Organic LETTERS

Letter

pubs.acs.org/OrgLett

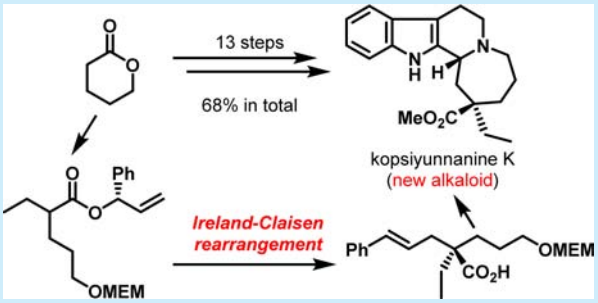
Asymmetric Total Synthesis of Kopsiyunnanine K, a Monoterpenoid Indole Alkaloid with a Rearranged Skeleton

Ryoko Tokuda, Yoshiki Okamoto, Tetsuya Koyama, Noriyuki Kogure, Mariko Kitajima, and Hiromitsu Takayama*

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

Supporting Information

ABSTRACT: A new monoterpenoid indole alkaloid, kopsiyunnanine K, was isolated from *Kopsia arborea*. Its intriguing rearranged structure and absolute configuration, which were inferred from spectral data and a possible biosynthetic pathway, were determined on the basis of a 13-step asymmetric total synthesis.



The genus *Kopsia*, which belongs to family Apocynaceae, is a rich source of monoterpenoid indole alkaloids possessing structural diversity and a wide range of biological activities.[1] As a result of our continuing chemical studies on novel bioactive alkaloids,[2] we were able to accomplish the structure elucidation of several unique monoterpenoid indole alkaloids from *Kopsia arborea*, which is native to the Yunnan Province in China[3] (Figure 1). Further investigations have led to the isolation of an

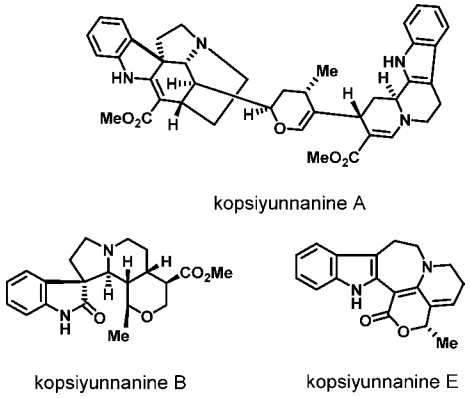


Figure 1. Structures of kopsiyunnanines A, B, and E.

intriguing new alkaloid named kopsiyunnanine K (**1**), which has an unprecedented azepine-fused tetrahydro-β-carboline ring skeleton (Figure 2). We herein describe the structure elucidation of the alkaloid based on spectroscopic analysis and biogenetic consideration and the asymmetric total synthesis consisting of 13 steps.

The crude base obtained from the aerial part of *K. arborea* was purified by repeated chromatography to afford new indole alkaloid **1** (0.0015% yield based on the crude base). Compound **1**

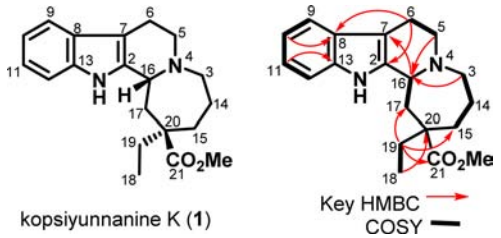


Figure 2. Structure and key COSY and HMBC correlations of kopsiyunnanine K (**1**).

$\{[\alpha]_D^{24}$ −60.0 (*c* 0.02, MeOH)$\}$, named kopsiyunnanine K, was found to have the molecular formula $C_{20}H_{26}N_2O_2$ from HRESI-MS [*m*/*z* 327.20725 (M + H)$^+$]. The UV spectrum was characteristic of an indole chromophore with absorption maxima at 290.0, 280.0, and 224.0 nm. ^{1}H and ^{13}C NMR measurements revealed a nonsubstituted A ring of an indole system, a methyl ester, an ethyl group, and one methine group and two methylene groups attached to a nitrogen (Table 1). ^{1}H−^{1}H COSY (Figure 2) suggested the existence of three consecutive methylene groups (C-3−C-14−C-15). HMBC correlations (Figure 2) indicated connections among C-3, C-5, and C-16 through a nitrogen atom and among C-15, C-17, the ethyl group, and the methyl ester through the C-20 quaternary carbon. Moreover, correlations of H-16 with C-7 and H-6 with C-2 and C-8 suggested that C-16 was connected to C-2 of the indole moiety. From these data, compound **1** was proposed to be a monoterpenoid indole alkaloid bearing the azepine-fused tetrahydro-β-carboline ring system, which has never been discovered in monoterpenoid indole alkaloids. The absolute

Received: June 13, 2016
Published: June 29, 2016

DOI: 10.1021/acs.orglett.6b01704
Org. Lett. 2016, 18, 3490−3493

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) Spectral Data of Kopsiyunnanine K (1) (in $CDCl_3$)

	kopsiyunnanine K (1)	
position	δ_H (multi, J, Hz)	δ_C
2		136.6
3	3.12 (ddd, 12.1, 6.5, 1.5)	60.6
	2.55−2.63 (overlapped)	
5	3.03 (ddd, 11.5, 4.1, 4.1)	52.2
	2.55−2.63 (overlapped)	
6	2.90 (dddd, 14.9, 9.5, 4.1, 1.9)	21.7
	2.74 (dddd, 14.9, 4.1, 4.1, 1.6)	
7		107.9
8		126.9
9	7.47 (d, 7.6)	118.0
10	7.07 (ddd, 7.6, 7.6, 1.1)	119.0
11	7.13 (ddd, 7.6, 7.6, 1.1)	121.2
12	7.36 (d, 7.6)	110.7
13		136.2
14	1.77−1.94 (2H, overlapped)	24.2
15	2.13 (ddd, 13.1, 10.4, 1.2)	36.7
	1.77−1.94 (overlapped)	
16	3.64 (d, 6.1)	56.4
17	2.55−2.63 (overlapped)	41.0
	1.77−1.94 (overlapped)	
18	0.78 (3H, t, 7.6)	9.2
19	1.69 (m)	33.8
	1.63 (m)	
20		49.9
21		179.2
CO_2CH_3	3.79 (3H, s)	52.1
NH	8.52 (s)	

configurations at C-16 and C-20 were deduced as follows. The CD spectrum of **1** showed a Cotton effect opposite to that of decarbomethoxydihydrogambirtannine (**2**), a yohimbane-type alkaloid possessing 3*S* configuration, which led us to propose that the configuration at C-16 in **1** was *R* (Figure 3). The

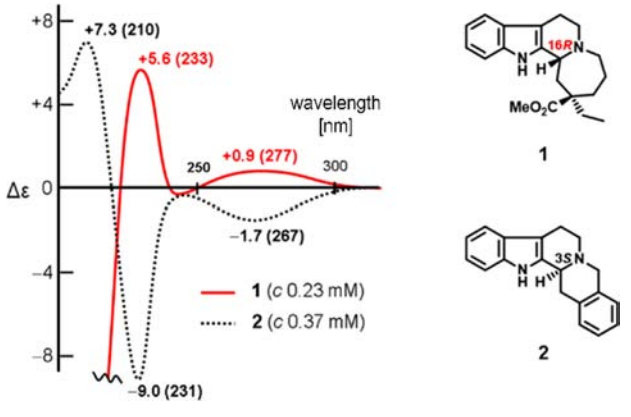
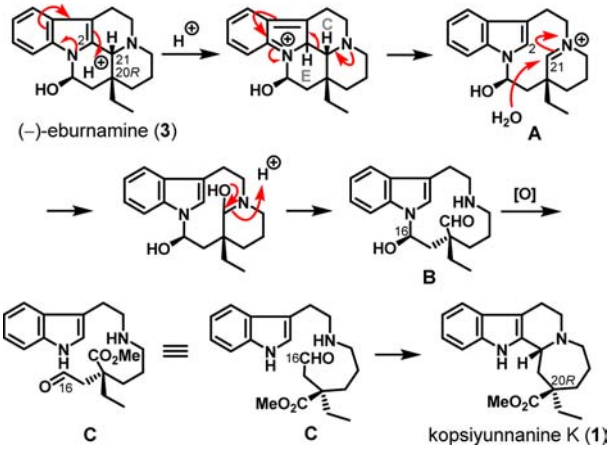


Figure 3. CD spectra of **1** and **2**.

configuration at C-20 was deduced from a biogenetic point of view. Biogenetically, **1** could be generated from (−)-eburnamine (**3**), which coexists in *K. arborea*, as shown in Scheme 1. The bond cleavage between C-2 and C-21 positions in **3** occurs by initial protonation at the C-2 position of the indole moiety to give the C/E ring-opening intermediate **A**. Next, hydrolysis of an iminium function in **A** gives aldehyde **B**. By oxidation and

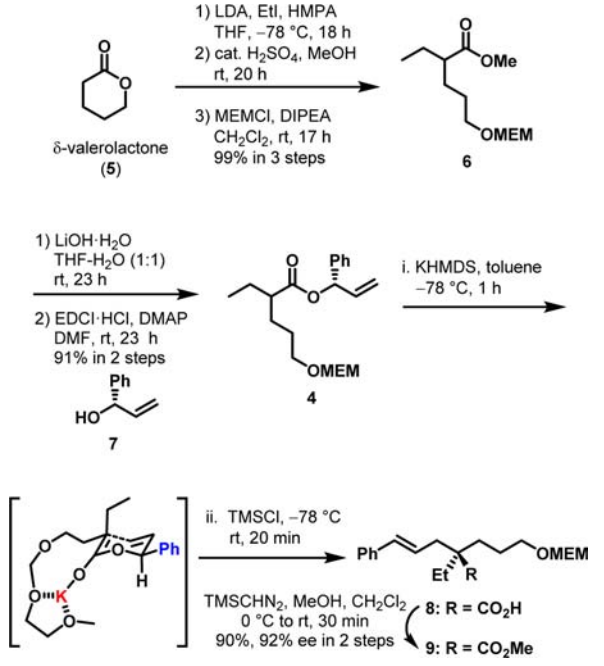
Scheme 1. Possible Biogenetic Route of Kopsiyunnanine K (1)



esterification of the aldehyde function in **B**, followed by the formation of an aldehyde group at C-16 from the hemiaminal function in **B**, a possible biogenetic precursor **C** of kopsiyunnanine K (**1**) is generated. Next, **1** would be formed by Pictet−Spengler reaction of **C**. This hypothesis allowed us to suggest that **1** has the rearranged skeleton with C-20*R* configuration.

To clarify the structure and the absolute configuration at C-16 and C-20 of **1**, asymmetric total synthesis was performed (Scheme 2). We initially prepared ester derivative **4** from *δ*-

Scheme 2. Synthesis of Chiral Ester 9



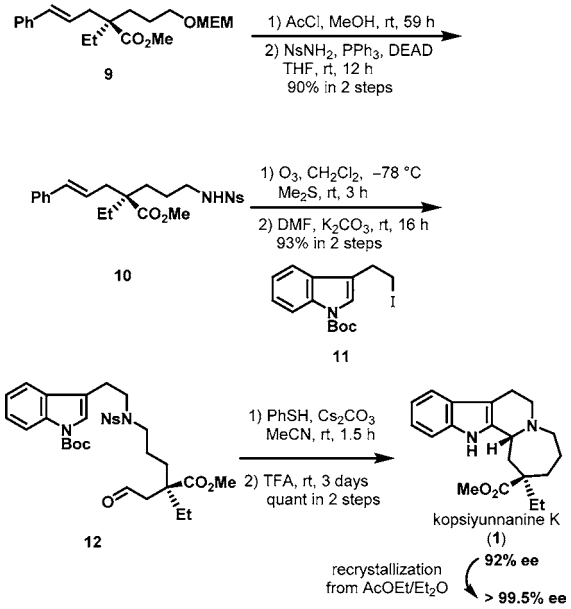
valerolactone (**5**) via a five-step operation: alkylation of **5** with EtI, methanolysis, MEM protection of the primary alcohol, alkaline hydrolysis of **6**, and condensation of the resultant carboxylic acid with chiral alcohol **6**.[4] Asymmetric Ireland−Claisen rearrangement of MEM-protected allyl alcohol derivative **4** was performed[5] under the optimum conditions using KHMDS and TMSCl in toluene. Methylation of the resultant carboxylic acid **7** gave ester **9** in 90% yield with 92% ee in two steps. An

DOI: 10.1021/acs.orglett.6b01704
Org. Lett. 2016, 18, 3490−3493

efficient chirality transfer process of the Ireland−Claisen rearrangement can be explained by using a transition state depicted in Scheme 2. In the chairlike transition state, the phenyl group takes the pseudoequatrial position. Furthermore, in the ketene acetal moiety, the side chain with a MEM group favors the equatorial position with the aid of the chelate effect. Actually, when a MOM group or a TBS group was used for the protection of the primary alcohol in place of the MEM group in **4**, the enantiomeric excesses of the products formed by the Ireland−Claisen rearrangement decreased (MOM, 81% ee; TBS, 0.3% ee).

Next, an amine function was introduced to **9** by deprotection of the MEM group followed by the Mitsunobu reaction with $NsNH_2$ to afford amide **10** (Scheme 3). After ozonolysis of **10**,

Scheme 3. Synthesis of Kopsiyunnanine K (1)



alkylation of the resultant aldehyde−amide with indole unit **11**[6,7] was executed to give aldehyde **12**. Deprotection of the Ns group on the N_b position in **12** followed by intramolecular diastereoselective Pictet−Spengler reaction of the resultant amine in the presence of trifluoroacetic acid gave kopsiyunnanine K (**1**) as a single diastereomer in a quantitative yield. Recrystallization of the product afforded optically pure **1**.

The structure and the 16*R*,20*R* configuration of synthetic **1** were confirmed by X-ray crystallographic analysis (Figure 4).

Synthetic **1** was identical in all respects to the natural compound, including the optical property {synthetic: $[\alpha]_D^{23}$ −68.1 (*c* 0.04, MeOH), natural: $[\alpha]_D^{24}$ −60.0 (*c* 0.02, MeOH)}.

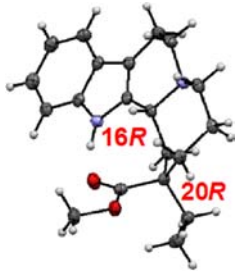


Figure 4. Crystal structure of **1**.

Therefore, the structure and the absolute configuration of kopsiyunnanine K were established, as shown in formula **1**.

In conclusion, we have succeeded in the asymmetric total synthesis of kopsiyunnanine K (**1**), an indole alkaloid that was newly isolated from *Kopsia arborea*, via an asymmetric Ireland−Claisen rearrangement and an intramolecular diastereoselective Pictet−Spengler reaction, and proved its unique rearranged skeleton and absolute configuration. Its biological activity is currently being evaluated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01704.

Experimental procedures for the isolation of kopsiyunnanine K (**1**), preparation of compounds **4**−**6**, **9**−**12**, and synthetic **1**, and copies of NMR spectral data for natural **1**, compounds **4**−**6**, **9**−**12**, and synthetic **1** (PDF)

X-ray data of compound **1** (CIF)

■ 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. 26293023 and 16H05094, and The Uehara Memorial Foundation.

■ REFERENCES

(1) (a) Wong, S.; Chong, K.; Lim, K.; Lim, S.; Low, Y.; Kam, T. *Org. Lett.* **2016**, *18*, 1618−1621. (b) Yap, W.; Gan, C.; Sim, K.; Lim, S.; Low, Y.; Kam, T. *J. Nat. Prod.* **2016**, *79*, 230−239. (c) Wong, S.; Gan, C.; Lim, K.; Ting, K.; Low, Y.; Kam, T. *Org. Lett.* **2015**, *17*, 3628−3631. (d) Cheenpracha, S.; Raksat, A.; Ritthiwigrom, T.; Laphookhieo, S. *Nat. Prod. Commun.* **2014**, *9*, 1441−1443. (e) Ahmad, K.; Hirasawa, Y.; Nugroho, A. E.; Hadi, A. H. A.; Morita, H. *Heterocycles* **2012**, *86*, 1611−1619. (f) Yang, Y.; Zuo, W.; Zhao, Y.; Dong, W.; Mei, W.; Dai, H. *Planta Med.* **2012**, *78*, 1881−1884. (g) Chen, J.; Li, X.; Li, N.; Lu, J.; Xu, X.; Duan, H.; Qin, L. *Chem. Nat. Compd.* **2012**, *48*, 834−835. (h) Tan, M.; Yin, C.; Tang, C.; Ke, C.; Lin, G.; Ye, Y. *Planta Med.* **2011**, *77*, 939−944. (i) Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334−5336. (j) Yap, W.; Gan, C.; Low, Y.; Choo, Y.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T. *J. Nat. Prod.* **2011**, *74*, 1309−1312. (k) Kam, T.; Lim, K. Alkaloids of *Kopsia*. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2008; Vol. *66*, pp 1−111.

(2) (a) Kitajima, M.; Watanabe, K.; Maeda, H.; Kogure, N.; Takayama, H. *Org. Lett.* **2016**, *18*, 1912−1915. (b) Takanashi, N.; Suzuki, K.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2016**, *57*, 375−378. (c) Ishida, H.; Kimura, S.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Biomol. Chem.* **2015**, *13*, 7762−7771. (d) Ishida, H.; Kimura, S.; Kogure, N.; Kitajima, M.; Takayama, H. *Tetrahedron* **2015**, *71*, 51−56. (e) Azuma, M.; Yoshikawa, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Am. Chem. Soc.* **2014**, *136*, 11618−11621. (f) Terada, Y.; Kitajima, M.; Taguchi, F.; Takayama, H.; Horie, S.; Watanabe, T. *J. Nat. Prod.* **2014**, *77*, 1831−1838. (g) Harada, M.; Asaba, K.; Iwai, M.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2012**, *14*, 5800−5803.

(3) (a) Kitajima, M.; Koyama, T.; Wu, Y.; Kogure, N.; Zhang, R.; Takayama, H. *Nat. Prod. Commun.* **2015**, *10*, 49−51. (b) Kitajima, M.; Murakami, Y.; Takahashi, N.; Wu, Y.; Kogure, N.; Zhang, R.; Takayama, H. *Org. Lett.* **2014**, *16*, 5000−5003. (c) Kogure, N.; Suzuki, Y.; Wu, Y.; Kitajima, M.; Zhang, R.; Takayama, H. *Tetrahedron Lett.* **2012**, *53*,

DOI: 10.1021/acs.orglett.6b01704
Org. Lett. 2016, 18, 3490−3493

6523−6526. (d) Wu, Y.; Kitajima, M.; Kogure, N.; Wang, Y.; Zhang, R.; Takayama, H. *Chem. Pharm. Bull.* **2010**, *58*, 961−963. (e) Wu, Y.; Suehiro, M.; Kitajima, M.; Matsuzaki, T.; Hashimoto, S.; Nagaoka, M.; Zhang, R.; Takayama, H. *J. Nat. Prod.* **2009**, *72*, 204−209. (f) Wu, Y.; Kitajima, M.; Kogure, N.; Wang, Y.; Zhang, R.; Takayama, H. *J. Nat. Med.* **2009**, *63*, 283−289. (g) Wu, Y.; Kitajima, M.; Kogure, N.; Zhang, R.; Takayama, H. *Tetrahedron Lett.* **2008**, *49*, 5935−5938 and 6596.

(4) Singh, V. O.; Han, H. *Org. Lett.* **2007**, *9*, 4801−4804.

(5) Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501−2503.

(6) Alkylation of an aldehyde−amide intermediate with N_a-Boc-tryptophol did not proceed under the usual Mitsunobu conditions. Thus, we employed iodide derivative **11**.

(7) Cheng, J.; Qin, J. Patent Appl. CN 103012274A, 2013.

DOI: 10.1021/acs.orglett.6b01704
Org. Lett. 2016, 18, 3490−3493