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Asymmetric Total Synthesis of an Iboga-Type Indole Alkaloid, Voacangalactone, Newly Isolated from *Voacanga africana*

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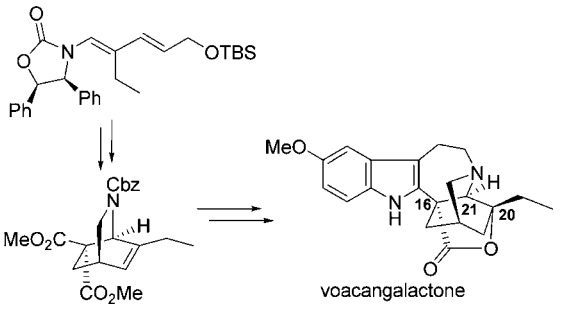
ABSTRACT



A new hexacyclic iboga-type indole alkaloid, voacangalactone (1), was isolated from *Voacanga africana*, and its structure including the absolute configuration was established by asymmetric total synthesis involving such key steps as the asymmetric Diels–Alder reaction using an aminodiene and the construction of an isoquinuclidine ring and an indole skeleton.

Voacanga africana belonging to Apocynaceae has been used as a traditional medicine in Africa. Both root bark and seeds are a rich source of monoterpenoid indole alkaloids having unique structures and biological activities. Recently, we found two iboga-type alkaloids that showed cannabinoid CB1 receptor antagonistic activity from *V. africana* root bark.[1] These are the first examples of natural alkaloids having cannabinoid CB1 receptor antagonistic activity. We also reported that iboga-type alkaloids isolated from *V. africana* inhibited capsaicin-induced contraction in the mouse rectum possibly via inhibition of a transient receptor potential vanilloid type 1 (TRPV1)-mediated pathway.[2] Further investigation of the crude base of this plant has led to the isolation of a new hexacyclic iboga-type alkaloid: voacangalactone (Figure 1). Herein we report the structure determination based on spectroscopic analyses and asymmetric total synthesis.

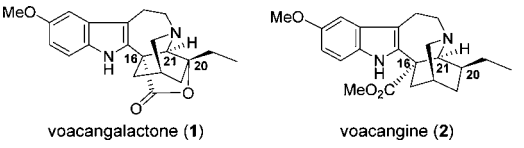


Figure 1. Structures of voacangalactone (**1**) and voacangine (**2**).

The crude base obtained from the root bark of *V. africana* was purified by repeated chromatography to afford new alkaloid **1** (0.013% yield based on the crude base). Compound **1**, named voacangalactone, was found to have the molecular formula $C_{21}H_{24}N_2O_3$ from HREI-MS [*m*/*z* 352.1788 (M^+)]. The ^1H and ^{13}C NMR spectra were similar to those of voacangine (**2**) except for the presence of signals for an oxygenated quaternary carbon at C-20 and the absence of signals for a methyl group at the carbomethoxy function, a structure common to iboga-type alkaloids (Table 1). 2D NMR correlations indicated that compound **1** had a voacangine skeleton with a lactone

(1) Kitajima, M.; Iwai, M.; Kikura-Hanajiri, R.; Goda, Y.; Iida, M.; Yabushita, H.; Takayama, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1962–1964.

(2) Lo, M. W.; Matsumoto, K.; Iwai, M.; Tashima, K.; Kitajima, M.; Horie, S.; Takayama, H. *J. Nat. Med.* **2011**, *65*, 157–165.

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

	voacangalactone (**1**)	
	$^{1}H^{a}$	$^{13}C^{b}$
2		137.1
3	3.24–3.20 (overlapped) 3.09 (br-d, 9.9)	50.3
5	3.33 (br-ddd, 14.5, 3.1, 3.1) 3.24–3.20 (overlapped)	54.2
6	3.42 (ddd 16.5, 12.9, 3.1) 2.72 (br-d, 16.5)	20.1
7		109.7
8		128.7
9	6.93 (d, 2.0)	100.0
10		154.2
11	6.82 (dd, 8.5, 2.0)	111.7
12	7.24 (d, 8.5)	112.0
13		129.4
14	2.24 (br-s)	26.2
15	2.07–2.03 (overlapped) 1.81 (d, 14.6)	35.9
16		45.8
17	2.31 (ddd, 14.2, 3.1, 3.1) 2.07–2.03 (overlapped)	37.5
18	1.02 (3H, dd, 7.4, 7.4) 1.98 (dq, 14.8, 7.4)	7.3
19	1.80 (dq, 14.8, 7.4)	29.4
20		88.1
21	3.51 (s)	65.6
10-OMe	3.86 (3H, s)	56.1
CO		178.1
NH	9.48 (br-s)	

[a] 600 MHz. [b] 150 MHz.

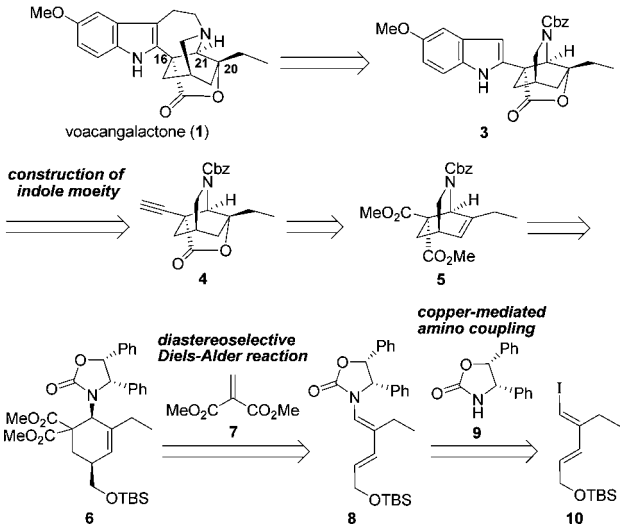
moiety consisting of C-16, C(O), O, C-20, and C-21. To the best of our knowledge, this is the first example of natural iboga-type alkaloids having such a function. Then, we attempted the total synthesis of voacangalactone to reveal its relative and absolute configurations.

Our synthetic plan for voacangalactone (**1**) is shown in Scheme 1. The indole moiety of the target compound could be constructed at the last stage by transformation of alkyne derivative **4**, which could be obtained from a key intermediate, such as **5** having an isoquinuclidine core common to iboga-type indole alkaloids. Chiral isoquinuclidine **5** could be formed via the diastereoselective Diels–Alder reaction of 1,1-disubstituted alkene **7** and chiral aminodiene **8** having a chiral auxiliary, the latter of which could be synthesized by copper-mediated amino coupling of iodoalkene **10** and commercially available oxazolidinone **9**.

We initially prepared iodoalkene **10** from diethyl ethylmalonate (**11**) in seven steps (Scheme 2). The introduction of a diiodomethyl group into **11**, hydrolysis and decarboxylation of **12**, LAH reduction of carboxylic acid, and MnO_2 oxidation of the resultant allylic alcohol gave known aldehyde **14**.[3] Wittig reaction of aldehyde **14** to

(3) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990** 47–65.

Scheme 1. Retrosynthetic Analysis



elongate the carbon chain, DIBAL reduction of the methyl ester group of diene **15**, and finally TBS protection of the resultant primary alcohol afforded iodoalkene **10**. Chiral aminodiene **8**, the substrate for the diastereoselective Diels–Alder reaction, was obtained in 81% yield by the copper-mediated amino coupling of prepared iodoalkene **10** with oxazolidinone **9** by applying Buchwald's condition (CuI, DMEDA, $CsCO_3$, THF).[4]

Then, we attempted the diastereoselective Diels–Alder reaction of chiral aminodiene **8** with highly reactive 1,1-disubstituted alkene **7**[5] that was prepared from dimethyl malonate. The reaction of aminodiene **8** with **7** in CH_2Cl_2 at room temperature proceeded smoothly to form desired cyclohexene derivative **6** in 97% yield as the sole product. The relative and absolute configurations of **6** were determined by X-ray crystallographic analysis.[6]

The high diastereoselectivity of the Diels–Alder reaction could be explained as follows. The attack of alkene **7** occurred from the less-hindered face of the *anti* structure of aminodiene **8**, which was more stable than the *syn* conformer, induced by the stabilizing interaction between the dipoles of dienyl and oxazolidinone moieties[7] (Figure 2).

Next, we turned our attention to the construction of an isoquinuclidine core in the iboga-type skeleton (Scheme 3). Reductive cleavage of the oxazolidinone ring of **6** under conventional conditions [$Pd(OH)_2$/C, H_2] afforded **16**. However, expected amine **17** could not be obtained even under heated or high-pressure conditions. After several attempts, we successfully synthesized **17** through a one-pot operation from **6**, i.e., reductive cleavage of oxazolidinone,

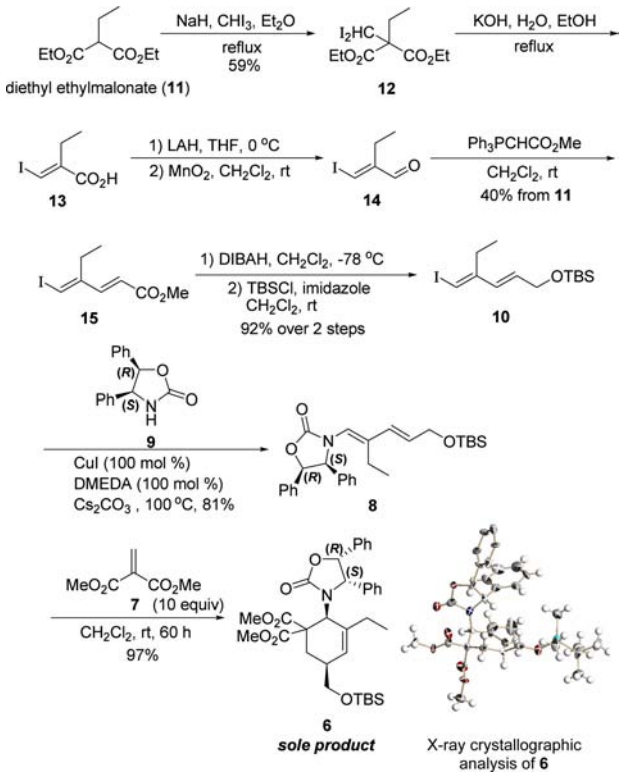
(4) Jiang, L.; Job, J. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669.

(5) Bachman, G. B.; Tanner, H. A. *J. Org. Chem.* **1939**, *4*, 493–501. Freshly prepared alkene **7** (CH_2Cl_2 solution) was used for the Diels–Alder reaction since **7** was quite unstable and easily polymerized.

(6) See the Supporting Information.

(7) Robitte, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-B rynaert, J. *J. Org. Chem.* **2003**, *68*, 9809–9812.

Scheme 2



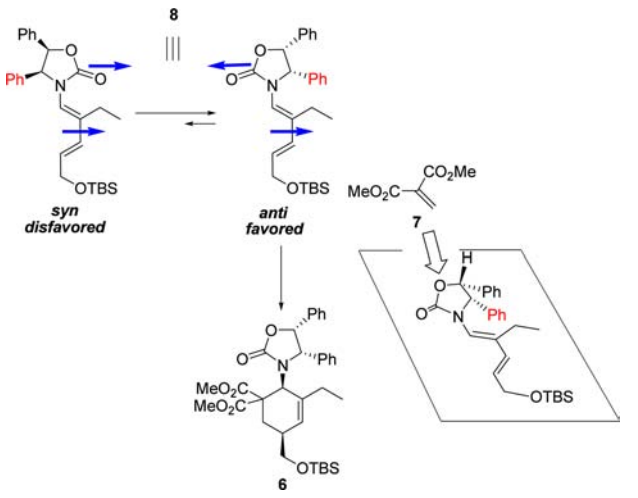
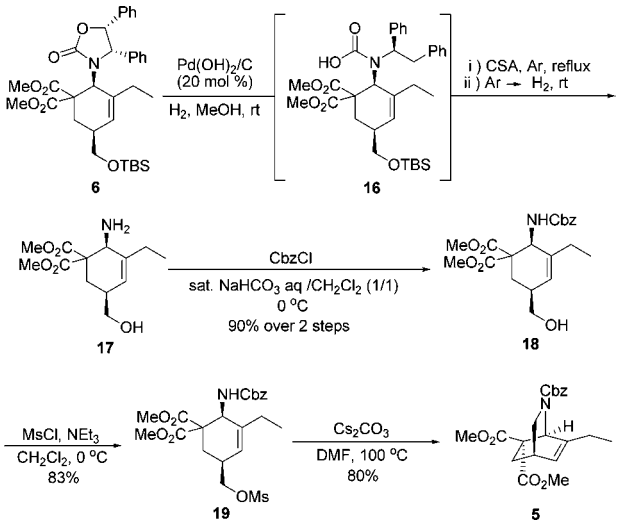


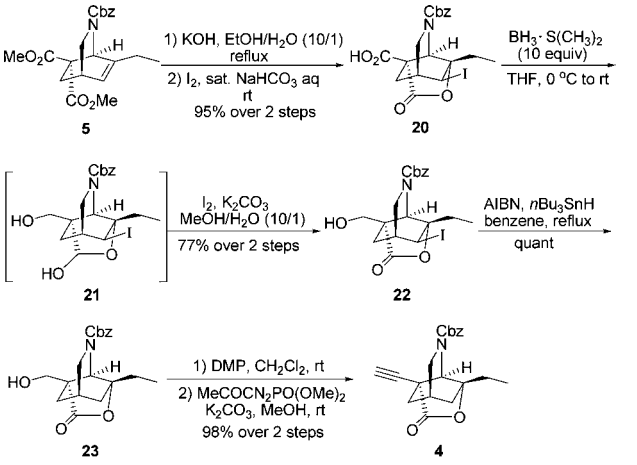
Figure 2. Possible mechanism in the diastereoselective Diels–Alder reaction.

decarboxylation of **16** by treatment with CSA under Ar atmosphere, and a second reductive cleavage of the N–C bond under H_2 atmosphere. Cbz protection of the amine residue in **17** afforded **18** in 90% overall yield from **6**. The primary alcohol in **18** was then converted into *O*-mesyl group to produce **19**, which was treated with Cs_2CO_3 in DMF to give isoquinuclidine derivative **5**.

Scheme 3



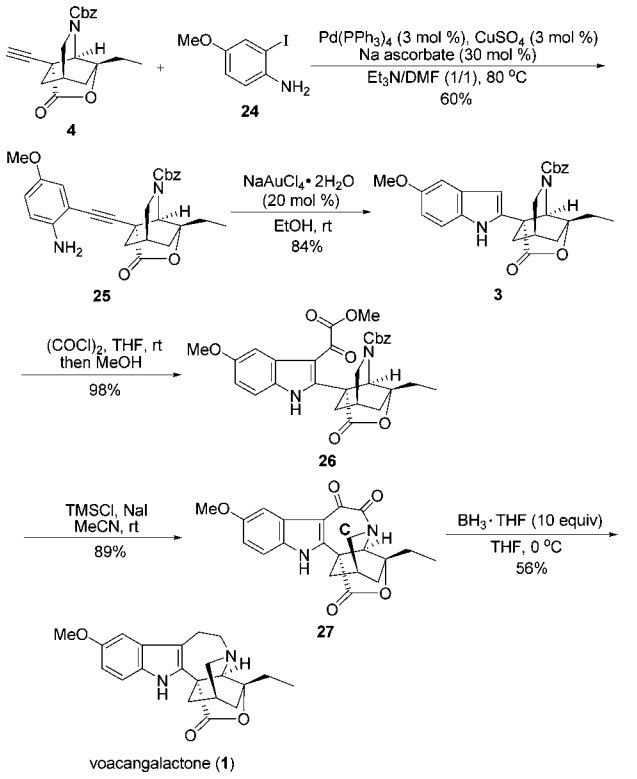
Scheme 4



To construct an indole moiety in voacangalactone (**1**), we conducted the transformation of **5** into alkyne derivative **4** (Scheme 4). Following Reding and Fukuyama's procedures,[8] **5** was converted into carboxylic acid **20** by alkaline hydrolysis and subsequent iodolactonization. Next, we attempted the transformation of carboxylic acid **20** into alcohol **22**. Several reaction conditions were examined for the selective reduction of the carboxylic residue of **20**, but desired alcohol **22** was obtained in low yields. The best result was obtained with a stepwise method, i.e., conversion of **20** into lactol **21** by reduction with an excess amount of $BH_3 \cdot S(CH_3)_2$ and the subsequent selective oxidation of the lactol hydroxyl group with iodine, affording desired **22** in 77% yield from **20**. Deiodination of **22** proceeded in a quantitative yield by refluxing with AIBN

(8) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973–976.

Scheme 5



and nBu$_3$SnH in benzene to afford **23**, and **23** was converted into desired alkyne derivative **4** by DMP oxidation and successive Seyferth–Gilbert homologation using the Ohira–Bestmann reagent in 98% yield.

The Sonogashira cross coupling of **4** and iodoaniline derivative **24**[9] proceeded in 60% yield by treatment with $Pd(PPh_3)_4$, $CuSO_4$, and sodium ascorbate in Et_3N/DMF (1/1),[10] and resulting compound **25** was transformed into indole **3** in 84% yield by the Au-catalyzed cyclization reaction following Utimoto's method[11] ($NaAuCl_4 \cdot 2H_2O$ in EtOH) (Scheme 5).

To accomplish the asymmetric total synthesis of voacangalactone (**1**), we attempted to construct a seven-membered C-ring. Side chain extension at the indole β-position in **3** was achieved by treatment with $(COCl)_2$ and methanolysis of the resulting carboxylic chloride. Deprotection of the Cbz group in **26** by treatment with TMSCl/NaI in MeCN produced the desired secondary amine that was spontaneously cyclized to **27** in 89% yield. At the final stage, the two carbonyl groups in **27** were simultaneously reduced with an excess amount of $BH_3 \cdot THF$ to furnish target alkaloid **1** in 56% yield. Synthetic **1** ($[\alpha]_D^{26}$ −34.2 (c 0.12, MeOH)) was completely identical in all respects (mass, UV, IR, ^{1}H and ^{13}C NMR, CD) with natural voacangalactone. Therefore, the structure of voacangalactone including the absolute configuration was established to be formula 1.

In conclusion, we have succeeded in the asymmetric total synthesis of the new alkaloid, voacangalactone (**1**), isolated from *Voacanga africana*, which enabled us to determine its structure including its absolute configuration. The synthesis involved the preparation of optically active isoquinuclidine derivative **5**, a key intermediate for the syntheses of iboga-type alkaloids, via the diastereoselective Diels–Alder reaction. Further synthetic study of this class of alkaloids is under investigation in our laboratory.

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Supporting Information Available. Experimental procedure, copies of ^{1}H and ^{13}C NMR spectral data for compounds **3**–**6**, **8**, **10**, **15**, **18**–**20**, **22**, **23**, **25**–**27** and synthetic voacangalactone (**1**), and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(9) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117–122.
(10) Bag, S. S.; Kundu, R.; Das, M. *J. Org. Chem.* **2011**, *76*, 2332–2337.
(11) (a) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799–1802. (b) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 1236–1237.