Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Stereoselective Access to the Core Structure of Macroline-Type Indole Alkaloids: Total Synthesis of Macroline and Alstomicine

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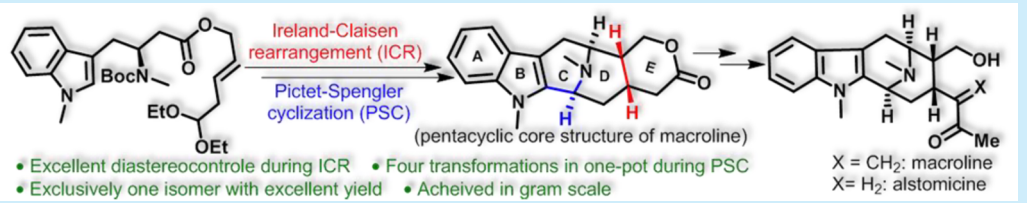
Supporting Information



ABSTRACT: Rapid synthesis of the pentacyclic core structure of macroline-type indole alkaloids, and its application in the total synthesis of macroline and alstomicine is described. The core structure was accomplished in a highly stereocontrolled manner via two key steps, Ireland−Claisen rearrangement and Pictet−Spengler cyclization, commencing from a readily available starting material L-tryptophan, which obviated the need of a particular chiral source as an external catalyst, reagent, or internal auxiliary.

Some plant families are affluent in alkaloids, of which the Apocynaceae is a good example. The Apocynaceae family has at least 150 genera and 1700 species and is distributed over a tropical region of Central America, Africa, and Asia.[1] *Alstonia macrophylla* (family of Apocynaceae), one of the famous species of the genus *Alstonia*, is commonly employed in traditional medicine of Thailand for diverse applications.[2] A drink prepared from its leaves and stem bark is used to treat stomach aches and for the putrefaction of urine.[3] A recent report with biological and pharmacological studies on *A. macrophylla* revealed that it exhibits antimicrobial, antimalarial, antioxidant, antidiabetic, anti-inflammatory, antidiarrheal, CNS depressant, antifertility, and antiprotozoal activities.[4]

Plants of the genus *Alstonia*, well-known as a rich source of novel alkaloids with an azabicyclo[3.3.1] substructure annelated to an indole ring, churned out a variety of simple and complex indole alkaloids such as macroline, sarpagine, and ajmaline.[5] The preponderance of macroline-type indole, bisindole (macroline-macroline, macroline-sarpagine/ajmaline), and oxindole alkaloids is an imperative feature of the genus *Alstonia*.[5,6] Over the period, pentacyclic macroline indole alkaloids were isolated predominantly from this genus,[7] for instance, alstonerine (**1**),[7a] alstophylline (**2**),[7a] alstophyllal (**3**),[7b] alstonerinal (**4**),[7c] N_4-demethylalstonerine (**5**),[7d] N_4-demethylalstonerinal (**6**),[7d] N_1-demethylalstophylline (**7**),[7e] N_1-demethylalstophyllal (**8**),[7e] alstohentine (**9**),[7f] macrocarpines A−C (**10**−**12**),[7b] talcarpine (**13**),[7b] N_4-methyl-N_4,21-*seco*-talpinine (**14**),[7b] 19,20-dehydro-10-methoxytalcarpine (**15**),[7g] anhydromacrosalhine-methine (**16**),[7h] raumacline (**17**),[7i] N_4-methylraumacline (**18**),[7i] and alstolactones (**19**−**20**)[7d,e] (Figure 1).

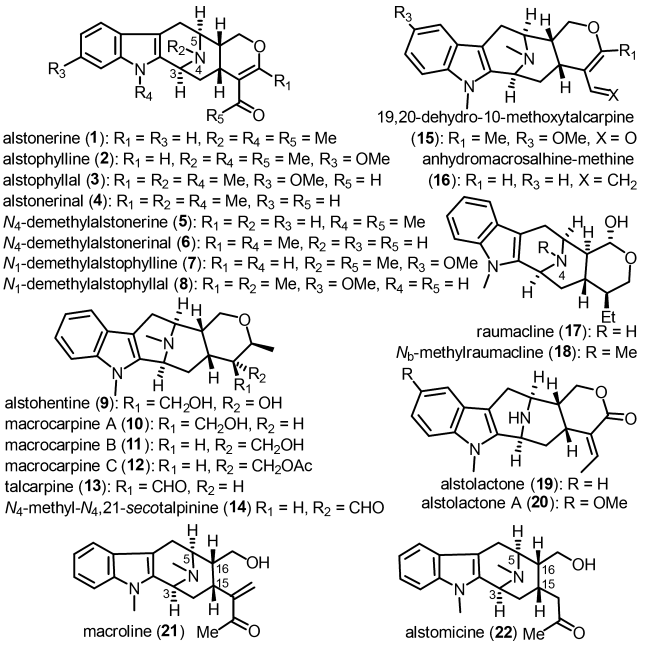


Figure 1. Representative macroline indole alkaloids.

A tetracyclic indole base, macroline (**21**), has not yet been found as such in nature, but it is believed that **21** is a likely

Received: June 20, 2018

DOI: 10.1021/acs.orglett.8b01921
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biosynthetic precursor of various monomeric indole alkaloids (**2**, **3**, and alstonisine)[8−10] and bisindole alkaloids (villalstonine, alstonisidine, macralstonine, and macralstonidine)[11−13] and is a degradation product of villastonine.[14] Alstomicine (**22**), structurally similar to **21** but without exomethylene, was isolated by T. S. Kam from the leaf extracts of the Malayan species *A. macrophylla*.[7f] This has structural features similar to the ring-opened *seco*-macroline oxindole, alstonoxine A,[15] and the ring-opened derivative of **1**.[7f] Additionally, it is a degradation product,[15] monomeric unit,[7b,16] and proposed biosynthetic precursor of several novel and bioactive alkaloids.[17]

Given our interest in the total synthesis of bioactive natural products from proposed biosynthetic pathways,[18] we became intrigued with the synthesis of macroline type indole alkaloids, macroline (**21**) and alstomicine (**22**). These target molecules **21**/**22** could be amenable precursors in accessing a range of indole alkaloids based on the proposed biosynthetic pathways. Their fascinating and synthetically challenging structure with four annulated rings, three contiguous asymmetric centers out of four total, and to the best of our knowledge, thus far, no synthetic attempts on **22** also prompted us to devise a synthetic strategy for this indole alkaloid framework. Herein, we communicate an expedient synthetic approach to the pentacyclic core **23**, and its application in the first total synthesis of alstomicine (**22**) and the total synthesis of macroline (**21**).

Our synthetic plan is depicted in Figure 2, in which the synthesis of macroline/alstomicine could be achieved from a

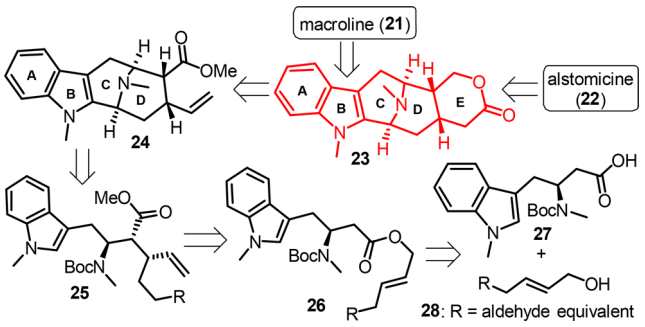
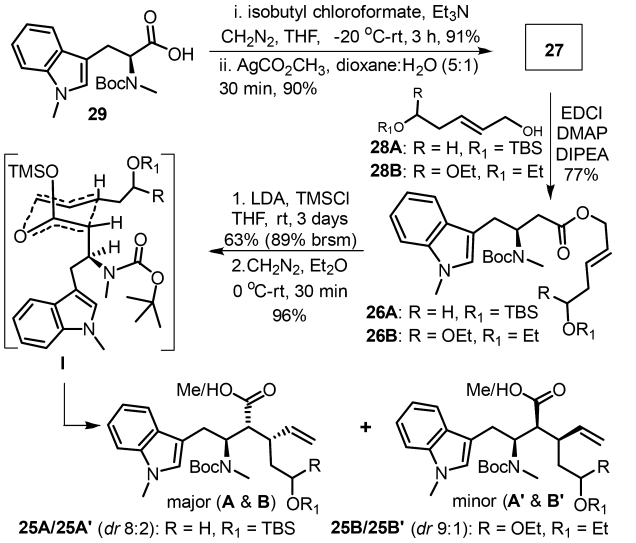


Figure 2. Proposed retrosynthetic route for **21** and **22**.

pentacyclic advanced intermediate **23** (introducing exomethylene followed by a methyl group for **21** and the addition of methyllithium for **22**). An efficient synthetic route to access pentacyclic core **23** would provide not only **21**/**22** but also a way to obtain some other pentacyclic indole alkaloids, as shown in Figure 1. We envisioned the synthesis of **23** from **24** with minimal functional group transformations. Yoneda first reported a tetracyclic core similar to **24**, but it was devoid of the entire functional crew.[19] Then, it was significantly improved including accessing in gram scale and was also employed in accomplishing the elegant total syntheses of diverse monomeric as well as dimeric indole alkaloids by continuous efforts from Cook's group.[20] Also, some seminal and notable works on this tetracyclic core were reported by Magnus,[21] Balley,[22] and others.[23] Recently, biology-oriented synthesis of similar tetracyclic scaffolds led to the discovery of a new class of Mycobacterium protein tyrosine phosphate (MptpB) inhibitors.[24] In our approach, the C and D ring system of the tetracyclic core in **24** was devised from **25** by using Pictet−Spengler cyclization. The challenging/critical stereochemistry in compound **25** was envisioned from allylic ester **26** by using Ireland−Claisen rearrangement. In turn, **26** could be derived from the coupling reaction between acid **27** and allylic alcohol having aldehyde equivalent i.e., **28**, shown in Figure 2.

The synthesis of **24** was begun with known acid **29**,[25] prepared in two steps from the commercially available L-tryptophan. One-carbon homologation of the acid **29** to **27** was achieved in two steps (Scheme 1). First, treating **29** with Et_3N, isobutyl

Scheme 1. Synthesis of Ireland−Claisen Rearrangement Products 25

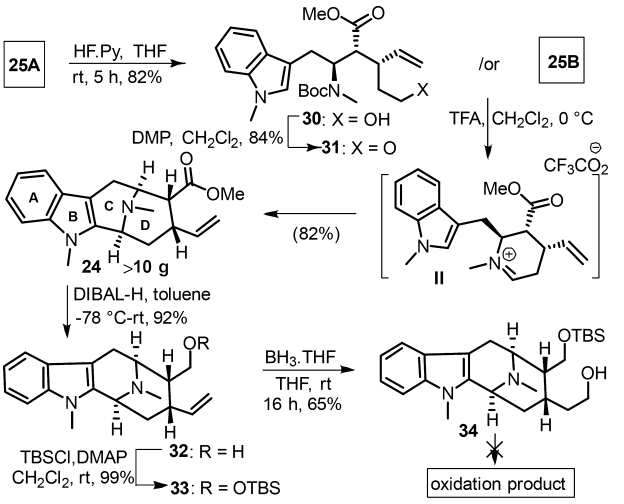


chloroformate and subsequent addition of diazomethane provided the diazoketone intermediate. Subsequently, it was treated with a catalytic amount of silver acetate to furnish the homologated acid **27** in 81% yield. Next, the coupling of **27** with allylic alcohol fragment **28A**/**28B**[26] using EDCI afforded the requisite allylic ester **26A**/**26B** in 77−78% yields, setting the stage for crucial Ireland−Claisen rearrangement (ICR). Keeping in mind that the stereochemical outcome of ICR would rely upon on efficient control of the ketene acetal geometry, the allylic ester **26A** was treated with LDA and TMSCl to provide the (*E*)-trimethylsilyl ketene acetal.[27] Then, stirring the reaction mixture at rt for 3 days furnished an inseparable mixture of acids with excellent diastereoselectivity (*dr* 8:2, based on the ^{1}H NMR) that was treated with an excess of diazomethane to result in separable esters **25A** and **25A′** (63% combined yield, 89% based on recovery of **26A**). Similarly, **26B** under ICR reaction condition provided an inseparable mixture of acids with improved diastereoselectivity (*dr* 9:1), which upon reacting with diazomethane afforded separable **25B** and **25B′** in a similar yield. Complete stereochemistry of major compounds **25A** and **25B** was established only after achieving **24** (Scheme 2). Here, we proposed that the facile selectivity and minimization of steric factors in chairlike transition state **I** (Scheme 1) account for the formation of major diastereomer **25A** and **25B** in the Ireland−Claisen rearrangement.[28]

Toward the synthesis of **24**, the *O*-silyl group of **25A** was deprotected using HF·pyridine to generate the primary hydroxyl group **30** in 82% yield, which was oxidized to the corresponding aldehyde **31** in 84% yield by using Dess−Martin periodinane (Scheme 2). As per our plan, in one pot, **25B** (the equivalent of **31**) is expected to undergo a series of transformations, Boc and acetal groups deprotection, followed by iminium ion formation and Pictet−Spengler reaction. In this direction, upon treatment

DOI: 10.1021/acs.orglett.8b01921
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of 34 and Attempts To Oxidize the Hydroxyl Group

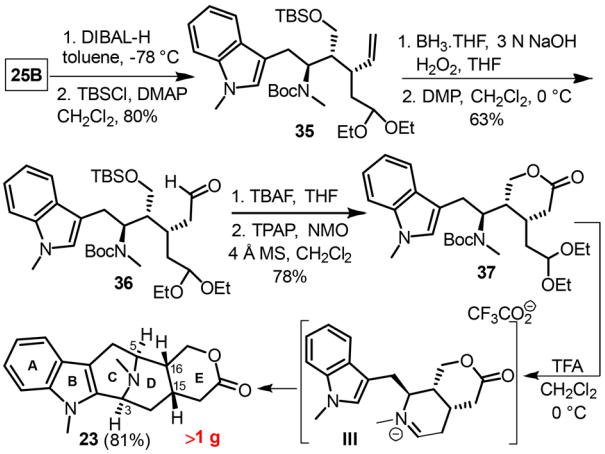


of **25B**/**31** with TFA, as anticipated, directly provided the desired tetracyclic core **24** in 82% yield with complete diastereoselectivity in favor of the desired isomer (Scheme 2). The structure and relative stereochemistry of **24** was unequivocally established by using incisive NMR studies such as 2D-NOESY and *J*-coupling analysis, (Supporting Information, SI). We proposed the plausible reaction mechanism for **24**, as shown in Scheme 2, where **25B** on exposure to TFA would provide **31**, and subsequent Boc group deprotection would result in the formation of incipient six-membered cyclic iminium ion **II**, which would undergo Pictet–Spengler cyclization[29] to give tetracyclic **24**.

Having enough quantity of **24** (achieved up to 10 g) in our hand, we turned our attention toward functionalization of the terminal olefin. In this direction, first, the ester **24** was reduced with DIBAL-H to furnish primary alcohol **32**, which was protected as TBS ether to provide *O*-silyl protected alkene **33** in 91% yield (2 steps). Hydroboration was then carried out on alkene **33** using BH_3·THF followed by oxidation (H_2O_2 and NaOH) to deliver the primary alcohol **34** in 65% yield. Unfortunately, the alcohol **34** was found to be inert to the oxidations; numerous attempts to oxidize either to an aldehyde or carboxylic acid were unsuccessful. Mostly, we recovered the starting material and found decomposition in some cases. Standard oxidation reactions proved unrewarding.[30] At this point, we decided to oxidize the olefin in **33** to the corresponding aldehyde by ozonolysis. Again, the reaction of alkene **33** with ozone either in CH_2Cl_2 or MeOH was unsuccessful. Further oxidation attempts on alkene **33** with OsO_4 also ended up dihydroxylation only on the indole ring (not shown). The highly electron-rich nature of indole ring could be the leading cause of decomposition on ozonolysis and OsO_4-catalyzed dihydroxylation.

With this unexpected roadblock toward the synthesis of advanced intermediate, we surmised prefunctionalization of olefin before the Pictet–Spengler cyclization. If successful, this would simplify the process further in achieving the pentacyclic core **23**. Research in this direction, first, ester **25B** was subjected to DIBAL-H reduction to yield primary hydroxyl group that was protected as TBS ether to provide **35** in 80% yield (two steps). Then, a two-step reaction sequence (hydroboration/3 N NaOH, H_2O_2, followed by Dess–Martin periodinane oxidation) was carried out to deliver aldehyde **36** in a yield of 63%. Subsequent silyl ether deprotection using TBAF followed by oxidation of resulted hemiacetal with TPAP furnished the six-membered lactone **37** in 78% yield (2 steps). Next, the compelling Pictet–Spengler reaction was carried out in the presence of TFA in CH_2Cl_2. To our delight, the pentacyclic core **23** was obtained in 81% yield and exclusively one isomer likely via the transition state **III**, as shown in Scheme 3. The structure and relative

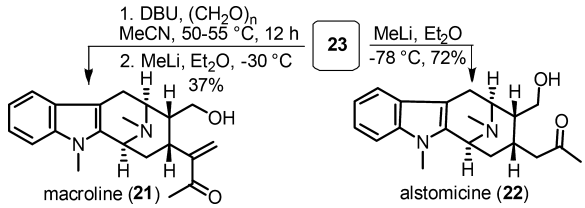
Scheme 3. Synthesis of Pentacyclic Core 23



stereochemistry of **23** were unequivocally assigned by using 1D and 2D NMR analysis (SI). This core **23** possesses the same stereoconfiguration at C(3), C(5), C(15), and C(16) as those in the macroline class, which represents the majority of the isolated indole alkaloids. An intermediate similar to **23** was reported from entirely different routes; , moreover, accessing indole alkaloids from these approaches requires additional protection/deprotection and functional group manipulations.[31]

Having achieved advanced core structure **23** in gram scale in a very efficient manner, we have proceeded to complete the total synthesis of **21** and **22**, summarized in Scheme 4. First, macroline

Scheme 4. Total Synthesis of Macroline (21) and Alstomicine (22)



(**21**) in 37% yield was achieved in a two-step sequence: introducing exomethylene followed by the addition of methyllithium.[32] Finally, the much desired first total synthesis of alstomicine (**22**) was accomplished in 72% yield on treating pentacyclic core **23** with methyllithium.[32b] The spectral data of synthesized **21** and **22** well matched with data reported in the literature (SI). The specific rotation of macroline (**21**) $[\alpha]_D^{28}$ = +17.7 (*c* 0.09, EtOH) resembled one reported in the literature,[20j] $[\alpha]_D^{28}$ = +18.9 (*c* 0.1, EtOH), but alstomicine (**22**) ($[\alpha]_D^{25}$ = −15.0 (*c* 0.14, $CHCl_3$)) differed to a great extent with the reported value ($[\alpha]_D$ = +74 (*c* 0.14, $CHCl_3$)).[7f]

In conclusion, we have developed a practical synthetic route to the advanced pentacyclic core and employed it in the total

DOI: 10.1021/acs.orglett.8b01921
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synthesis of alstomicine and macroline. The success of this approach relied on the effective control of the anticipated diastereoselectivity at two crucial transformations: Ireland−Claisen rearrangement and Pictet−Spengler cyclization. During the latter reaction step, four transformations in one pot (one-pot multireaction processes) has highly simplified the process for macroline indole alkaloids with up to five annulated rings and up to four stereocenters. All stereoconfigurations present in the target molecules were obtained from the readily available starting material L-tryptophan (by taking advantage of the existing single chiral center), which is distinct from the previous approaches where more expensive D-tryptophan is used. The synthesis of further monomeric and more potent dimeric indole alkaloids by using this strategy is in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01921.

Supplementary schemes, tables, experimental procedures, 2D NMR, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Science & Engineering Research Board (SERB), India for National Post-Doctoral Fellowship (to M.C.) and CSIR/UGC-India for Senior Research fellowships (to V.D.K., S.K.M., and S.S.R.B.). Thanks are also due to the Indo-French Centre for Promotion of Advanced Research (IFCPAR, No. 5305-1) and CSIR (12th FYP-ORIGIN (CSC-0108)) for financial support and Dr. B. Jagadeesh, Head, Analytical for 2D NMR support. Manuscript number: IICT/Pubs./2018/186.

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DOI: 10.1021/acs.orglett.8b01921
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