mixture for a longer time led to complete conversion of the starting material **36a**, and a 55% combined yield of the atropodiastereomers was observed (Table 3, entry 8). Use of $Pd_2(dba)_3$ also provided similar results (Table 3, entry 9). At this point no further optimization was performed. Subsequently, the more direct Scholl-type oxidative dehydrodimerization of the model substrate **35** was attempted.

Scholl Type Oxidative Dehydrodimerization-Model Reaction. With samples of the atropodiastereomeric biaryls (**38a** and **38b**) obtained from the Suzuki-Miyaura coupling on the model substrate **35** in hand, the desired products could now be identified from a potential mixture of regioisomers which could arise during the oxidative coupling of the model substrate. Since one was examining the effect of existing chiral centers on the atropselectivity, it was decided to use achiral catalysts for this process. Of the various protocols of the Scholl type oxidation discussed earlier, it was decided to carry out a hypervalent iodine(III) mediated protocol developed by Kita et al.[69,80] and a thallium(III) mediated oxidative dehydrodimerization approach developed by Taylor et al.[65,81] Both methods employ a combination of a two-electron oxidant and a Lewis acid ($BF_3{\cdot}Et_2O$) in solvents such as CH_2Cl_2 or MeCN, at temperatures ranging from −78 °C to room temperature. Although hypervalent iodine(III) has been extensively used for intramolecular coupling reactions,[69,82] there has been little progress made in the intermolecular mode.[78,83] Thallium(III) has also been successfully employed intramolecularly for the synthesis of isoquinoline alkaloids,[84] lignans,[85] and colchinol derivatives[86] as well as aporphine alkaloids.[87] Effective oxidative dimerizations of 2-substituted indoles[88] and indolocarbazoles[89] by thallium(III) trifluoroacetate have also been reported. The intermolecular oxidative dimerization of a polysubstituted indole core by Keller et al.[90] provided a suitable precedent for which to effect the oxidative dimerization in the system under study here.

Illustrated in Table 4 are the results of the intermolecular oxidative dehydrodimerization reaction on the model tetrahydro *β*-carboline **35**. Addition of PIFA (0.6 to 1.02 equiv) at 0 °C provided very little formation of the desired dimers **38a** and **38b** (Table 4, entries 1 and 2). The same trend was observed for the thallium trifluoroacetate mediated oxidation (Table 4, entry 7), although all the PIFA-oxidations seemed to produce a lot of baseline and colored impurities. A lower reaction temperature of −40 °C (both the reagents and the substrate added at the same temperature) seemed to have an immediate effect on the reaction, and higher yields were obtained in both PIFA (Table 4, entry 4) and the thallium mediated oxidations (Table 4, entry 8), more so in the latter case. A decrease in the reaction temperature to −78 °C (Table 4, entry 5) or replacing PIFA with phenyliodine(III) diacetate [PIDA (−40 °C)] resulted in a considerable amount of starting material **35** (Table 4, entry 6) remaining unreacted. A similar effect was observed upon the use of the milder Tl(III) acetate as the oxidant (Table 4, entry 10). Although some starting material **35** (11%) remained unreacted, a combined yield of 67% was obtained in favor of **38b**, the axial chirality of which was determined to be *P*(*S*) by X-ray analysis.[27] Importantly, the model oxidative dehydrodimerization was completely regioselective (without any preactivation), and the combination of the milder Tl(III) acetate with $BF_3{\cdot}Et_2O$, which provided the optimum yield (Table 4, entry 10), could now be attempted to construct the desired C9−C9′ bond in **1**. It was also clear that an oxidative biaryl coupling at a later stage in the synthesis, especially on the natural *sarpagine* framework, was essential for ensuring complete atropselectivity in the process. This was a key finding from the lack of stereospecificity in the model work.

Thallium(III) Mediated Oxidative Coupling of (+)-Lochnerine (6). As illustrated in Scheme 11, the monomeric *sarpagine* alkaloid lochnerine (**6**) was subjected to the modified conditions of the Tl(III) mediated oxidative dimerization. A combination of $Tl(O_2CCH_3)_3$ (0.65 equiv) and $BF_3{\cdot}Et_2O$ (3.0 equiv) in acetonitrile at −40 °C afforded the key C9−C9′ biaryl **40** as the sole atropdiastereomer in 60% yield (based on 12% recovered starting material) with complete regioselectivity. The free indole N_a-H, highly basic N_b-nitrogen and the primary hydroxyl function at C-17 remained unaffected.

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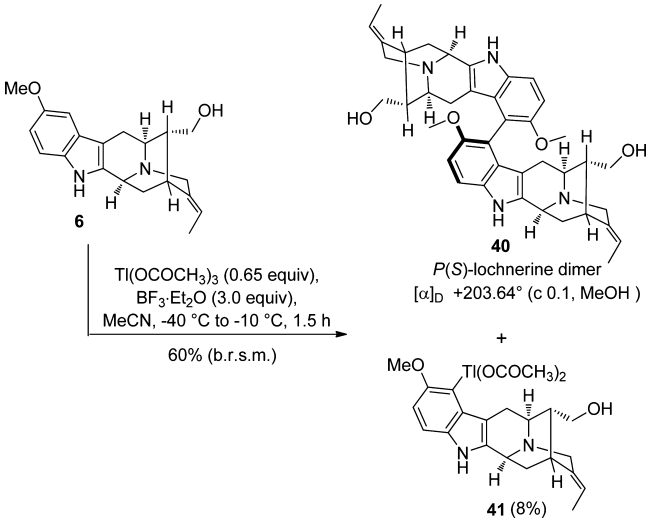
Scheme 11. Thallium(III) Mediated Oxidative Coupling of (+)-Lochnerine (6)[a]



[a]b.r.s.m: based on recovered starting material.

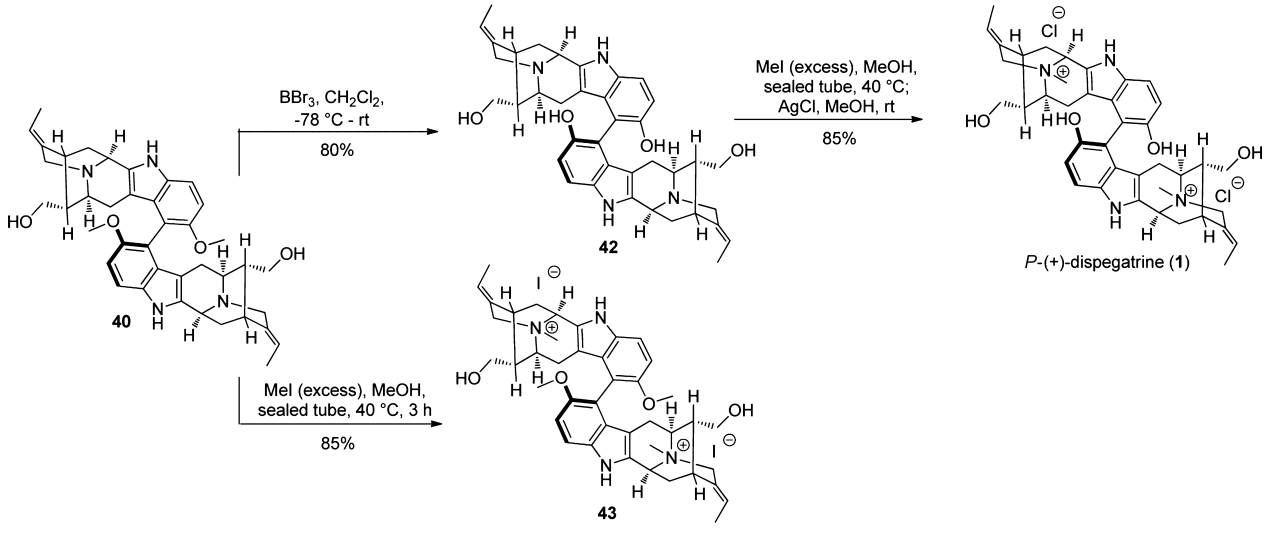
The formation of the biaryl **40**, accompanied by the competing electrophilic aromatic thallation byproduct **41** at C-9, is in complete agreement with the detailed mechanistic studies by Kochi et al.[91] Increasing the equivalents of $Tl(O_2CCH_3)_3$ led to increased conversion of indole **6** to the organothallium byproduct **41** and baseline impurities. X-ray crystallographic analysis of **40** established the axial chirality at the C9−C9′ bond as *P*(*S*).[27] The natural *sarpagine* configuration in indole **6** imparted complete stereocontrol in the key biaryl coupling step thereby forming a single atropodiastereomer **40**. This would be in agreement with a potential biomimetic coupling in the plant since none of the other atropodiastereomers was reported during isolation and semisynthesis by Yu et al.[10]

The Regiospecific, Stereospecific Total Synthesis of *P*-(+)-Dispegtarine (1). Completion of the total synthesis of (+)-dispegatrine (**1**) was then achieved in two more steps. As illustrated in Scheme 12, the C10−C10′ methoxy groups in **40** were demethylated with 9 equivalents of BBr_3/CH_2Cl_2 at −78 °C to furnish the sarpagine dimer **42** in 80% yield. The highly zwitterionic nature of **42** was evident from the ^{1}H NMR of the compound which showed a large downfield shift of the C-3 and C-21 protons as is generally observed in N_b-quaternary *sarpagine* compounds. Due to this reason, the N_b-methylation of the highly polar dimer **42** was sluggish, and very little formation of **1** was observed at room temperature. Eventually, heating the reaction mixture in a sealed tube at 40 °C led to complete conversion of the starting material **42** into *P*-(+)-dispegatrine (**1**). A LRMS (FAB) of the sample at this stage was taken to confirm the formation of the desired product **1**. Further treatment with AgCl/MeOH at room temperature completed the total synthesis of *P*-(+)-dispegatrine (**1**). The synthetic material **1** exhibited ^{1}H NMR spectrum that compared favorably with the reported values.[10] The coupling constants and splitting pattern were in excellent agreement with the literature values,[10] except for the chemical shifts of protons H-3,3′ and 5,5′ which were observed for the natural material in D_2O.[27] To obtain better spectroscopic data, it was decided to synthesize the bismethyl ether of **1**, by subjecting the dimer **40** to N_b-quaternization first. Complete conversion to the bisquaternary salt **43** was achieved with a large excess of MeI/MeOH, both at room temperature or 40 °C. Analogous to blumeanine (isolated as its diacetate),[13] chromatographic purification and isolation of this bisquaternary salt **43** was much easier in comparison to **1**. The 2D NMR correlation experiments were then carried out on the dimer **43** to establish the position of the H-3,3′ and H-5,5′ protons.[27] These NMR experiments were in complete agreement with the assigned positions of H-3,3′ and H-5,5′ in *P*-(+)-**1**.[27] In the absence of an authentic sample[92] [for circular dichroism (CD) analysis or thin layer chromatography (TLC) comparison], it is impossible to unequivocally report that synthetic **1** is identical to the natural product even though the ^{1}H NMR is in good agreement.[93] However, the fact that the biomimetic coupling by Yu et al.[10] gave only the natural isomer and our oxidative coupling gave the *P*-atropodiastereomer from similar scaffolds strongly suggests that they are the same.

CONCLUSION

In conclusion, the regio- and diastereospecific doubly convergent first total synthesis of the *P*-atropodiastereomer of

Scheme 12. Completion of the Total Synthesis of *P*-(+)-Dispegatrine (1)



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the dimeric indole alkaloid (+)-dispegatrine (**1**) has been accomplished from 5-methoxy-D-tryptophan methyl ester (**17**). *p*-Anisidine was converted into **17** on a large scale by employing the modified regiospecific bromination procedure. Stereospecific conversion of **17** into the optically active *sarpagine* framework **16** was achieved by the asymmetric Pictet-Spengler reaction. The ketone **16** was then employed to complete the first total synthesis of the monomeric 10-oxysubstituted alkaloids (+)-spegatrine (**2**), (+)-10-methoxy-vellosimine (**5**), (+)-lochnerine (**6**), (+)-sarpagine (**7**), lochvinerine (**9**), and (+)-lochneram (**11**). Intermolecular nonphenolic oxidative dimerizations of highly functionalized substrates are very rare, and the work described in this paper provides an efficient method to carry out such couplings, thereby providing an alternative to the phenolic oxidative couplings which oftentimes produces complex mixtures with sensitive substrates. Both reductive cross coupling (Suzuki) and direct oxidative coupling were first studied on the electron-rich indole model substrate **35** and provided excellent insight into the regioselectivity and atropselectivity of the process. Based on the results of the model study, advantage was taken of the natural *sarpagine* configuration in lochnerine (**6**), a thallium-(III)acetate mediated oxidative dimerization of which provided the atropodiastereomer *P*-**40** exclusively. Completion of the total synthesis of **1** was then achieved in two more steps from **40**. The total synthesis of the bisquaternary alkaloid **1** is thus notable for its brevity, principally because it employed lochnerine (**6**) as the substrate for the key biaryl coupling, inspite of the presence of the free indole N_a-H, free hydroxyl group at C-17 and a highly basic N_b-nitrogen function. In addition, the use of thallium(III) acetate as the oxidant for direct oxidative dehydrodimerization of electron-rich substrates such as **6** and **35** has expanded the scope of this oxidant in intermolecular heterobiaryl synthesis.

EXPERIMENTAL SECTION

The experimental details for the synthesis of alkaloids **1**, **2**, **5**−**7** and compounds **16**, **38a**, **38b**, and **40**−**43** are contained in the SI of reference 27b. General procedures for borylation (entries 1−7, Table 2) and SMC (entries 1−8, Table 3) are analogous to the preparation for **39** and **38a,b** respectively. For general experimental considerations see SI.

3-(((2*R*,5*S*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-5-methoxy-2-(trimethylsilyl)-1*H*-indole (21a) and the Regioisomer 2-(((2*R*,5*S*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-5-methoxy-1*H*-indole (21b). In a round-bottom flask (2 L) equipped with a magnetic stirrer were added *tert*-butyl (2-iodo-4-methoxyphenyl)carbamate **20** (1 g, 2.86 mmol), the internal alkyne **19** (1.016 g, 3.15 mmol), palladium(II) acetate (38.5 mg, 0.171 mmol), potassium carbonate (989 mg, 7.16 mmol), lithium chloride (133 mg, 3.150 mmol), and DMF (20 mL). The reaction mixture was degassed under vacuum (argon) and then heated at 100 °C under a slow stream of argon for 36 h. The mixture was cooled to rt, and then EtOAc (400 mL) was added to the solution, after which it was then filtered through Celite to remove the Pd black and inorganic salts. The solution which resulted was diluted with additional EtOAc (20 mL), and it was then washed with water (5 × 15 mL) and brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified (short flash column) to give the 5-methoxy indole **21a**, accompanied by the byproduct **21b**. Column chromatography of the crude mixture in EtOAc/hexanes provided the desired indole **21a** (873 mg, 68%) and the regioisomer **21b** (140 mg, 13%).

21a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.24 (d, 1H, J = 8.8 Hz), 7.17 (d, 1H, J = 2.3 Hz), 6.85 (dd, 1H, J = 8.8, 2.4 Hz), 4.31−3.97 (m, 5H), 3.91 (t, 1H, J = 3.4 Hz), 3.86 (s, 3H), 3.52 (dd, 1H, J = 14.2, 3.7 Hz), 2.87 (dd, 1H, J = 14.2, 9.4 Hz), 2.35−2.25 (m, 1H), 1.31 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz), 1.06 (d, 3H, J = 6.8 Hz), 0.70 (d, 3H, J = 6.8 Hz), 0.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C), 162.8 (C), 153.5 (C), 134.8 (C), 133.5 (C), 129.9 (C), 122.5 (C), 112.5 (CH), 111.1 (CH), 102.0 (CH), 60.6 (CH_2), 60.5 (CH_2), 60.4 (CH), 58.5 (CH), 55.9 (CH_3), 31.9 (CH_2), 31.5 (CH), 19.1 (CH_3), 16.5 (CH_3), 14.2 (2 × CH_3), −0.6 (3 × CH_3); EIMS (*m*/*e*, relative intensity) 443 ($M^{\bullet+}$, 26), 232 (100), 212 (39), 190 (13), 169 (34), 73 (20); HRMS (EI-trisector) *m*/*z*: Calcd for $C_{24}H_{37}N_3O_3Si$ 443.2604, Found 443.2590.

21b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.18 (d, 1H, J = 8.7 Hz), 7.03 (d, 1H, J = 2.4), 6.79 (dd, 1H, J = 8.7, 2.4 Hz), 6.22 (br,s, 1H), 4.30−4.14 (m, 5H), 3.89 (t, 1H, J = 5.6 Hz), 3.86 (s, 3H), 3.42 (dd, 1H, J = 14.7, 3.2 Hz), 3.01 (dd, 1H, J = 14.7, 8.7 Hz), 2.30−2.19 (m, 1H), 1.41−1.34 (m, 6H), 1.02 (d, 3H, J = 6.9 Hz), 0.75 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8 (C), 161.9 (C), 153.8 (C), 137.9 (C), 131.0 (C), 128.7 (C), 111.0 (CH), 110.8 (CH), 101.9 (CH), 100.6 (CH), 61.0 (CH), 60.9 (CH_2), 60.8 (CH_2), 55.8 (CH), 55.7 (CH_3), 32.7 (CH_2), 32.2 (CH), 18.9 (CH_3), 16.9 (CH_3), 14.3 (CH_3), 14.2 (CH_3); EIMS (*m*/*e*, relative intensity) 371 ($M^{\bullet+}$, 32), 342 (7), 211 (36), 169 (38), 160 (100), 145 (13), 117 (26); HRMS (EI-trisector) *m*/*z*: Calcd for $C_{21}H_{29}N_3O_3$ 371.2209, Found 371.2200.

3-(((2*R*,5*S*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-5-methoxy-1*H*-indole (26). To a solution of **25** (55 g, 0.116 mol) in dry CH_2Cl_2 (536 mL) under nitrogen was added 2,6-lutidine (38 g, 0.353 mol) and TMSOTf (31.4 g, 0.141 mol) dropwise at 0 °C. The solution which resulted was stirred at 0 °C for 30 min and then allowed to warm to rt (12 h). The reaction mixture was then poured into a cold saturated aq solution of $NaHCO_3$ (300 mL). The organic layer was separated, and the combined organic layers were washed with brine (240 mL) and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue was purified by chromatography (hexanes/ethyl acetate, 6/1) to afford **26** as a colorless oil (38 g, 93%). The ^{1}H NMR spectra was in excellent agreement with the literature values.[32]

(*R*)-Ethyl-2-(benzylamino)-3-(5-methoxy-1*H*-indol-3-yl)-propanoate (27). To a solution of tryptophan ethyl ester **17** (29 g, 110.6 mmol) in dry ethanol (500 mL) at 0 °C under nitrogen was added benzaldehyde (24.07 g, 226.89 mmol) and anhydrous Na_2SO_4 (78.6 g, 553.4 mmol). The solution was stirred at 0 °C for 5 h, cooled to −10 °C, and treated portionwise with $NaBH_4$ (4.44 g, 117.2 mmol) over a period of 3 h keeping the temperature below −5 °C to prevent epimerization at C-3 and the formation of unwanted tetrahydro β-carboline. After the mixture was allowed to stir for an additional 1 h, ice water (15 mL) was added, and the mixture was allowed to warm to room temperature. The methanol was removed under reduced pressure, and the aq residue was extracted with EtOAc (3 × 360 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent under reduced pressure the residue was purified by flash chromatography (EtOAc:hexanes, 3:1) to afford the N_a-H, N_b-benzyl-7-methoxy-D-tryptophan ethyl ester **27** as an oil in 90% (35 g) yield. FTIR ($CHCl_3$) 3405, 2930, 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (br, 1H), 7.32−7.22 (m, 6H), 7.04 (dd, 2H, J = 15.1, 2.2 Hz), 6.86 (dd, 1H, J = 8.8, 2.3 Hz), 4.12 (q, 2H, J = 7.1 Hz), 3.87 (d, 1H, J = 14.6 Hz), 3.85 (s, 3H), 3.69 (dd, 2H, J = 13.4, 7.2 Hz), 3.16 (dd, 1H, J = 13.5, 6.0 Hz), 3.09 (dd, 1H, J = 13.5, 6.0 Hz), 1.95 (br, 1H), 1.18 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.9, 154.0, 139.8, 131.4, 128.3, 128.2, 128.0, 127.0, 123.6, 112.4, 111.8, 111.2, 100.7, 61.3, 60.6, 55.9, 52.2, 29.5, 14.2; EIMS (*m*/*e*, relative intensity) 352 ($M^{\bullet+}$, 100), 279 (50), 236 (11); HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ Calcd for $C_{21}H_{25}N_2O_3$ 353.1865, Found 353.1856.

(1*S*,3*R*)-Ethyl-2-benzyl-6-methoxy-1-(3-methoxy-3-oxopropyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (28). To a round-bottom flask (500 mL) that contained a solution of optically active N_a-H, N_b-benzyl-D-tryptophan ethyl ester **27** (21 g, 59.6 mmol) in dry CH_2Cl_2 (300 mL) was added the aldehyde, 4-oxobutyric acid methyl ester (17.23 g, 148.4 mmol), and AcOH (3.6 g, 59.9 mmol) at 0 °C. The reaction mixture which resulted was stirred at rt overnight. TFA (6.8 g, 59.6 mmol) in dry CH_2Cl_2 (75 mL) was then

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added at 0 °C. The reaction mixture which resulted was stirred at rt for 4 days and then cooled in an ice bath and brought to pH 8 with an aq solution of NH_4OH (14%). The aq layer was separated and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue which resulted was purified by flash chromatography (silica gel, EtOAc:hexanes, 1:4) to provide **28** (25 g, 93%) as a white crystalline solid. $[\alpha]_D^{20}$ −41.08 (*c* 2.6, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.38 (d, 2H, *J* = 7.2 Hz), 7.33 (t, 2H, *J* = 7.2 Hz), 7.28 (d, 1H, *J* = 7.8 Hz), 7.24 (d, 1H, *J* = 8.4 Hz), 7.02 (d, 1H, *J* = 2.4 Hz), 6.86 (dd, 1H, *J* = 9.0, 2.4 Hz), 4.33−4.27 (m, 1H), 4.26−4.20 (m, 1H), 4.01 (dd, 1H, *J* = 9.0, 4.8 Hz), 3.90 (s, 3H), 3.88 (d, 2H, *J* = 13.8 Hz), 3.59 (d, 1H, *J* = 13.8 Hz), 3.53 (s, 3H), 3.13 (dd, 1H, *J* = 15.6, 9.6 Hz), 3.02 (dd, 1H, *J* = 15.6, 4.8 Hz), 2.45 (dt, 1H, *J* = 16.8, 7.2 Hz), 2.34 (dt, 1H, *J* = 16.8, 6.6 Hz), 2.11−2.06 (m, 1H), 2.01−1.95 (m, 1H), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3 (C), 173.0 (C), 154.1 (C), 139.4 (C), 135.1 (C), 131.3 (C), 129.2 (2 × CH), 128.2 (2 × CH), 127.4 (C), 127.1 (CH), 111.6 (2 × CH), 107.3 (C), 100.4 (CH), 60.8 (CH_2), 56.7 (CH), 56.0 (CH_3), 54.6 (CH), 53.3 (CH_2), 51.5 (CH_3), 29.6 (CH_2), 29.0 (CH_2), 21.1 (CH_2), 14.4 (CH_3); EIMS (*m*/*e*, relative intensity) 450 ($M^{\bullet+}$, 59), 418 (26), 377 (51), 363 (100), 327 (50), 285 (22), 227 (13); HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ Calcd for $C_{26}H_{31}N_2O_5$ 451.2233, Found 451.2222; Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.87; H, 6.74; N, 6.98.

(6*S*,10*S*)-Methyl-12-benzyl-9-hydroxy-2-methoxy-6,7,10,11-tetrahydro-5*H*-6,10-epimino-cycloocta[*b*]indole-8-carboxylate (30). To a solution of the *trans* diester **28** (10 g, 22.1 mmol) in dry toluene (400 mL), which had been predried by azeotropic removal of H_2O by a Dean−Stark Trap (refluxed 6 h) under argon, was added sodium hydride (8.8 g of 60% NaH dispersion in mineral oil, 221.9 mmol) at 0 °C. Dry methanol (18.0 mL, 443.9 mmol) was added carefully to the above mixture dropwise at 0 °C (a large amount of H_2 was evolved at this point). The mixture which resulted was allowed to warm to rt for 0.5 h and then heated to reflux for an additional 72 h (Note: The top of the flask was covered with aluminum foil to prevent carbonization of the intermediate lactam **29**.). The reaction mixture was then allowed to cool to rt and quenched with ice cold H_2O (200 mL). The organic layer was separated, and the aq layer was then extracted with CH_2Cl_2 (3 × 400 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the mineral oil was separated by decantation. The residue which resulted was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:4) to provide the N_a-H, β-ketoester **30** (7.9 g, 88%) as a yellow colored solid. FTIR ($CHCl_3$) 3398, 2922, 1659, 1621, 1441 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.03 (s, 1H), 7.58 (s, 1H), 7.40 (d, 2H, *J* = 7.2 Hz), 7.36 (t, 2H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 7.2 Hz), 7.22 (d, 1H, *J* = 8.4 Hz) 6.99 (d, 1H, *J* = 2.4 Hz), 6.85 (dd, 1H, *J* = 9.0, 2.4 Hz), 4.02 (d, 1H, *J* = 5.4 Hz), 3.89 (s, 3H), 3.86 (d, 1H, *J* = 13.2 Hz), 3.81 (d, 1H, *J* = 6.0 Hz), 3.76 (d, 1H, *J* = 13.8 Hz), 3.70 (s, 3H), 3.19 (dd, 1H, *J* = 15.6, 6.0 Hz), 2.91 (d, 1H, *J* = 15.6 Hz), 2.85 (dd, 1H, *J* = 15.6, 5.4 Hz), 2.35 (d, 1H, *J* = 15 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6 (C), 171.7 (C). 154.2 (C), 138.3 (C), 134.3 (C), 130.7 (C), 128.8 (2 × CH), 128.5 (2 × CH), 127.5 (C), 127.3 (CH), 111.7 (CH), 111.6 (CH), 106.3 (C), 100.4 (CH), 94.4 (C), 56.0 (CH_3), 56.0 (CH_2), 55.2 (CH), 51.5 (CH_3), 49.8 (CH), 28.9 (CH_2), 22.1 (CH_2); EIMS (*m*/*e*, relative intensity) 404 ($M^{\bullet+}$, 62), 372 (28), 289 (100), 199 (66), 156 (45); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{25}N_2O_4$ 405.1814, Found 405.1788.

(6*S*,10*S*)-2-Methoxy-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (32). To a solution of the β-ketoester **30** (18 g, 0.045 mol) in 1,4-dioxane (350 mL) was added 33% aq KOH (350 mL). The reaction mixture which resulted was heated to reflux for 48 h. The solution was allowed to cool to rt, and the 1,4-dioxane was removed under reduced pressure. The mixture that remained was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexanes:EtOAc, 3:1) to afford the N_b-benzyl tetracyclic ketone **31** (12.6 g, 82%) which was taken forward to the next step without subjecting it to any analytical characterization.

To a solution of the tetracyclic ketone **31** (8.94 g, 25.8 mmol) in dry EtOH (50 mL) was added a saturated solution of EtOH/HCl(g) dropwise until the solid completely dissolved. The solvent was removed under reduced pressure to furnish an HCl salt of the N_b-benzyl tetracyclic ketone **31**. Then EtOH was added to the salt and removed under reduced pressure. This process was repeated 3 times to remove excess hydrogen chloride. The HCl salt of **31** was degassed under reduced pressure at rt and backfilled with argon (2 times). Dry Pd/C (10% by wt, 1.99 g, 1.54 mmol) was added to the above HCl salt followed by slow addition of dry ethanol (100 mL). The mixture was degassed under reduced pressure at rt and backfilled with argon (2 times) and then with H_2. The mixture which resulted was allowed to stir at rt under an atmosphere of hydrogen (1 atm) for 12 h. After analysis by TLC (silica gel plate was exposed to NH_3 vapors) indicated the absence of starting material **31**, the catalyst was removed by filtration through Celite, and the solid was washed with EtOH (3 × 15 mL). The organic layers were combined, and the solvent was removed under reduced pressure to give a yellow residue, which was dissolved in a mixture of $CHCl_3$ (200 mL) and ice water, after which the solution was brought to pH 8 by addition of a solution of aq NH_4OH (14%). The aq layer was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with brine (200 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography on silica gel (EtOAc:hexanes, 5:1) to provide the N_b-H tetracyclic ketone **32** (6.1 g, 92% yield) as a yellow colored oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (br, 1H), 7.29 (s, 1H), 7.23 (d, 1H, *J* = 9.0 Hz), 6.93 (d, 1H, *J* = 2.4 Hz), 6.86 (dd, 1H, *J* = 9.0, 2.4 Hz), 4.33 (m, 1H), 3.98 (d, 1H, *J* = 6.6 Hz), 3.88 (s, 3H), 3.12 (dd, 1H, *J* = 16.2, 6.6 Hz), 2.82 (d, 1H, *J* = 16.8 Hz), 2.54−2.44 (m, 2H), 2.21−2.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.0 (C), 154.3 (C), 134.9 (C), 130.7 (C), 127.4 (C), 112.0 (CH), 111.6 (CH), 107.5 (C), 100.3 (CH), 59.9 (CH), 55.9 (CH_3), 46.3 (CH), 35.2 (CH_2), 32.2 (CH_2), 26.0 (CH_2); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1290, Found 257.1302.

(6*S*,10*S*)-12-((*Z*)-2-Iodobut-2-en-1-yl)-2-methoxy-7,8,10,11-tetrahydro-5*H*-6,10-epimino cycloocta[*b*]indol-9(6*H*)-one (33). To a solution of the N_a-H, N_b-H tetracyclic ketone **32** (6.0 g, 23.4 mmol) and molecular sieves (5.0 g) in anhydrous acetonitrile (250 mL) under an inert atmosphere was added K_2CO_3 (12.9 g, 93.7 mmol) and *Z*-1-bromo-2-iodo-2-butene[46] (7.9 g, 30.4 mmol), and the mixture which resulted was stirred at rt for 8 h. Analysis by TLC (silica gel, $CHCl_3$:EtOH, 4:1) indicated the absence of tetracyclic ketone **32**. The solids were removed by filtration and washed with EtOAc (3 × 100 mL). The combined organic layers were concentrated under reduced pressure to provide a light yellow residue. Purification of the crude product by flash chromatography (silica gel, EtOAc/hexanes, 1:9) provided the N_b-*Z*-2′-iodo-2′-butenyl, tetracyclic ketone **33** (7.76 g, 76%) as a yellow colored solid. FTIR ($CHCl_3$) 2929, 1707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.24 (d, 1H, *J* = 8.7 Hz), 6.94 (d, 1H, *J* = 2.3 Hz), 6.86 (dd, 1H, *J* = 8.7, 2.4 Hz), 5.85 (q, 1H, *J* = 6.3 Hz), 4.03 (d, 1H, *J* = 2.6 Hz), 3.88 (s, 3H), 3.72 (d, 1H, *J* = 6.5 Hz), 3.39 (dd, 2H, *J* = 17.5, 13.9 Hz), 3.11 (dd, 1H, *J* = 16.7, 6.6 Hz), 2.69 (d, 1H, *J* = 16.7 Hz), 2.56−2.46 (m, 2H), 2.16−1.99 (m, 2H), 1.82 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2 (C), 154.2 (C), 133.0 (C), 132.7 (CH), 130.8 (C), 127.2 (C), 111.9 (CH), 111.6 (CH), 108.5 (C), 106.7 (C), 100.3 (CH), 64.1 (CH), 63.4 (CH_2), 55.9 (CH_3), 49.9 (CH), 34.5 (CH_2), 30.4 (CH_2), 21.7 (CH_3), 20.6 (CH_2); EIMS (*m*/*e*, relative intensity) 436 ($M^{\bullet+}$, 52), 408 (6), 379 (100), 309 (10), 281 (23); HRMS (EI-trisector) *m*/*z*: Calcd for $C_{19}H_{21}IN_2O_2$ 436.0648, Found 436.0663.

(+)-Lochneram (11). To a stirred solution of **6** (100 mg, 0.308 mmol) in freshly distilled MeOH (2 mL) at 0 °C was added MeI (2 mL), and the reaction was allowed to warm to rt in the dark (24 h) until disappearance of the starting material **6** (TLC, silica gel). The solvent and excess MeI was removed under reduced pressure to provide the crude N_b-methiodide salt. The solvent was removed under reduced pressure, and the residue passed through a short column of

activated neutral alumina using $CHCl_3$/MeOH (16:1) as eluant to provide (+)-lochneram (**11**, 122 mg) in 85% yield as a clear oil. ^{1}H NMR (600 MHz, CD_3OD) δ 7.31 (d, 1H, J = 9.0 Hz), 7.04 (br, s, 1H), 6.87 (d, 1H, J = 8.4 Hz), 5.68 (q, 1H, J = 6.6 Hz), 4.91 (1H, peak is embedded in CD_3OD peak), 4.46 (d, 1H, J = 15.6 Hz), 4.25 (d, 1H, J = 15.6 Hz), 3.85 (s, 3H), 3.58 (d, 3H, J = 7.8 Hz), 3.31 (d, 1H, J = 4.8 Hz, part of the peak is embedded in CD_3OD peak), 3.15−3.10 (m, 5H), 2.55 (t, 1H, J = 12.0 Hz), 2.21−2.17 (m, 2H), 1.74 (d, 3H, J = 6.6 Hz); ^{13}C NMR (150 MHz) δ 154.5 (C), 132.4 (C), 131.7 (C), 127.7 (C), 126.5 (C), 120.7 (CH), 112.6 (CH), 112.0 (CH), 100.3 (C), 99.8 (CH), 65.4 (CH), 64.4 (CH_2), 62.4 (CH), 61.0 (CH_2), 54.8 (CH_3), 46.7 (CH_3), 43.6 (CH), 32.0 (CH_2), 26.0 (CH), 23.9 (CH_2), 11.6 (CH_3); HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{27}N_2O_2$ $(M)^+$ 339.2073; Found 339.2057. The spectral data for **11** were identical to those reported in the literature.[1a,22]

Lochvinerine (9). A mixture of anhydrous potassium *tert*-butoxide (313 mg, 0.279 mmol) and methyl-triphenylphosphonium bromide (911 mg, 0.25 mmol) in dry benzene (14 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **16** (124 mg, 0.40 mmol) in THF (5 mL) was then added into the above orange-colored solution dropwise at rt. The mixture which resulted was stirred at rt for 4 h. The mixture was diluted with EtOAc (50 mL), washed with H_2O (3 × 10 mL) as well as brine (25 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the oil that resulted was chromatographed (silica gel, $CHCl_3$/MeOH; 15:1) to provide the olefin **34** (111 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.18 (d, 1H, J = 8.7 Hz), 6.95 (d, 1H, J = 2.4 Hz), 6.79 (dd, 1H, J = 8.7, 2.5 Hz), 5.27 (q, 1H, J = 6.7 Hz), 4.86−4.84 (m, 2H), 4.15 (dd, 1H, J = 9.8, 2.2 Hz), 3.87−3.85 (s, 4H), 3.70 (br, s, 2H), 3.31 (d, 1H, J = 2.5 Hz), 3.13 (dd, 1H, J = 15.3, 5.4 Hz), 2.96 (dd, 1H, J = 15.3, 1.5 Hz), 2.14 (ddd, 1H, J = 12.0, 10.1, 1.7 Hz), 1.93−1.85 (m, 1H), 1.66 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C), 152.8 (C), 138.6 (C), 137.6 (C), 131.3 (C), 127.9 (C), 114.6 (CH), 111.4 (CH), 110.9 (CH), 105.1 (CH_2), 104.7 (C), 100.5 (CH), 56.6 (CH), 55.9 (CH_2), 55.9 (CH_3), 50.5 (CH), 36.7 (CH), 36.3 (CH_2), 26.3 (CH_2), 12.3 (CH_3); EIMS (m/e, relative intensity) 306 ($M^{\bullet+}$, 100), 291 (16), 265 (12), 251 (10), 198 (40), 183 (16), 156 (10), 77 (10). This material was employed directly in the next step without any further characterization.

To a solution of olefin **34** (124 mg, 0.40 mmol) in THF (12 mL) was added 9-BBN (0.5 M in THF, 5 mL, 2.43 mmol) dropwise at 0 °C. The solution was allowed to warm to rt and stirred for 1.5 h. The reaction mixture was then cooled to 0 °C, $NaBO_3{\cdot}4H_2O$ (1.1 g, 7.28 mmol) was added, and the reaction temperature was allowed to warm to rt. The mixture that resulted was stirred for 2 h at rt, diluted with CH_2Cl_2 (200 mL), washed with H_2O (3 × 50 mL) as well as brine (100 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, $CHCl_3$/MeOH; 9:1) to provide lochvinerine **9** (98 mg, 75%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) 10.2 (br, s, 1H), 7.30 (d, 1H, part of the peak is embedded in $CDCl_3$ peak), 6.87 (d, 1H, J = 2.2 Hz), 6.80 (dd, 1H, J = 8.8, 2.3 Hz), 5.16 (q, 1H, J = 6.8 Hz), 4.43 (d, 1H, J = 5.8 Hz), 3.88−3.84 (m, 4H), 3.71 (d, 1H, J = 17.6 Hz), 3.52 (dd, 1H, J_2 = 7.2 Hz, part of the peak is embedded in MeOH peak), 3.50 (1H is embedded in MeOH peak), 3.11 (d, 1H, J = 16.6 Hz), 3.36−3.24 (m, 2H), 2.93 (br, s, 1H), 2.35−2.33 (m, 1H), 2.19 (s, 1H), 2.03−1.95 (m, 2H), 1.63 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0 (C), 140−132 (2 quaternary carbons not observed), 131.7 (C), 125.7 (C), 117.3 (CH), 112.5 (CH), 111.9 (CH), 104.2 (C), 100.2 (CH), 60.3 (CH_2), 55.7 (CH_3), 54.9 (CH_2), 53.9 (CH), 50.6 (CH), 40.9 (CH), 26.5 (CH_2), 25.7 (CH), 21.4 (CH_2), 12.7 (CH_3); HRMS (ESI-TOF) m/z: $(M + H)^+$ Calcd for $C_{20}H_{25}N_2O_2$ 325.1916; Found 325.1920. The spectral data for **9** were identical to those reported in the literature.[21]

(1*S*,3*R*)-Ethyl-2-benzyl-5-iodo-6-methoxy-1-(3-methoxy-3-oxopropyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole-3-carboxylate (36a). Procedure with NIS: To a solution of indole **35** (100 mg, 0.22 mmol) in acetonitrile (8 mL), cooled to 0 °C, TFA (24.7 μL, 0.32 mmol) was added dropwise and this was followed by NIS (34 mg, 0.26 mmol). The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to rt (16 h). The reaction mixture was diluted with ethyl acetate (13 mL), cooled in an ice bath and adjusted to pH 8 with cold aqueous NH_4OH solution (10%). The organic layer was separated, washed with brine (3 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow color oil. Column chromatography (silica gel, ethyl acetate/hexanes; 1 : 4) provided the 9-iodoindole **36a** (89 mg, 70%) and the C-11 iodo regioisomer **36b** (13 mg, 10%). Procedure with IBX: To a solution of **35** (750 mg, 1.61 mol) in acetonitrile (20.7 mL), cooled to 0 °C, was added dropwise TFA (2.3 mL), followed by IBX (226 mg, 0.807 mol), and I_2 (497 mg, 1.77 mol). The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to rt (8 h). The reaction mixture was diluted with ethyl acetate (30 mL), cooled in an ice bath, and adjusted to pH 8 with a solution of cold aq NH_4OH (10%), followed by treatment with a saturated aq solution of $Na_2S_2O_3$ (35 mL) to remove excess iodine. The organic layer was separated, washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a reddish brown oil. Flash column chromatography (silica gel, ethyl acetate/hexanes; 2:8) provided **36a** (780 mg, 82%) as a white crystalline solid and the regioisomer **36b** (76 mg, 8%) as a light yellow colored oil.

36a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.34 (m, 3H), 7.32 (br,s, 1H), 7.30−7.28 (m, 1H), 7.22 (d, 1H, J = 8.7 Hz), 6.90 (d, 1H, J = 8.7 Hz), 4.40−4.23 (m, 2H), 4.02 (dd, 1H, J = 11.2, 4.8 Hz), 3.94 (s, 3H), 3.89 (d, 1H, J = 13.4 Hz), 3.80 (dd, 1H, J = 10.6, 3.1 Hz), 3.74−3.63 (m, 4H), 3.49−3.44 (m, 4H), 3.38 (d, 1H, J = 13.2 Hz), 2.65 (ddd, 1H, J = 17.5, 9.5, 5.4 Hz), 2.40 (dt, 1H, J = 17.5, 5.3 Hz), 2.06−1.95 (m, 1H), 1.93−1.81 (m, 1H), 1.39 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (C), 172.7 (C), 152.3 (C), 139.2 (C), 137.8 (C), 133.9 (C), 129.2 (2 × CH), 128.9 (C), 128.1 (2 × CH), 126.9 (CH), 109.2 (CH), 107.9 (CH), 107.7 (C), 60.8 (CH_2), 58.3 (CH_3), 55.8 (CH), 53.3 (CH), 52.6 (CH_2), 51.2 (CH_3), 29.8 (CH_3), 29.6 (CH_2), 29.3 (CH_2), 22.2 (CH_2), 14.3 (CH_3) (One of the quaternary carbon atoms is embedded in the above carbons.); EIMS (m/e, relative intensity) 590 ($M^{\bullet+}$, 14), 517 (55), 503 (100), 377 (20), 339 (22), 303 (14); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{32}IN_2O_5$ 591.1356, Found 591.1332.

The structure was confirmed by X-ray analysis (see SI).

36b. EIMS (m/e, relative intensity) 590 ($M^{\bullet+}$, 14), 517 (55), 503 (100), 377 (20), 339 (22), 303 (14); HRMS (ESI-TOF) m/z: $(M + H)^+$ Calcd for $C_{27}H_{32}IN_2O_5$ 591.1356, Found 591.1254. The identity of the regioisomer **36b** was confirmed by comparison of the crude ^{1}H NMR with **36a**. HRMS was also performed on the same sample. No further characterization was carried out.

(1*S*,3*R*)-Ethyl-2-benzyl-5-bromo-6-methoxy-1-(3-methoxy-3-oxopropyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole-3-carboxylate (37a). To a solution of indole **35** (500 mg, 1.07 mol) in acetonitrile (40 mL), cooled to 0 °C, was added dropwise TFA (0.12 mL, 1.61 mol), and this was followed by NBS (229 mg, 1.29 mol). The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to rt (16 h). The reaction mixture was diluted with ethyl acetate (30 mL), cooled in an ice bath, and adjusted to pH 8 with cold aq NH_4OH solution (10%). The organic layer was separated, washed with brine (3 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a reddish brown oil. Column chromatography (silica gel, ethyl acetate/hexanes; 1:4) provided the 9-bromoindole **37a** (380 mg, 65%) and the regioisomer **37b** (68 mg, 13%).

37a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 7.19 (d, 1H, J = 8.7 Hz), 6.94 (d, 1H, J = 8.8), 4.41−4.22 (m, 2H), 4.02 (dd, 1H, J = 11.2, 4.9 Hz), 3.95 (s, 3H), 3.89 (d, 1H, J = 13.2 Hz), 3.79 (dd, 1H, J = 10.8, 3.1 Hz), 3.62 (s, 3H), 3.57 (d, 1H, J = 4.9 Hz), 3.48−3.36 (m, 5H), 2.64 (ddd, 1H, J = 17.4, 9.5, 5.3 Hz), 2.40 (dt, 1H, J = 17.5, 5.3 Hz), 2.06−1.95 (m, 1H), 1.93−1.80 (m, 1H), 1.39 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (C), 172.7 (C), 150.0 (C), 139.2 (C), 137.7 (C), 134.0 (C), 129.2 (2 × CH), 128.1 (2 × CH), 126.9 (CH), 126.3 (C), 108.9 (CH), 108.1 (CH), 107.0 (C), 103.0 (C), 60.8 (CH_2), 58.2 (CH_3), 56.0 (CH), 53.2 (CH), 52.6 (CH_2), 51.2 (CH_3), 29.8 (CH_3), 29.3 (CH_2), 27.7 (CH_2), 22.1 (CH_2), 14.3 (CH_3); EIMS (m/e, relative intensity) 544 ($M^{\bullet+}$, 5), 542 ($M^{\bullet+}$, 5), 471

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(14), 469 (17), 457 (99), 455 (100), 377 (36); HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ Calcd for $C_{27}H_{32}BrN_2O_5$ 543.1488, Found 543.1503.

37b. The identity of the regioisomer **37b** was confirmed by comparison of the crude ^{1}H NMR to that of **36b**. No further characterization was carried out.

(1*S*,3*R*)-Ethyl-2-benzyl-6-methoxy-1-(3-methoxy-3-oxopropyl)-9-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (39) [Entry 8, Table 2]. General procedure for entries 1−7 is the same as described below.

To a resealable Schlenk tube possessing a Teflon screw valve were added **36a** (118 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and 2-(dicyclohexylphosphanyl)biphenyl (DCPB, 14 mg, 0.04 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out a total of three times). Freshly degassed 1,4-dioxane (2.5 mL) was added via a syringe through the septum, followed by the addition of dry Et_3N (0.11 mL, 80 mg, 0.80 mmol) and pinacol borane (0.09 mL, 77 mg, 0.6 mmol). The septum was then replaced with a Teflon screw valve under a positive argon pressure, and the Schlenk tube was sealed. The reaction mixture was heated to 100 °C and stirred at that temperature for 3 h. At the end of this period the reaction mixture was cooled to rt, diluted with EtOAc (10 mL), and passed through a short pad of Celite. The Celite pad was further washed with EtOAc (20 mL), and the combined filtrates were washed with water (20 mL) and brine (20 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue thus obtained was purified by flash chromatography on a silica gel column, eluted with 4:1 hexanes/EtOAc to afford **39** as a white solid (110 mg, 93%). mp: 182.6−183.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, 2H, J = 6.6 Hz), 7.32 (d, 2H, J = 6.6 Hz), 7.26 (m, 2H), 6.89 (d, 1H, J = 8.7 Hz), 4.29 (m, 2H), 4.06 (dd, 1H, J = 10.5, 6.0 Hz), 3.88 (s, 3H), 3.81 (d, 1H, J = 13.2 Hz), 3.75 (dd, 1H, J = 10.8, 3.0 Hz), 3.60 (s, 3H), 3.49 (s, 3H), 3.40 (d, 1H, J = 13.2 Hz), 3.15 (m, 2H), 2.62 (m, 1H), 2.42 (m, 1H), 1.97 (m, 1H), 1.84 (m, 1H), 1.49 (s, 12H), 1.37 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 172.9 (C), 157.8 (C), 139.4 (2 × C), 136.8 (C), 133.1 (C), 129.5 (C), 129.3 (2 × CH), 128.0 (2 × CH), 126.8 (CH), 110.4 (CH), 107.8 (CH), 106.5 (C), 83.9 (2 × C), 60.7 (CH_2), 58.3 (CH_3), 56.3 (CH), 53.2 (CH), 52.7 (CH_2), 51.2 (CH_3), 29.6 (CH_2), 29.6 (CH_3), 27.9 (CH_2), 25.1 (4 × CH_3), 21.8 (CH_2), 14.3 (CH_3); HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ Calcd for $C_{33}H_{44}BN_2O_7$ 591.3236, Found 591.3265; Anal. Calcd for $C_{33}H_{43}BN_2O_7$: C, 67.12; H, 7.34; N, 4.74. Found: C, 66.91; H, 7.53; N, 4.60.

(1*R*,1′*R*,3*S*,3′*S*)-Diethyl-2,2′-dibenzyl-6,6′-dimethoxy-1,1′-bis(3-methoxy-3-oxopropyl)-9,9′-dimethyl-2,2′,3,3′,4,4′,9,9′-octahydro-1*H*,1′*H*-[5,5′-bipyrido[3,4-*b*]indole]-3,3′-dicarboxylate (38a) and Its Atropodiastereomer (1*S*,1′*S*,3*R*,3′*R*)-Diethyl 2,2′-dibenzyl-6,6′-dimethoxy-1,1′-bis(3-methoxy-3-oxopropyl)-9,9′-dimethyl-2,2′,3,3′,4,4′,9,9′-octahydro-1*H*,1′*H*-[5,5′-bipyrido[3,4-*b*]indole]-3,3′-dicarboxylate (38b) [Entry 9, Table 3]. General procedure for entries 1−8 is the same as described below.

To a resealable Schlenk tube possessing a Teflon screw valve were added **36a** (11.8 mg, 0.02 mmol), **39** (17.6 mg, 0.03 mmol), $Pd(OAc)_2$ (0.44 mg, 0.002 mmol), *S*-Phos (1.6 mg, 0.004 mmol), and K_3PO_4 (8.4 mg, 0.04 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out a total of three times). Freshly degassed THF (1 mL) and water (0.1 mL) were added via syringe through the septum. The septum was then replaced with a Teflon screw valve under a positive argon pressure, and the Schlenk tube was sealed. The reaction mixture was heated to 50 °C and stirred at that temperature for 48 h. At the end of this period, the reaction mixture was cooled to rt and was passed through a short pad of Celite. The Celite pad was further washed with EtOAc (10 mL), and the combined filtrate was washed with water (5 mL) and brine (5 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue thus obtained was purified by flash chromatography on a silica gel column, eluted with 1:1 hexanes/EtOAc to afford **38a** as an off-white solid (6.8 mg, 38%), **38b** (3.3 mg, 19%) as a light yellow solid, and recovered **35** (20%).

The ^{1}H NMR spectras for **38a** and **38b** were identical to that reported in the communication.[27b]

Oxidative Dehydrodimerization of the Model Substrate 35. *Entry 1*. To a stirred solution of the β-carboline **35** (150 mg, 0.32 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was added solid PIFA (84 mg, 0.194 mmol) and boron trifluoride diethyl etherate dropwise (114.5 mg, 0.807 mmol), after which the reaction mixture was allowed to warm to rt and stirred for 2 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated the presence of the starting material **35**, and atropodiastereomers **38a** and **38b**, with a considerable amount of colored impurities formed at the baseline. No further purification for the separation of the diastereomers was attempted.

Entry 2. To a stirred solution of the β-carboline **35** (100 mg, 0.215 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C was added solid PIFA (95 mg, 0.219 mmol) and boron trifluoride diethyl etherate dropwise (122.2 mg, 0.861 mmol), after which the reaction mixture was allowed to warm to rt and stirred for 8 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated complete conversion of the starting material **35**. The reaction mixture was diluted CH_2Cl_2 (25 mL) and cooled to 0 °C, after which it was brought to pH = 8 with a cold aq solution of saturated $NaHCO_3$. The aq layer which resulted was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with a saturated aq solution of $NaHSO_3$ (2 × 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a dark oil. The crude diastereomeric mixture was purified by flash chromatography on silica gel (hexanes/ethyl acetate) to provide a combined yield of **38a** + **38b**: 21 mg (11%), with a diastereomeric ratio of 3:2 in favor of **38a**.

Entry 3. To a stirred solution of the β-carboline **35** (100 mg, 0.215 mmol) in dry CH_2Cl_2 (2.0 mL) at −40 °C was added solid PIFA (95 mg, 0.219 mmol) and boron trifluoride diethyl etherate (122.2 mg, 0.861 mmol) dropwise, after which the reaction mixture was allowed to warm to rt and stirred for 1.5 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated complete conversion of the starting material **35**. Fewer baseline impurities were observed as a result of lowering the reaction temperature in this case. The workup and purification procedure were the same as entry 2: combined yield of **38a** + **38b**: 39 mg (20%) with a diastereomeric ratio of 3:2 in favor of **38a**.

Entry 4. To a stirred solution of the β-carboline **35** (55 mg, 0.118 mmol) in dry CH_2Cl_2 (1.0 mL) under an inert atmosphere at −40 °C was added a solution of PIFA (40 mg, 0.094 mmol) and boron trifluoride diethyl etherate (50.41 mg, 0.355 mmol) in CH_2Cl_2 (2.0 mL), which had been precooled to −40 °C via a double ended needle transfer. The reaction mixture which resulted was stirred at −40 °C for 0.5 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated complete conversion of the starting material **35** and a much cleaner reaction. The workup and purification procedure were the same as entry 2: combined yield of **38a** + **38b**: 33 mg (30%) with a diastereomeric ratio of 4:1 in favor of **38a** via analysis of the integration values of the ^{1}H NMR spectrum.

Entry 5. To a stirred solution of the β-carboline **35** (63 mg, 0.135 mmol) in dry CH_2Cl_2 (1.0 mL) under an inert atmosphere at −78 °C was added a solution of PIFA (47 mg, 0.108 mmol) and boron trifluoride diethyl etherate (57.5 mg, 0.405 mmol) in CH_2Cl_2 (2.0 mL) precooled to −78 °C via a double ended transfer needle. The reaction mixture which resulted was stirred at −78 °C for 0.5 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/ MeOH (v/v, 9:1)] indicated the presence of unreacted starting material **35** along with the diastereomers **38a** and **38b**. The workup and purification procedure were the same as entry 2: combined yield of **38a** + **38b**: 31.4 mg (25%, based on recovered starting material) with a diastereomeric ratio of 4:1 in favor of **38a**.

Entry 6. To a stirred solution of the β-carboline **35** (50 mg, 0.107 mmol) in dry CH_2Cl_2 (1.0 mL) under an inert atmosphere at −40 °C was added a solution of PIDA (27.7 mg, 0.086 mmol) and boron trifluoride diethyl etherate (45.8 mg, 0.322 mmol) in CH_2Cl_2 (2.0 mL) precooled to −40 °C via a double ended transfer needle. The reaction mixture which resulted was stirred at −40 °C for 2.5 h. Analysis of the

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reaction mixture by TLC [silica gel, $CHCl_3$/ MeOH (v/v, 9:1)] indicated very little formation of the diastereomers **38a** and **38b** with a considerable amount of starting material **35** remaining. The workup and purification procedure were the same as entry 2. No further purification for the separation of the diastereomers (**38a** and **38b**) was attempted.

Entry 7. To a stirred solution of the β-carboline **35** (50 mg, 0.107 mmol) in dry MeCN (2.0 mL) under an inert atmosphere at rt was added solid thallium(III) trifluoroacetate (46.7 mg, 0.086 mmol) and boron trifluoride diethyl etherate (45.8 mg, 0.322 mmol) dropwise, and the solution which resulted was allowed to stir at rt for 15 min. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated the absence of starting material **35** and formation of traces of atropdiastereomers **38a** and **38b**. No further purification for the separation of the diastereomers was attempted.

Note: Thallium compounds are toxic. Do not breathe, ingest, or get on skin: Use Caution.

Entry 8. To a stirred solution of the β-carboline **35** (50 mg, 0.108 mmol) in dry acetonitrile (2.0 mL) under an inert atmosphere at −40 °C was added a solution of thallium(III) trifluoroacetate (46.7 mg, 0.086 mmol) and boron trifluoride diethyl etherate dropwise (45.8 mg, 0.322 mmol) in MeCN (2.0 mL), which was precooled to −40 °C, via a double ended transfer needle. The reaction mixture which resulted was stirred at −40 °C for 20 min. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated a cleaner reaction had occurred with complete conversion of the starting material **35** and formation of the two atropodiastereomers (**38a** and **38b**). The cold reaction mixture was diluted with CH_2Cl_2 (25 mL), and the solvent was removed under reduced pressure to give a brown residue. The residue was dissolved in fresh CH_2Cl_2 (25 mL) and cooled to 0 °C after which it was brought to pH = 8 with a cold aq solution of saturated $NaHCO_3$. The aq layer which resulted was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with brine (2 × 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a dark brown oil. The crude diastereomeric mixture was purified by flash chromatography on silica gel (hexanes/ethyl acetate) to provide a combined yield of **38a** + **38b**: 37.9 mg (38%) with a diastereomeric ratio of 2:3 in favor of **38b**.

Entry 9. To a stirred solution of the β-carboline **35** (50 mg, 0.108 mmol) in dry acetonitrile (2.0 mL) under an inert atmosphere at −78 °C was added a solution of thallium(III) trifluoroacetate (29.2 mg, 0.054 mmol) and boron trifluoride diethyl etherate (38.2 mg. 0.269 mmol) in MeCN (2.0 mL) precooled to −78 °C via a double ended transfer needle. The reaction mixture which resulted was stirred at −78 °C for 40 min. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated formation of the two atropdiastereomers (**38a** and **38b**), and complete conversion of the starting material **35** with a considerable amount of impurities formed at the baseline. The workup and purification procedure were the same as entry **8**: combined yield of **38a** + **38b**: 29.9 mg (30%) with a diastereomeric ratio of 3:7 in favor of **38b**.

Entry 10. To a stirred solution of the β-carboline **35** (200 mg, 0.430 mmol) in dry acetonitrile (10 mL) under an inert atmosphere at −40 °C was added a solution of thallium(III) acetate (115.0 mg, 0.301 mmol) and boron trifluoride diethyl etherate (183.0 mg, 1.29 mmol) in MeCN (10 mL) precooled to −40 °C via a double ended transfer needle. The reaction mixture which resulted was stirred at −40 °C for 1.25 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9:1)] indicated the presence of starting material **37** and formation of the two atropdiastereomers (**38a** and **38b**). The workup and purification procedure were the same as entry **8**: combined yield of **38a** + **38b**: 227 mg (67%) with a diastereomeric ratio of 3:7 in favor of **38b**; recovered starting material **35** (28 mg, 14%). Recrystallization of **38b** from ethanol gave light brown crystals. X-ray analysis of **38b** established the axial chirality (at the C9−C9′) as *P*(*S*).

■ ASSOCIATED CONTENT

Supporting Information

ORTEP drawings for compounds **16** and **36a**, ^1H and ^{13}C NMR spectra for all new compounds **9**, **11**, **21a/b**, **27**, **28**, **30**−**34**, **36a/b**, **37a**, **39** and X-ray data for compounds **16** and **36a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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