Organic LETTERS

Letter

pubs.acs.org/OrgLett

Asymmetric Total Synthesis of Novel Pentacyclic Indole Alkaloid, Kopsiyunnanine E, Isolated from *Kopsia arborea*

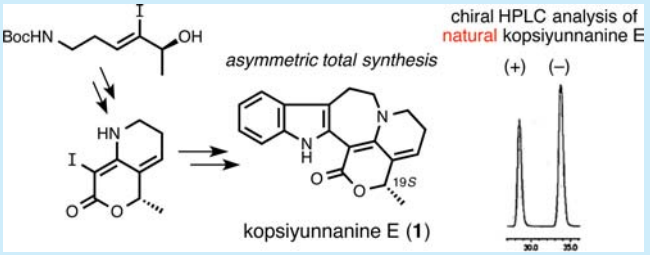
Mariko Kitajima,[†] Yosuke Murakami,[†] Nobuaki Takahashi,[†] Yuqiu Wu,[†] Noriyuki Kogure,[†] Rong-Ping Zhang,[‡] and Hiromitsu Takayama*[,†]

[†]Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan

[‡]Department of Pharmaceutical Sciences, Kunming Medicinal University, Kunming 650031, Yunnan Province, China

Supporting Information

ABSTRACT: A new pentacyclic indole alkaloid, kopsiyunnanine E, was isolated from Yunnan *Kopsia arborea*, and its structure, which was inferred from spectroscopic data, was established by a 16-step asymmetric total synthesis that proved that the natural alkaloid was not enantiomerically pure.



The genus *Kopsia*, belonging to the family Apocynaceae, is a rich source of monoterpenoid indole alkaloids that often possess unusual skeletons and significant bioactivities,[1] many of which are intriguing targets of total synthesis.[2] In our continuing studies of novel and biologically active alkaloids,[3] we have reported the structural elucidation of several unusual alkaloids, such as kopsiyunnanines A, B, and C1 (Figure 1), isolated from the aerial part of *Kopsia arborea*.[4] Further investigation of the crude base of this plant has led to the isolation of a new pentacyclic indole alkaloid, named kopsiyunnanine E (**1**), which has a unique 1,2,3,5-tetrahydro-7*H*-pyrano[4,3-*b*]pyridin-7-one moiety (Figure 2). Herein we report the structure elucidation based on spectroscopic analyses and the asymmetric total synthesis consisting of 16 steps, which proved that the natural alkaloid contained predominantly the (−)-enantiomer rather than the (+)-enantiomer.

The crude base obtained from the aerial part of *K. arborea* was purified by repeated chromatography to afford new alkaloid **1** (0.003% yield based on the crude base). Compound **1** [$[\alpha]^{25}_{D}$ −14.9 (*c* 0.06, $CHCl_3$)], named kopsiyunnanine E, was found to have the molecular formula $C_{19}H_{18}N_2O_2$ from HREI-MS [*m*/*z* 306.1370 $(M)^+$]. The UV spectrum showed unusual long-wavelength absorptions at 425.5, 411.5, 302.5, 268.5 (sh), 250.5, and 224.0 nm, suggesting the existence of a highly conjugated system. ^1H and ^{13}C NMR measurements revealed a non-substituted A ring of an indole system, a lactone function, two methylene groups bearing nitrogen, one tetrasubstituted olefin, one trisubstituted olefin, and one methyl group coupled with an oxymethine proton (Table 1). HMBC correlations indicated connections among C3, C5, and C21 through a nitrogen atom and among C15, C21, and the oxygenated −CH−CH_3 fragment through the C20 olefinic carbon. In addition, linkage of C19 of the −$CHCH_3$ fragment with carbonyl carbon C17 through an oxygen atom was observed, which formed the lactone function.

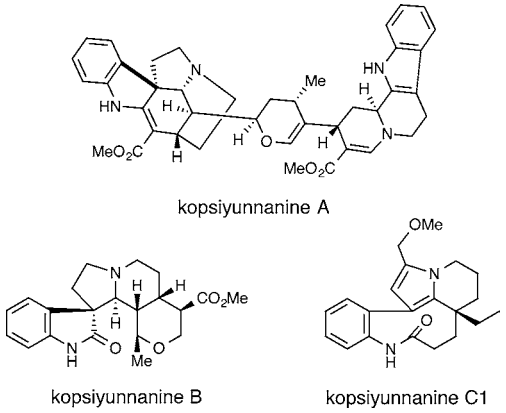


Figure 1. Structures of kopsiyunnanines A, B, and C1.

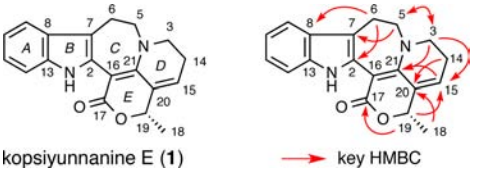


Figure 2. Structure and key HMBC correlations of kopsiyunnanine E (**1**).

From these data, compound **1** was proposed to be a pentacyclic indole alkaloid with a unique 1,2,3,5-tetrahydro-7*H*-pyrano[4,3-*b*]pyridin-7-one moiety. Among the more than 2000 known monoterpenoid indole alkaloids, arboflorine[5] is the only example with a similar carbon skeleton.

Received: July 31, 2014
Published: September 24, 2014

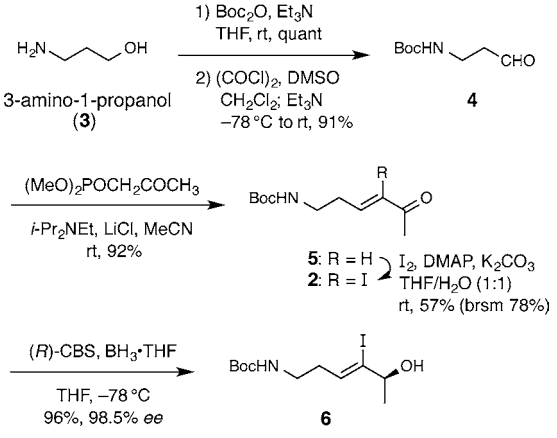
dx.doi.org/10.1021/ol502265q | *Org. Lett.* 2014, 16, 5000−5003

Table 1. ^{1}H and ^{13}C NMR Data for Natural Kopsiyunnanine E (1) (in $CDCl_3$)

position	kopsiyunnanine E (**1**) ^{1}H[a]	^{13}C[b]
2		131.2
3	3.57 (ddd, 12.3, 10.0, 5.1)	51.4
	3.43 (ddd, 12.3, 6.0, 6.0)	
5	3.67 (ddd, 13.0, 7.6, 2.3)	56.8
	3.73 (ddd, 13.0, 6.3, 2.4)	
6	3.25 (ddd, 15.9, 6.3, 2.3)	27.3
	3.14 (ddd, 15.9, 7.6, 2.4)	
7		111.0
8		128.0
9	7.48 (d, 7.2)	117.0
10	7.05 (dd, 7.2, 7.2)	118.8
11	7.11 (dd, 7.2, 7.2)	121.3
12	7.34 (d, 7.2)	110.7
13		134.3
14	2.57 (m)	24.5
	2.48 (m)	
15	6.26 (dd, 4.1, 3.4)	127.3
16		91.9
17		168.6
18	1.58 (3H, d, 6.9)	19.4
19	4.94 (m)	72.3
20		133.2
21		149.7
NH	10.8 (br s)	

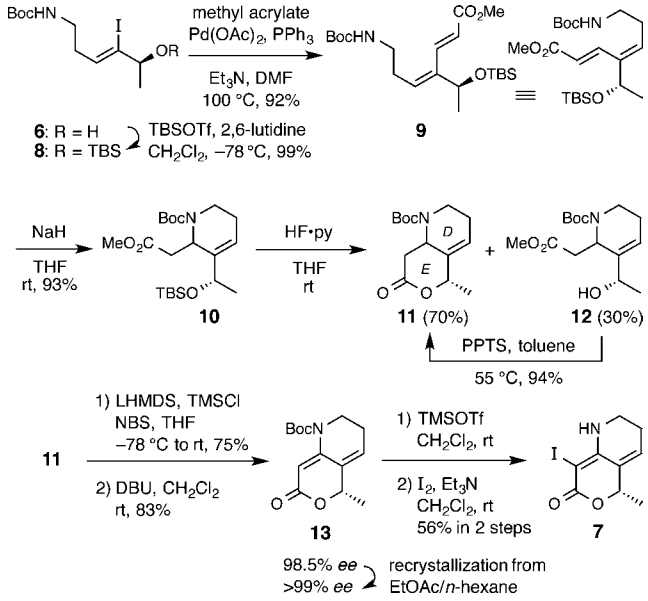
[a]600 MHz. [b]125 MHz.

Scheme 1. Synthesis of Chiral Allyl Alcohol 6

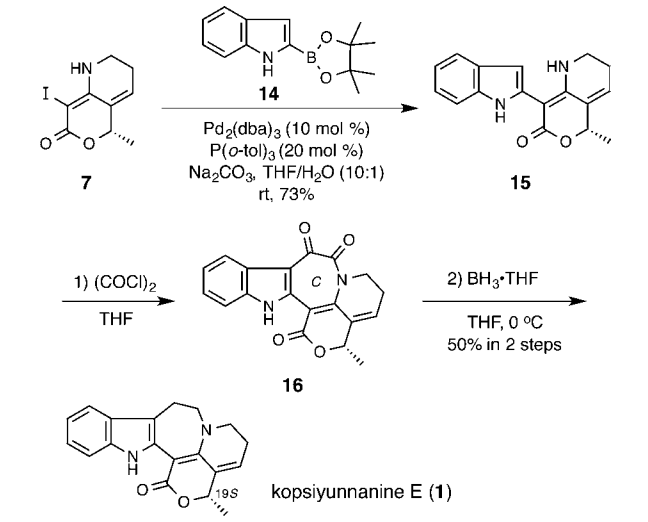


To clarify the novel structure as well as the absolute configuration at C19 of kopsiyunnanine E, an asymmetric total synthesis was performed. We initially prepared α-iodo-α,β-unsaturated ketone **2** from 3-amino-1-propanol (**3**) via a four-step operation that included the Horner–Wadsworth–Emmons reaction of known aldehyde **4**[6] with dimethyl 2-oxopropylphosphonate and the α-iodination of resultant α,β-unsaturated ketone **5** with I_2 in the presence of DMAP and K_2CO_3 in THF/H_2O[7] (Scheme 1). The asymmetric reduction of α-iodo-α,β-unsaturated ketone **2** with (*R*)-Corey–Bakshi–Shibata (CBS) reagent[8] afforded chiral allyl alcohol **6** in 96% yield with 98.5% ee. The absolute configuration of the newly generated chiral center was assigned as *S* by the modified Mosher method using (*S*)- and (*R*)-MTPA [α-methoxy-α-(trifluoromethyl)phenyl acetyl] esters of **6**.[9]

Scheme 2. Synthesis of Alkenyl Iodide 7



Scheme 3. Synthesis of Kopsiyunnanine E (1)



Chiral alcohol **6** thus obtained was converted into alkenyl iodide **7**, which was used for the cross-coupling reaction with an indole unit (Scheme 2). After TBS protection of the hydroxyl group in **6**, the Heck reaction of **8** with methyl acrylate yielded conjugated ester **9** in 92% yield. The intramolecular aza-Michael reaction proceeded by treating **9** with NaH in THF to give piperidine derivative **10** in 93% yield. Lactonization was occurred concomitantly with deprotection of the TBS group in **10** by HF·pyridine to afford *D*/*E* ring lactone **11** together with alcohol **12**, and **12** was converted into **11** by treatment with PPTS in toluene in good yield. Introduction of a double bond in **11** was accomplished via α-bromination followed by elimination to give $\alpha,\beta,\gamma,\delta$-unsaturated ester **13**. Enantiomeric excess of **13** was increased to >99% ee by recrystallization from EtOAc/*n*-hexane. Alkenyl iodide **7**, the substrate for the Suzuki–Miyaura cross coupling, was prepared via Boc deprotection and α-iodination[10] of **13**.

The cross coupling of alkenyl iodide **7** with indole-2-boronic acid pinacol ester (**14**) in the presence of $Pd_2(dba)_3$ (10 mol %), P(*o*-tol)$_3$ (20 mol %), and Na_2CO_3 in THF/H_2O[11] produced

dx.doi.org/10.1021/ol502265q | Org. Lett. 2014, 16, 5000–5003

indole−amine **15** in 73% yield (Scheme 3). Next, we attempted to construct a seven-membered C-ring.[3d] Side-chain extension at the indole β-position in **15** was achieved by treatment with $(COCl)_2$ in THF. This was accompanied by spontaneous cyclization to give unstable dicarbonyl compound **16**. Finally, the two carbonyl groups were reduced with BH_3·THF to afford kopsiyunnanine E (**1**) $[[\alpha]^{25}_D$ −70.0 (*c* 0.24, $CHCl_3$)] in 50% yield (two steps). Synthetic **1** was identified by comparing its chromatographic behavior and UV, ^{1}H NMR, ^{13}C NMR, and mass spectra with those of the natural compound. The observed optical rotation of the synthetic compound having 19*S* configuration showed levorotation, similar to the natural product; however, its specific rotation was very different from that of the natural product $[[\alpha]^{25}_D$ −14.9 (*c* 0.06, $CHCl_3$)]. Then, we synthesized racemic **1** starting from achiral allyl alcohol **6**, and analyzed the enantiomeric purity of both synthetic (±)-**1** and (*S*)-(−)-**1** (>99% ee) and the natural product using chiral column chromatography. We found that natural kopsiyunnanine E contained predominantly the (−)-enantiomer rather than the (+)-enantiomer in the ratio of 61.6:38.4 (Figure 3). To date, there are some reports on the alkaloids that exist as a scalemic mixture (nonracemic mixture of both enantiomers).[12]

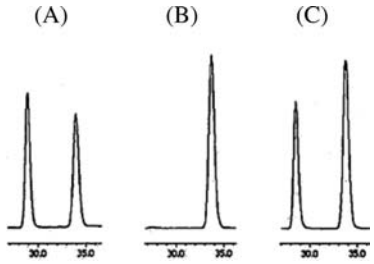
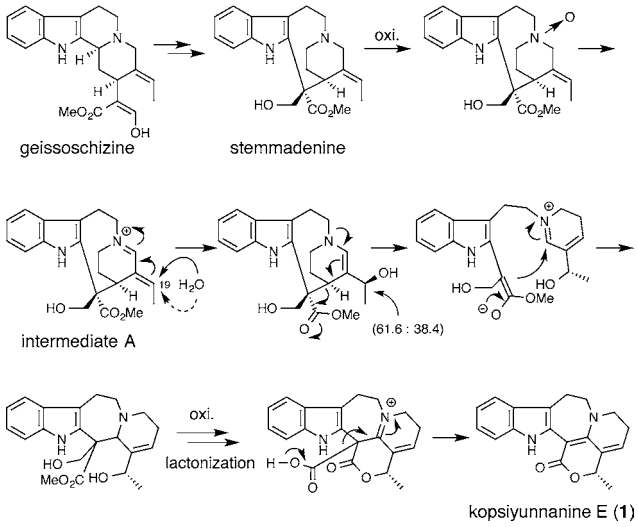


Figure 3. Chiral HPLC analysis of synthetic (±)-**1** (A), synthetic (*S*)-(−)-**1** (B), and natural (C) kopsiyunnanine E (conditions: CHIRALPAK AD-H; EtOH/*n*-hexane = 1:1; flow rate, 0.7 mL/min; column temperature, 40 °C).

Scheme 4. Possible Biogenetic Route of Kopsiyunnanine E (1)



Biosynthetically, kopsiyunnanine E (**1**) might be derived from geissoschizine via stemmadenine, which coexisted in this plant, as shown in Scheme 4. The reason why the natural **1** is not enantiomerically pure is probably due to the nondiastereoselective attack of the water molecule on C19 position in a plausible biogenetic intermediate A.

In conclusion, we have succeeded in the asymmetric total synthesis of a novel skeletal type of indole alkaloid, kopsiyunnanine E (**1**), which was newly isolated from *Kopsia arborea*, and proved that the natural alkaloid was not enantiomerically pure.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the isolation of kopsiyunnanine E (**1**) and the preparation of compounds **2**, **4**−**13**, **15**, **16**, synthetic **1**, racemic **6**, and **S1**−**S3**; chiral HPLC analysis of natural, synthetic (*S*)-(−)-, and racemic **1**; and copies of ^{1}H and ^{13}C NMR spectral data for compounds **2**, **4**−**13**, **15**, **16**, **S1**−**S3**, and synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: takayamah@faculty.chiba-u.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Nos. 25293023 and 26293023.

■ REFERENCES

(1) (a) Kam, T.; Lim, K. Alkaloids of *Kopsia*. In *The Alkaloids*, Cordell, G. A., Ed.; Academic Press: San Diego, 2008; Vol. *66*, pp 1−111. (b) Ahmad, K.; Hirasawa, Y.; Nugroho, A. E.; Hadi, A. H. A.; Morita, H. *Heterocycles* **2012**, *86*, 1611−1619. (c) Yang, Y.; Zuo, W.; Zhao, Y.; Dong, W.; Mei, W.; Dai, H. *Planta Med.* **2012**, *78*, 1881−1884. (d) Chen, J.; Li, X.; Li, N.; Lu, J.; Xu, X.; Duan, H.; Qin, L. *Chem. Nat. Compd.* **2012**, *48*, 834−835. (e) Tan, M.; Yin, C.; Tang, C.; Ke, C.; Lin, G.; Ye, Y. *Planta Med.* **2011**, *77*, 939−944. (f) Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334−5336. (g) Yap, W.; Gan, C.; Low, Y.; Choo, Y.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T. *J. Nat. Prod.* **2011**, *74*, 1309−1312.

(2) (a) Arai, S.; Nakajima, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5569−5572. (b) Hsu, S.; Cheng, H.; Huang, A.; Ho, T.; Hou, D. *Eur. J. Org. Chem.* **2014**, *15*, 3109−3115. (c) Hoshi, M.; Kaneko, O.; Nakajima, M.; Arai, S.; Nishida, A. *Org. Lett.* **2014**, *16*, 768−771. (d) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127−19130. (e) Leal, R. A.; Beaudry, D. R.; Alzghari, S. K.; Sarpong, R. *Org. Lett.* **2012**, *14*, 5350−5353. (f) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17−46. (g) Iwama, Y.; Okano, K.; Sugimoto, K.; Tokuyama, H. *Org. Lett.* **2012**, *14*, 2320−2322. (h) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183−188 and references cited therein.

(3) (a) Terada, Y.; Horie, S.; Takayama, H.; Uchida, K.; Tominaga, M.; Watanabe, T. *J. Nat. Prod.* **2014**, *77*, 285−297. (b) Kitajima, M.; Ohara, S.; Kogure, N.; Santiarworn, D.; Takayama, H. *Tetrahedron* **2013**, *69*, 9451−9456. (c) Kitajima, M.; Iwai, M.; Kogure, N.; Kikura-Hanajiri, R.; Goda, Y.; Takayama, H. *Tetrahedron* **2013**, *69*, 796−801. (d) Harada, M.; Asaba, K.; Iwai, M.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2012**, *14*, 5800−5803. (e) Kitajima, M.; Ohara, S.; Kogure, N.; Wu, Y.; Zhang, R.; Takayama, H. *Heterocycles* **2012**, *85*, 1949−1959. (f) Kitajima, M.; Iwai, M.; Kikura-Hanajiri, R.; Goda, Y.; Iida, M.; Yabushita, H.; Takayama, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1962−1964.

(4) (a) Kogure, N.; Suzuki, Y.; Wu, Y.; Kitajima, M.; Zhang, R.; Takayama, H. *Tetrahedron Lett.* **2012**, *53*, 6523−6526. (b) Wu, Y.; Kitajima, M.; Kogure, N.; Wang, Y.; Zhang, R.; Takayama, H. *Chem. Pharm. Bull.* **2010**, *58*, 961−963. (c) Wu, Y.; Kitajima, M.; Kogure, N.;

Wang, Y.; Zhang, R.; Takayama, H. *J. Nat. Med.* **2009**, *63*, 283−289. (d) Wu, Y.; Suehiro, M.; Kitajima, M.; Matsuzaki, T.; Hashimoto, S.; Nagaoka, M.; Zhang, R.; Takayama, H. *J. Nat. Prod.* **2009**, *72*, 204−209. (e) Wu, Y.; Kitajima, M.; Kogure, N.; Zhang, R.; Takayama, H. *Tetrahedron Lett.* **2008**, *49*, 5935−5938 and 6596.

(5) Lim, K.; Kam, T. *Org. Lett.* **2006**, *8*, 1733−1735.

(6) (a) Delfourne, E.; Kiss, R.; Le Corre, L.; Dujols, F.; Bastide, J.; Collignon, F.; Lesur, B.; Frydman, A.; Darro, F. *J. Med. Chem.* **2003**, *46*, 3536−3545. (b) Gray, C. J.; Parker, R. C. *Tetrahedron* **1975**, *31*, 2940−2943.

(7) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263−1266.

(8) Corey, E. J. R.; Bakshi, K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

(9) For details, see the Supporting Information.

(10) Kim, J. M.; Na, J. E.; Kim, N. *Tetrahedron Lett.* **2003**, *44*, 6317−6318.

(11) Robbins, D. W.; Hartwig, J. F. *Org. Lett.* **2012**, *14*, 4266−4269.

(12) For review, see: Finefield, J.; Sherman, D. H.; Kreitman, M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4802−4836.

dx.doi.org/10.1021/ol502265q | *Org. Lett.* 2014, 16, 5000−5003