Short Communication

Natural Product Communications
Volume 15(11): 1–4

DOI: 10.1177/1934578X20967871
journals.sagepub.com/home/npx

SAGE

A Unified Total Synthesis of Isocyclocapitelline and Cyclocapitelline

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Abstract

A facile and concise synthesis of β-carboline alkaloids, such as (–)-isocyclocapitelline and (+)-cyclocapitelline, has been achieved from commercially available geraniol through a unified strategy. The key steps involved in this synthesis are Sharpless epoxidation, intramolecular ring opening of epoxide, Pictet-Spengler reaction, and dehydrogenative aromatization using 10% palladium/carbon in xylene under neutral conditions.

Keywords

β-carboline alkaloids, sharpless epoxidation, intramolecular epoxide opening, pictet-spengler reaction

Received: February 21st, 2020; Accepted: September 28th, 2020.

Substituted tetrahydrofuran (THF) ring containing natural products possess a highly complex structure with a diverse range of biological properties.[1,2] The tetrahydrofuran ring is frequently found in natural products, as well as in many biologically and pharmaceutically active compounds.[3-9] In particular, 2,5-disubstituted THFs is a key structure for a variety of biologically active natural products.[10,11] On the other hand, THFs are the synthons for the synthesis of complex natural products such as pheromones, pharmaceutical agents, polyether antibiotics, and marine toxins.[12-14] These fascinating structural features and intrinsic biological activities attracted many scientists toward the total synthesis of these natural products.[15-25]

β-Carboline alkaloids (Figure 1), such as (–)-isocyclocapitelline (**8a**) and (+)-cyclocapitelline (**8b**), were first isolated from the Rubiaceae family plant *Hedyotis capitella* (used as a folk medicine in China and Vietnam) by Gunter Adam et al in 1999.[26] Voltz et al reported the first total synthesis of these alkaloids (**8a**) and (**8b**) from α-hydroxyallenes through a gold-catalyzed cycloisomerization.[26,27] Subsequently, a modular approach has been reported for the synthesis of (–)-isocyclocapitelline (**8a**) and (+)-cyclocapitelline (**8b**) from *cis*-arbusculone and *trans*-arbusculone, respectively.[28] Herein, we have established a synthetic route which permits access to the synthesis of (–)-isocyclocapitelline (**8a**) and (+)-cyclocapitelline (**8b**) in a unified fashion, from commercially available terpene, geraniol, as a key precursor. The present synthesis is a highly concise and protection group free process to construct the β-carboline skeleton under mild conditions.

Results and Discussion

Our synthesis commenced with a familiar transformation in organic synthesis, which is Sharpless asymmetric epoxidation of the readily available monoterpene geraniol (**1**). The vital strategy in our synthesis is the preparation of chiral 2-((2*R*,5*S*)-5-(2-hydroxypropan-2-yl)-2-methyltetra-hydrofuran-2-yl)acetaldehyde (**5a**), a key intermediate in our synthesis, which was prepared by a sequence of transformations. Geraniol (**1**) was subjected to Sharpless epoxidation[29–31] using D-(–)-diisopropyl tartrate, $Ti(O^iPr)_4$, and tert-butyl hydroperoxide in dichloromethane (CH_2Cl_2) to afford the epoxy alcohol **2** in 95% yield. The reductive opening of epoxide **2** was accomplished by using sodium bis(2-methoxyethoxy)aluminum hydride (3.5 M in toluene, 1.1 equiv.), to give the diol **3**, with 90% yield. The diol **3** was further treated with *meta*-chloroperoxybenzoic acid in CH_2Cl_2, to afford the functionalized THF core as a mixture of diastereomers **4a** and **4b** in a 1:1 ratio, which was separated by column chromatography and obtained as pure compounds. Treatment of diol **3** with a chiral Shi[32] ketone A (derived from fructose) in the presence of oxone, potassium carbonate in acetonitrile and water over 8 hours gave the chiral THF core **4a**

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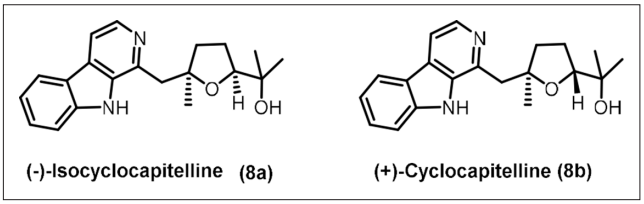
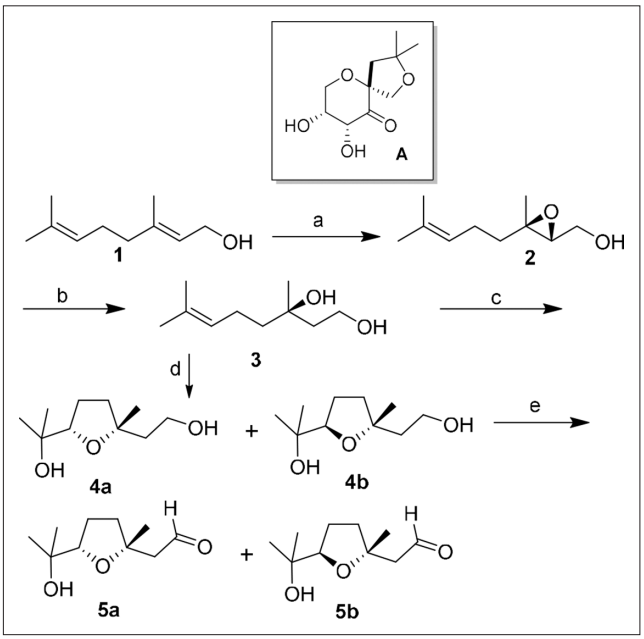


Figure 1. Representative examples of β-carboline alkaloids.

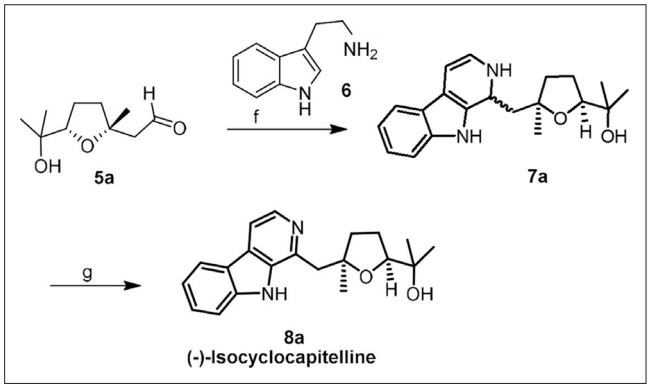
as a single isomer.[22,26] Disappearance of the signal (dd) at δ 5.11 ppm and the presence of signals at δ 131.5, 121.4 ppm in the ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra confirmed the formation of **4a** and **4b** from **3**. The spectroscopic data of **4a** are in agreement with that of the product formed with Shi ketone, which was further confirmed by its stereochemistry. Compound **4a** was further oxidized to aldehyde **5** under a nitrogen atmosphere, using pyridinium chlorochromate (PCC) as an oxidant in CH_2Cl_2 (60% yield) (Scheme 1). The characteristic triplet ^{1}H signal at δ 9.85 ppm and ^{13}C signal at δ 202.2 ppm confirmed the formation of aldehyde **5**.

Coupling of Aldehyde ***5a*** *and* ***5b*** *With Tryptamine (****6****)*

Aldehyde **5a** was treated with tryptamine (**6**) in the presence of TFA in CH_2Cl_2 under Pictet-Spengler[33] conditions to give



Scheme 1. Reagents and conditions: (a) (–)-diethyltryptamine, $Ti(O^{i}Pr)_4$, *tert*-butyl hydroperoxide, 4 Å MS, CH_2Cl_2, –30 °C, 95%; (b) dry tetrahydrofuran, sodium bis(2-methoxyethoxy) aluminum hydride (3.5 M in toluene, 1.1 equiv.), 90%; (c) *meta*-chloroperoxybenzoic acid, dichloromethane (CH_2Cl_2), 0 to room temperature, 4 hours, 80% (**4a** and **4b** in 1:1 ratio); (d) fructose-derived catalyst **A** (0.15 equiv.), oxone (1.8 equiv.), dimethyl ether, potassium carbonate (2 equiv.), acetonitrile:water (1:1), pH = 10.5, 8 hours, 81%; (e) pyridinium chlorochromate (PCC), CH_2Cl_2, reflux, 12 hours, 60%.



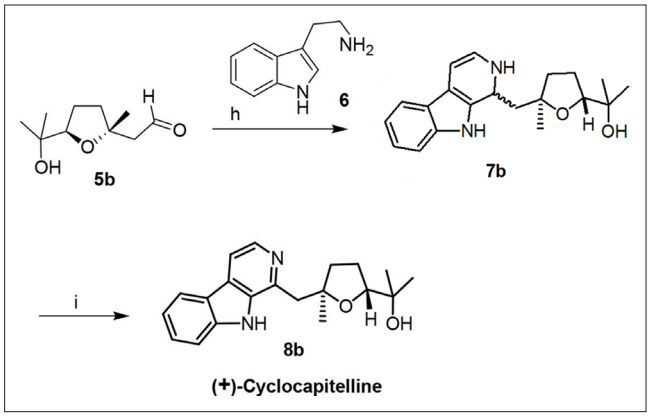
Scheme 2. Reagents and conditions: (f) tryptamine (**6**), trifluoroacetic acid, dichloromethane, 78 °C, 3 hours; (g) palladium/carbon, xylene, reflux, 8 hours, 75%.

tetrahydrocarboline **7**, which was further subjected to dehydrogenation with palladium (Pd)/carbon (C) in xylene under reflux conditions to furnish (−)-isocyclocapitelline (**7a**) in 75% yield over 2 steps, as shown in Scheme 2. The ^{1}H and ^{13}C NMR spectra of the synthesized product **8a** were in full agreement with those of the reported natural product.[34] The specific rotation of our synthesized compound was $[\alpha]_D^{25}$ = −72 (*c* 0.5, $CHCl_3$), which correlated with the natural product[34] $[\alpha]_D^{25}$ = −72 (*c* 0.5, $CHCl_3$).

Similarly, synthesis of (+)-cyclocapitelline (**8b**) was achieved from the aldehyde **5b** by adopting the above reaction conditions, as shown in Scheme 3.

The ^{1}H and ^{13}C NMR spectra of the synthesized product **8b** correlated with those of the reported natural product.[34] The specific rotation of our synthesized compound was $[\alpha]_D^{25}$ = +42.8 (*c* 0.5, $CHCl_3$), which was in agreement with the natural product[34] $[\alpha]_{D25}$ = +43 (*c* 0.5, $CHCl_3$).

General experimental details and spectroscopic data have been included in Supplementary Material 1.



Scheme 3. Reagents and conditions: (h) tryptamine (**6**), trifluoroacetic acid, dichloromethane, 78 °C, 3 hours; (i) palladium/carbon, xylene, reflux, 8 hours, 70% over 2 steps.

Conclusion

In summary, we have successfully established a unified strategy for the total synthesis of *Hedyotis* plant alkaloids (–)-isocyclocapitelline (**8a**) and (+)-cyclocapitelline (**8b**) from readily available geraniol (**1**). The vital reactions involved in this approach are the Sharpless asymmetric epoxidation, reductive cleavage of epoxide, intramolecular ring opening of epoxide, and Pictet-Spengler reaction. The overall strategy is a very facile, scalable, and protection group-free synthesis, which makes it a concise synthesis.

Acknowledgment

We thank the Vice-Chancellor of Osmania University for his support.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Kang EJ, Lee E. Total synthesis of oxacyclic macrodiolide natural products. *Chem Rev*. 2005;105(12):4348-4378. doi:10.1021/cr040629a
2. Lorente A, Merketegi JL, Albericio F, Alvarez M. A room temperature decarboxylation/C–H functionalization cascade by visible-light photoredox catalysis. *Chem Rev*. 2013;113(49):5672-5674.
3. Matsuura S, Shiratori O, Katagiri K. Antitumor activity of showdomycin. *J Antibiot*. 1964;17(6):234-237.
4. Nishimura H, Mayama M, Komatsu Y, et al. Showdomycin, a new antibiotic from a *Streptomyces* sp. *J Antibiot*. 1964;17:148-155.
5. Fang X-ping, Anderson JE, Chang C-jer, Fanwick PE, McLaughlin JL. Novel bioactive styryl-lactones: goniofufurone, goniopypyrone, and 8-acetylgoniotriol from *Goniothalamus giganteus*(annonaceae). X-Ray molecular structure of goniofufurone and of goniopypyrone. *J Chem Soc Perkin*. 1990;1(6):1655-1661.
6. Molinski TF, Dalisay DS, Lievens SL, Saludes JP. Drug development from marine natural products. *Nat Rev Drug Discov*. 2009;8(1):69-85. doi:10.1038/nrd2487
7. Hughes CC, Fenical W. Antibacterials from the sea. *Chem Eur J*. 2010;16(42):12512-12525. doi:10.1002/chem.201001279
8. Bhatnagar I, Kim SK. Marine antitumor drugs. *Mar Drugs*. 2010;8(10):2702-2720.
9. Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. Marine natural products. *Nat Prod Rep*. 2012;29(2):144-222. doi:10.1039/C2NP00090C
10. Wagner H, Harms K, Koert U, Meder S, Boheim G. Oligo-THF peptides: synthesis, membrane insertion, and studies of ion channel activity. *Angew Chem Int Ed Engl*. 1996;35(22):2643-2646. doi:10.1002/anie.199626431
11. Koert U, Al-Momani Lo'ay, Pfeifer JR. Synthetic ion channels. *Synthesis*. 2004;2004(08):1129-1146. doi:10.1055/s-2004-822385
12. Larrosa I, Romea P, Urpí F. Synthesis of six-membered oxygenated heterocycles through carbon–oxygen bond-forming reactions. *Tetrahedron*. 2008;64(12):2683-2723. doi:10.1016/j.tet.2007.11.092
13. Crane EA, Scheidt KA. Prins-type macrocyclizations as an efficient ring-closing strategy in natural product synthesis. *Angew Chem Int Ed Engl*. 2010;49(45):8316-8326. doi:10.1002/anie.201002809
14. Ohuchida S, Hamanaka N, Hayashi M. Synthesis of thromboxane A2 analogs-4: (±)-dithiathromboxane A2 sodium salt. *Tetrahedron*. 1983;39(24):4273-4280.
15. Srikrishna A, Sharma GVR. For the total syntheses of andirolactone, see: a radical cyclisation route to (±)-andirolactone, a spiro-γ-butyrolactone. *Tetrahedron Lett*. 1988;29(49):6487-6488.
16. Quayle P, Ward ELM, Taylor P. Transition metal promoted acetylene isomerisation reactions: application to the synthesis of (+/-)-andirolactone. *Tetrahedron Lett*. 1994;35(47):8883-8884. doi:10.1016/S0040-4039(00)78524-8
17. Rosa MO. New synthetic entries to (±)-andirolactone. *Synth Commun*. 1994;24(5):651-658.
18. Li Y, Zhang T, Li Y-L. First asymmetric synthesis of both enantiomers of andirolactone. *Tetrahedron Lett*. 2007;48(8):1503-1505. doi:10.1016/j.tetlet.2006.12.031
19. Dethe DH, Dherange BD, Boda R, Balu DD, Hg RB. $Hg(OAc)_2$ mediated highly regio- and/or diastereoselective allylic *tert*-acetylation of olefins. *Org Chem Front*. 2015;2:159-162. doi:10.1039/C4QO00310A
20. Arturo O, Zepeda GL, Tamariz J. Highly efficient synthesis of the natural spiro-terpenoid (±)-andirolactone. *Synthesis*. 1993;1993(4):375-377.
21. Tietze LF, Wolfram T, Holstein JJ, Dittrich B. First enantioselective total synthesis of (+)-(R)-pinnatolide using an asymmetric domino allylation reaction. *Org Lett*. 2012;14(16):4035-4037. doi:10.1021/ol301932d
22. Volz F, Wadman SH, Hoffmann-Röder A, Krause N. Gold catalysis in stereoselective natural product synthesis: (+)-linalool oxide, (−)-isocyclocapitelline, and (−)-isochrysotricine. *Tetrahedron*. 2009;65(9):1902-1910. doi:10.1016/j.tet.2008.11.104
23. Zhang J-X, Wang G-X, Xie P, Chen S-F, Liang X-T. The total synthesis of chrysotricine. *Tetrahedron Lett*. 2000;41(13):2211-2213. doi:10.1016/S0040-4039(00)00146-5

24. Peoffrey A, Cory P, Andrew CS, Mathew LP, Daryl SRD, Brian LP. Oxidative cyclization of tertiary pentenol derivatives forming 2,5,5-trisubstituted THF rings and the total synthesis of cyclocapitelline. *Tetrahedron Lett*. 2015;56(44):6052-6055.
25. Wang J, Pagenkopf BL. First total synthesis and structural reassignment of (-)-aplysiallene. *Org Lett*. 2007;9(18):3703-3706. doi: 10.1021/ol701797e
26. Volz F, Krause N. Golden opportunities in natural product synthesis: first total synthesis of (-)-isocyclocapitelline and (-)-isochrysotricine by gold-catalyzed allene cycloisomerization. *Org Biomol Chem*. 2007;5(10):1519-1521. doi:10.1039/B703995F
27. Hartung J, Drees S, Geiss B, Schmidt P, Vanadium SP. Vanadium(v)-catalyzed oxidation of (3 *R*)-linalool-the selective formation of furanoid linalool oxides and theiR Conversion into isocyclocapitelline derivatives. *Synlett*. 2003;2:0223-0226. doi:10.1055/s-2003-36793
28. Gajula S, Madhu M, Chintakrinda SK, Yadav JS, Mohapatra DK. A protecting-group-free synthesis of arbusculone, andirolactone, pinnatolide, ipomolactone, cyclocapitelline and isocyclocapitelline. *Tetrahedron Lett*. 2018;59(47):4172-4175. doi:10.1016/j.tetlet.2018.10.024
29. Gao Y, Klunder JM, Hanson RM, Masamune H, Ko SY, Sharpless KB. Catalytic asymmetric epoxidation and kinetic resolution: modified procedures including *in situ* derivatization. *J Am Chem Soc*. 1987;109(19):5765-5780. doi:10.1021/ja00253a032
30. Schomaker JM, Bhattacharjee S, Yan J, Borhan B. Diastereomerically and enantiomerically pure 2,3-disubstituted pyrrolidines from 2,3-aziridin-1-ols using a sulfoxonium ylide: a one-carbon homologative relaying expansion. *J Am Chem Soc*. 2007;129(7):1996-2003. doi:10.1021/ja065833p
31. Radhika L, Chandrasekhar S. Synthesis of the southern tripeptide (C_1 –N_{12}) Of sanglifehrins using asymmetric organocatalysis. *Synth Commun*. 2014;44(24):3602-3609. doi:10.1080/00397911.2014.947653
32. Doherty AM, Ley SV. Synthetic studies towards the acyltetronic acid iohophore M 139603. *Tetrahedron Lett*. 1986;27(1):105-108. doi:10.1016/S0040-4039(00)83953-2
33. Pictet A, Spengler T, Ber D. Pictet-Spengler condensation reactions catalyzed by a recyclable H-montmorillonite as a heterogeneous Brønsted acid. *Chem. Ges*. 1911;44(3):2030-2036.
34. Phuong NM, Van Sung T, Porzel A, Schmidt J, Merzweiler K, Adam G. β-Carboline alkaloids from *Hedyotis capitellata*. *Phytochemistry*. 1999;52(8):1725-1729. doi:10.1016/S0031-9422(99)00280-0