ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2024, **11**, 4869

Total synthesis of (–)-deglycocadambine†

Fang-Xin Wang, *[a] Ying-Tao Chen,‡[a] Hui Liu,‡[a] Heng-Shan Wang, [a] Hong Liang, [a] Zhen-Feng Chen [a] and Yonggui Robin Chi *[b,c]

Received 20th June 2024,
Accepted 9th July 2024

DOI: 10.1039/d4qo01122h

rsc.li/frontiers-organic

The first total synthesis of the monoterpene indole alkaloid (–)-deglycocadambine is achieved in 12 steps with (+)-genipin as the chiral starting material. The reported synthetic approach is characterized by an orchestrated cascade annulation between tryptamine and the highly functionalized dialdehyde precursor, rapidly introducing the unique 6/5/6/7/6-fused pentacyclic skeleton and the ketone functional group at C19 in a convergent manner. The successful implementation of transannular oxidative cyclization at C3 for bridged oxazolidine formation in the late-stage synthetic campaign ensured the final total synthesis of this molecule.

Introduction

(–)-Deglycocadambine (Fig. 1) is a member of the monoterpene indole alkaloids, a large family of metabolites that have attracted much attention from both synthetic and pharmaceutical chemists due to their high structural diversity and significant biological activities.[1] First isolated from the twigs and leaves of *Emmenopterys henryi* by Song and Zhao in 2013,[2] (–)-deglycocadambine has a characteristic 6/5/6/5/6/6 hexacyclic ring system, with its 6/5/6/7 tetracyclic nucleus containing a unique hydropyrido[1,2-*a*]azepine subunit, which can also be found in (–)-rubenine, (–)-kopsiyunnanine K, (–)-voacacines A and B and other cadambine-type alkaloids, as shown in Fig. 1.[3] Although preliminary studies revealed no promising activity, scarcity in nature precludes its systematic biological evaluation.[2] To the best of our knowledge, no synthetic route has been reported thus far for this molecule. Of note, in 1991, Brown *et al.* reported an elegant biologically inspired synthesis of (–)-cadambine from (–)-secologanin,[4,5] wherein a well-designed chemo- and regioselective reaction between tryptamine and a highly functionalized epoxide was conducted to efficiently introduce the seven-membered azepine ring of (–)-cadambine. Theoretically, hydrolysis of (–)-cadambine should give the desired aglycone (–)-deglycocadambine. Accordingly, the exploration of a general synthetic route for the total synthesis of (–)-deglycocadambine is required to pursue the novel molecular architecture and investigate the potential molecular functionality. Based on a rationally designed two-fold annulation sequence for the rapid installation of the 6/5/6/7/6-fused pentacyclic core, we report our synthetic efforts toward (–)-deglycocadambine.

Retrosynthetically, as shown in Scheme 1, (–)-deglycocadambine could be properly obtained from the pentacyclic precursor **A** by the formation of the bridged oxazolidine ring *via* the orchestrated transannular oxidative cyclization.[6] The stereospecific hydroxyl group at C19 of **A** could theoretically be

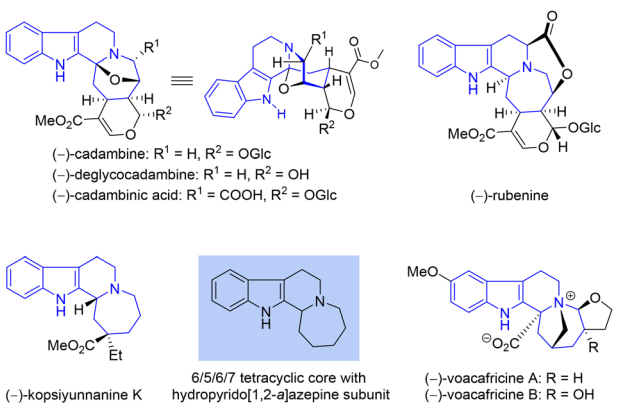
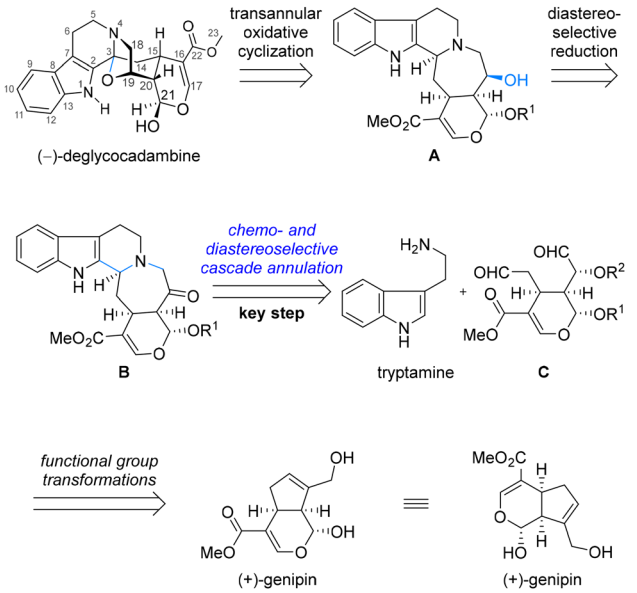


Fig. 1 Representative indole alkaloids with hydropyrido[1,2-*a*]azepine subunits embedded in the 6/5/6/7-fused tetracyclic core.

[a]*State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources/Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources (Ministry of Education of China), Collaborative Innovation Center for Guangxi Ethnic Medicine, School of Chemistry and Pharmaceutical Sciences, Guangxi Normal University, Guilin 541004, China.*
E-mail: wangfx@mailbox.gxnu.edu.cn
[b]*School of Chemistry, Chemical Engineering, and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg*
[c]*National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China*

†Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra, IR, and HRMS data. CCDC 2358655. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4qo01122h

‡These authors contributed equally to this work.

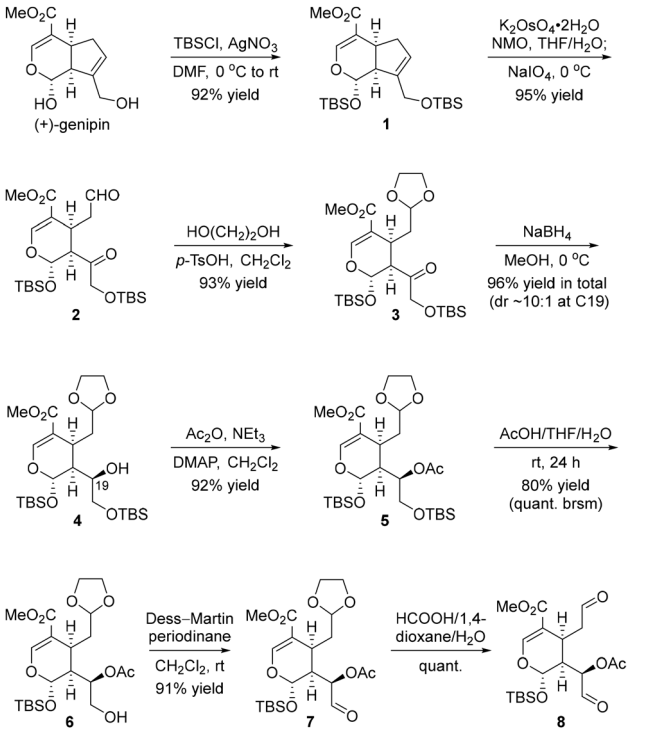


Scheme 1 Retrosynthetic analysis of (−)-deglycocadambine.

introduced *via* the diastereoselective reduction of the corresponding ketone in synthon **B**. The critical hydropyrido[1,2-*a*]azepine subunit embedded in **B** could be tentatively assembled by a rationally designed twofold annulation reaction between tryptamine and the highly functionalized dialdehyde **C**,[7] the latter of which could be formally derived from the commercially available (+)-genipin by means of continuous functional group transformations.

Results and discussion

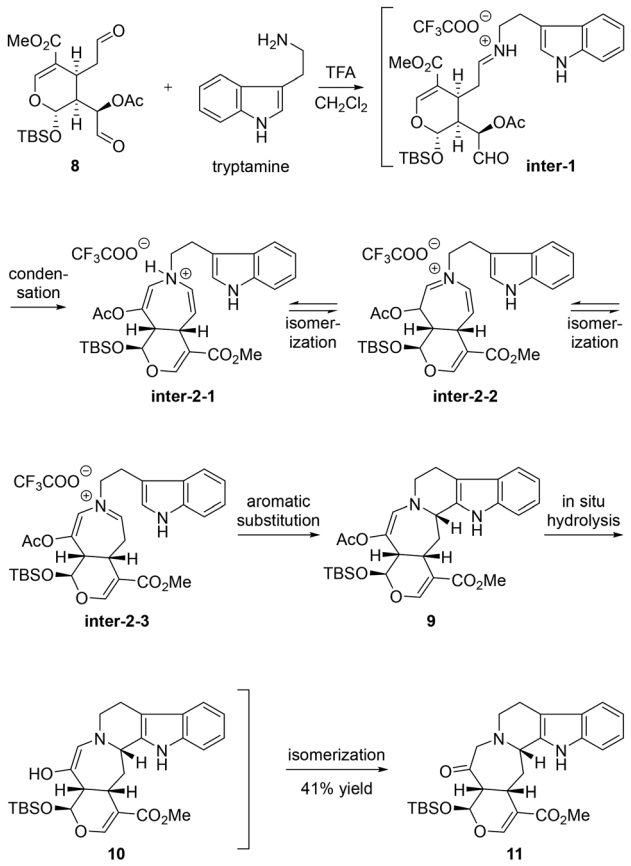
Initially, to access fragment **8** (Scheme 2), we selected commercially available iridoid (+)-genipin[8] (~$5 per g) from the chiral pool to start our synthetic campaign. Protection of both hydroxyl groups as TBS ethers was conducted in the presence of TBSCl and $AgNO_3$, giving **1** in 92% yield. The following chemoselective dihydroxylation/oxidative cleavage cascade reaction of the isolated alkene in the five-membered ring was performed, affording compound **2** in 95% yield, with the left-hand alkene embedded in the conjugated system remaining intact. After the two-step operation involving the chemoselective protection of the aldehyde in **2** as the acetal and the diastereoselective reduction of the ketone in **3**, alcohol **4** was produced as the major epimer (dr ~ 10 : 1) in an overall yield of 81%. Notably, for the reductive transformation from **3** to **4**, the observed stereochemistry at C19 could be explained by the Felkin–Anh model,[9] wherein the *Si* face attack was preferred. With **4** in hand, esterification of the secondary alcohol in the presence of Ac_2O gave, after chemoselective deprotection of the right-hand TBS ether, the primary alcohol **6**. Finally, oxidation of the hydroxyl group in **6** using Dess–Martin periodinane followed by chemoselective hydrolysis of the ethylene glycol acetal in **7** delivered the dialdehyde **8** without incident.



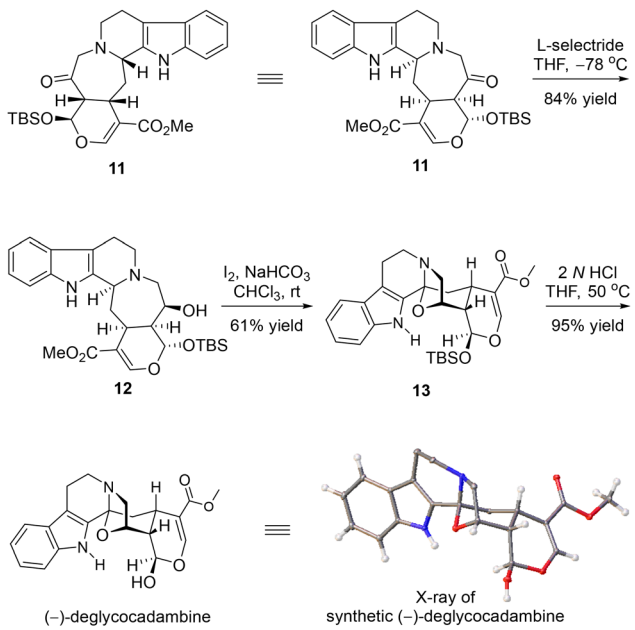
Scheme 2 Synthesis of dialdehyde **8**.

For the key cascade annulation of dialdehyde **8** and tryptamine, the pentacyclic ketone **11** was obtained as the sole identified product in 41% yield when the reaction mixture was exposed to TFA in CH_2Cl_2.[10,11] In this process, as shown in Scheme 3, it was postulated that tryptamine firstly condensed chemoselectively with the sterically more accessible aldehyde **8** to form **inter-1**, followed by the second condensation, delivering **inter-2-1**. **Inter-2-1** might isomerize to **inter-2-2** and further to **inter-2-3**. Among these isomers existing in dynamic equilibration, **inter-2-3** might be the most structurally favored for further aromatic substitution. The resulting pentacyclic compound **9** was further *in situ* hydrolyzed to give enol **10**, which was spontaneously isomerized to the more stable ketone **11**. The stereochemical outcome at C3 in **11** might be attributed to the much easier accessibility of the *Re* face of the iminium ion in **inter-2-3** as molecular modelling of **inter-2-3** revealed that the *Si* face attack presumably led to severe steric repulsion between the indole ring and H-15. Strategically, by using this elaborated twofold annulation protocol, we not only incorporated the synthetically challenging hydropyrido[1,2-*a*]azepine substructure but also finished the installation of ketone at C19 for further selective transformation at the same time. It should be noted that this is the first example for this cascade annulation wherein a complex and asymmetric dialdehyde was used to react with tryptamine.[7,12]

With **11** in hand, as shown in Scheme 4, a chemo- and diastereoselective reduction of a ketone using L-selectride as the reducing reagent gave alcohol **12** in 84% yield. The I_2-mediated transannular oxidative cyclization of the tertiary



Scheme 3 Synthesis of pentacyclic ketone **11**.



Scheme 4 Late-stage synthesis of (−)-deglycocadambine.

benzylic amine occurred smoothly to furnish compound **13**, with the last bridged oxazolidine ring characterized by the *N*,*O*-substituted quaternary stereocenter at C3 assembled efficiently.[6] When subjected to HCl in THF at elevated temperature, the TBS ether of **13** was directly deprotected to provide (−)-deglycocadambine, the absolute stereochemistry of which was unambiguously confirmed by X-ray crystallographic analysis.[13] The ^{1}H and ^{13}C NMR spectroscopic data of the synthetic sample are in accordance with the reported ones.[2,11]

Conclusions

In conclusion, a convergent synthetic strategy has been developed based on the ingenious use of a twofold annulation reaction between the dialdehyde and tryptamine to rapidly install the highly functionalized 6/5/6/7/6-fused pentacyclic ring system and a late-stage transannular oxidative cyclization to directly incorporate the bridged oxazolidine ring for the total synthesis of (−)-deglycocadambine, which was obtained in an overall yield of 9.5% over a longest linear sequence of 12 steps from (+)-genipin. Strategically, the bond-forming logic demonstrated in our protocol for installing the multicyclic ring system characterized by a unique hydropyrido[1,2-*a*]azepine subunit of (−)-deglycocadambine should enlighten the upcoming efforts towards chemical synthesis of other structurally related monoterpene indole alkaloids in our laboratory.

Author contributions

F.-X. W. and Y. R. C. directed the project. F.-X. W. and Y. R. C. conceived the synthetic route. F.-X. W., Y.-T. C. and H. L. conducted the synthetic work. F.-X. W., Y. R. C., Y.-T. C and H. L. analyzed the results. F.-X. W. and Y. R. C. wrote the manuscript. All authors commented on this manuscript and gave approval to the final version of this manuscript.

Data availability

Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra, IR, and HRMS data. CCDC 2358655. For ESI and crystallographic data in CIF or other electronic format see **https://doi.org/10.1039/D4QO01122H**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (22201050, 21772029, 21801051, 21807091, 21961006, 22071036, and 22061007); the Natural Science Foundation of Guangxi Zhuang Autonomous Region (2024GXNSFAA010091 and 2023GXNSFBA026329); the

Singapore National Research Foundation under its Competitive Research Program (NRF-CRP22-2019-0002); the Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG7/20 and RG5/19), MOE AcRF Tier 2 (MOE2019-T2-2-117), Nanyang Technological University; the Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004]; the 10 Talent Plan (Shicengci) of Guizhou Province ([2016]5649); the Science and Technology Department of Guizhou Province ([2018]2802 and [2019]1020); the State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources (CMEMR2022-A01); Guangxi Normal University; the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University; and Guizhou University.

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13 CCDC 2358655† for (–)-deglycocadambine contains the supplementary crystallographic data for this paper.