Longiberine and *O*-Methyllongiberine, Dimeric Protoberberine-Benzyl Tetrahydroisoquinoline Alkaloids from *Thalictrum longistylum*[1]

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Two benzyltetrahydroisoquinoline−protoberberine dimers, longiberine (**1**) and *O*-methyllongiberine (**2**), were isolated from the roots of *Thalictrum longistylum* and represent a new class of dimeric alkaloids. The structure of longiberine (**1**) was established by spectral and chemical methods. Reductive cleavage of *O*-ethyllongiberine (**4**) with Na/liquid NH_3 yielded (+)−(*S*)-*N*-methylcoclaurine (**5**), which determined one-half of the dimer, and 1D and 2D NMR studies arranged the substituents on the protoberberine nucleus. Chemical conversion of thalidezine (**6**) to **1** via the *O*-acetyl *N*,*N*-didemethyl derivative **9**, which was methylenated in the Mannich reaction and *N*-methylated by the Eschweiler−Clarke procedure, established the second asymmetric center as *S* and confirmed the ring size and the order of the substituents for **1**. Methylation of **1** with diazomethane formed the *O*-methyl derivative **2**, identical with the natural product.

The large family of benzylisoquinoline alkaloids contains a homodimeric class of several hundred members, the so-called bisbenzylisoquinolines, in addition to the smaller numbered heterodimers. In these the monomeric units are alkaloids derived biosynthetically from benzyltetrahydroisoquinolines.[2−4] The derived alkaloids, themselves, may form homodimers. The majority are biphenyl and/or diphenyl ether connected and could contain up to three linkages. Of the heterodimers, the aporphine−benzylisoquinolines[2a,5] are the largest group, while the aporphine−pavine,[1,2b] pavine−benzylisoquinoline,[2c] and cularine−morphinan[2d] groups are represented by only a few examples. For protoberberines, no heterodimers, and only two homodimers, are recorded.[2e]

This report is on the first protoberberine−benzyltetrahydroisoquinoline dimers, longiberine (**1**) and its *O*-methyl derivative **2**, obtained from the roots of *Thalictrum longistylum* DC. (Ranunculaceae). Earlier publications described 12 alkaloids from this plant, some of which possess hypotensive and antimicrobial activities.[6,7]

Results and Discussion

Longiberine (**1**) was obtained from the phenolic and nonphenolic Et_2O-soluble tertiary alkaloid fractions as a crystalline material, mp 169−170 °C, and showed a HRMS molecular ion as base peak, corresponding to the formula $C_{38}H_{40}N_2O_7$. The formula and the intense molecular ion peak support a dimeric structure with at least two linkages, most probably diphenyl ethers. The ^{1}H NMR spectrum showed one *N*-methyl and four *O*-methyl groups, leaving three unassigned oxygens, one of which must be a phenolic hydroxyl from the presence of absorption at 3540 cm^{-1} in the IR spectrum and the bathochromic shift with strong alkali in the UV spectrum. This was confirmed by formation of the monoacetate **3** showing a three-proton singlet at δ 2.33 in the ^{1}H NMR spectrum. The remaining two oxygens must be diphenyl ethers. The absence of a NH group as supported by lack of formation of an acetamide on acetylation and the total carbon-bound protons from the multiplicities of the ^{13}C NMR off-resonance decoupled and DEPT experiments, together with the phenolic proton, accounted for all the required hydrogens. The presence of seven methylene carbons (DEPT) was revealing, and comparing the methine and methylene chemical shifts to those of typical bisbenzyl tetrahydroisoquinolines showed one methine upfield and one methylene downfield from the usual positions. In **1**, they overlapped at δ 57.2 and could be assigned to positions C-8 and C-14 of a protoberberine unit.[8] This type of unit was supported by the presence of an isolated AB quartet for H_2-8 at δ 4.06 and 3.97 (J = 15.2 Hz).[9]

To gain information about the nature of the monomeric units, the classic Na/liquid NH_3 reductive cleavage procedure was applied to *O*-ethyllongiberine (**4**), which gave (+)-(*S*)-*N*-methylcoclaurine (**5**) as a phenolic product and was identified from its physical properties (TLC, IR, ^{1}H NMR, specific rotation, and CD) when compared to an authentic sample.[10] This established the "left-hand" unit, leaving three methoxyls and the phenolic group for the protoberberine component.

The HRMS of **1**, with a fragment ion at *m*/*z* 462 ($C_{27}H_{28}NO_6$) was formed by loss of the tetrahydroisoquinoline from cleavage between C-7′ and its oxygen and between C-1′ and the C-9′ benzylic carbon, along with accepting a proton.[11] Also, fragment ions at *m*/*z* 397 ($C_{22}H_{25}N_2O_5$) and 239 ($C_{16}H_{15}O_2$) from a *retro*-Diels−Alder fragmentation[12] of ring C of the protoberberine and cleavage between the benzylic carbon and the tetrahydroisoquinoline ring supported the head-to-head dimerization and location of the phenolic group in ring A. The fragment ion *m*/*z* 411 ($C_{23}H_{27}N_2O_5$) from the *O*-methyl derivative **2** being 14 daltons larger than the *m*/*z* 397 fragment from **1** confirmed the ring A location of the phenolic hydroxyl (see below).

The ^{1}H−^{1}H COSY and homonuclear decoupling experiments identified two 3-spin systems formed from a methine and a methylene (H-14, H_2-13 and H-1′, H_2-9′), and a 4-spin aromatic system for a 1,4-disubstituted benzene. Placement

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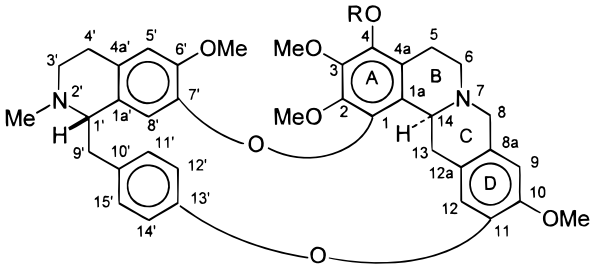
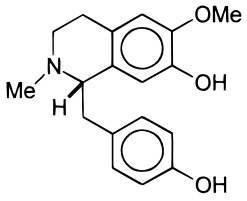


1 R = H
2 R = Me
3 R = Ac
4 R = Et



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of the substituents in the protoberberine unit and chemical shift assignments of the protons in **1** were made by NOESY and NOED experiments (Figure 1). The 2D NMR CH-correlation and COLOC experiments allowed the ^{13}C NMR assignments to be made except for the methylene carbons C-5, C-6, C-3′, C-4′, which were based on comparison with those of model monomeric units,[13,14] and the quaternary carbons C-1 and C-4, which were distinguished by their appearance in the fully ^{1}H-coupled ^{13}C NMR spectrum. C-1 (δ 141.0) appears as a very sharp singlet, while C-4 (δ 140.0) is more broadened and must result from the former having only one proton (H-14) three-bonds away, while the latter has two (H_2-5), as well as the phenolic proton.

Comparing the structures of **1** and thalidezine (**6**),[10] also isolated from *T. longistylum*,[15] indicated a very close relationship; and examining a Dreiding model of **6** showed that one of its conformations very easily led to a ring closure in which the *N*-methyl of the highly oxygenated tetrahydroisoquinoline ring could generate the C-8 methylene of the protoberberine unit (Figure 1). This cyclization is not unlike the biosynthetic process well documented for converting benzyl tetrahydroisoquinolines to protoberberines.[16] On the other hand, no conformation was possible that would allow cyclization with the *N*-methyl of the coclaurine unit. A synthetic transformation of **6**, with its stereochemical structure well established, to **1** was devised to confirm longiberine's structure and determine the absolute configuration at the protoberberine asymmetric center (C-14).

Thalidezine (**6**) was first acetylated to **7**, then *N*-demethylated with 2,2,2-trichloroethyl chloroformate[17] to generate first **8** then **9** with Zn−HOAc. Product **9** was treated with HCHO in HCl to form the protoberberine unit via the Mannich reaction[18] followed by the Eschweiler−Clarke reductive *N*-methylation of the isoquinoline unit by HCHO and HCO_2H.[19] During the last step, the acetate group was conveniently lost and the final product was **1**, identical (TLC, IR, ^{1}H NMR, and CD) with the natural product. Thus, longiberine has the same *S*,*S*-stereochemistry, substitution pattern, and ring size as **6**.

Longiberine (**1**) was treated with diazomethane, and the *O*-methylated product **2** was found to be identical with an

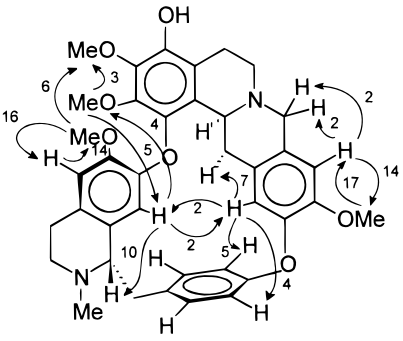
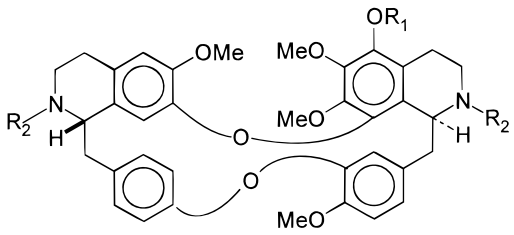


Figure 1. NOED enhancements (in percent) for longiberine (**1**) at 300 MHz in $CDCl_3$.

alkaloid isolated from the nonphenolic Et_2O-soluble tertiary alkaloid fraction. Its NMR spectral features are found in Table 1.

The biosynthesis of **1** undoubtedly occurs from **6** and, similarly, **2** most likely comes from hernandezine (**10**).[10] Indirect evidence comes from the Macheta collection of *T. longistylum*, from which **1** was not obtained but instead gave an excellent yield of **6** (2.6 g from 5.4 kg of roots). More importantly, if the biosynthesis involved phenol coupling of a preformed protoberberine, it would have to be 2,3,10-trioxygenated or 2,3,4,10-tetraoxygenated. The authors are unaware of any naturally occurring protoberberines with only one oxygen in ring D. The six protoberberines isolated from *T. longistylum* are all 9,10-dioxygenated.[7]



	R_1	R_2
6	H	Me
7	Ac	Me
8	Ac	$COCH_2CCl_3$
9	Ac	H
10	Me	Me

The molecular shape (Figure 1) of **1** as seen from a Dreiding model is triangular, with two of the sides, formed from the protoberberine unit and the tetrahyroisoquinoline ring, positioned at an angle of about 65°. They are nearly planar, but with a twist about the diphenyl ether linkage of about 40°. Both right- and left-handed twists appear possible. Figure 1 shows the left-handed form. The benzylic unit, at the base of the triangle, is positioned more or less perpendicular to the general plane of the other two sides.

The spectral data best fits the conformation for the protoberberine unit as one of the two possible *cis*-fused B/C ring arrangements in which both rings are in the half-chair conformation. It is supported by the weak Bohlmann band near 2800 cm^{-1} in the IR spectrum, which is observed for such cases, [20,21] (although that absorption has been long associated, when strong, with a trans disposition[22]) and by a bulky substituent at C-1, which causes the equilibrium to favor the cis form.[14] Also, the ^{13}C NMR chemical shift values for C-5 (δ 23.8) and C-6 (δ 48.0) are within the

Table 1. ^{1}H and ^{13}C NMR Data for **1** and **2**[a]

	1				**2**	
position	δ_H	δ_C	multiplicity	COLOC	δ_H	δ_C
1		141.0	s			143.2
1a		123.1	s			122.9[b]
2		141.4	s	MeO-2		144.6
3		137.8	s	MeO-3		142.4
4		140.0	s			145.2
4a		116.6	s			123.3[b]
5	2.85 hm	23.8	t			24.3
	2.79 hm					
6	2.99 hm	48.0	t			48.3
	2.77 hm					
8	4.06 d (15.2)	57.1	t		4.05 d (15.3)	57.3
	3.97 d (15.2)				3.99 d (15.3)	
8a		129.5	s	H_2-8, H-12, H-13α		129.5
9	6.68 s	111.2	d		6.68 s	111.3
10		149.4	s	H-9, H-12, MeO-10		149.5
11		149.2	s	H-9		149.4
12	6.26 s	121.9	d	H-13α	6.23 s	122.1
12a		133.7	s	H-8, H-9, H-13α		133.6
13	3.95α br d (13.9)	34.8	t		3.06α d (13.4)	35.3
	2.58β dd (13.1, 9.9)				2.57β dd (12.7, 10.3)	
14	3.51 br d (10.9)	57.1	d		3.50 d (10.0)	57.3
MeO-2	3.27 s	60.9	q		3.25 s	60.9
MeO-3	3.82 s	61.1	q		3.82 s	61.18
MeO-4					3.81 s	61.22
MeO-10	3.92 s	56.8	q		3.92 s	57.0
HO-4	5.50 br s					
1′	3.67 dd (11.4, 3.6)	65.0	d		3.66 dd (1.5, 3.4)	65.3
1a′		128.5	s	H-5′, H-9β′		128.6
3′	3.37 hm	45.3	t		3.40 hm	45.6
	2.87 hm					
4′	2.96 hm	24.9	t			25.2
	2.73 hm					
4a′		127.7	s	H-8′		128.2
5′	6.52 s	112.3	d		6.53 s	112.3
6′		148.8	s	H-5′, H-8′, MeO-6′		149.1
7′		142.3	s	H-5′, H-8′		142.3
8′	5.96 s	119.5	d		5.97 s	119.5
9′	3.20β dd (12.4, 3.8)	38.6	t		3.20β dd (13.4, 3.6)	39.0
	2.75α dd (12.2, 12.2)				2.75α dd (13.4, 13.4)	
10′		134.1	s	H-9β′, H-14′		134.3
11′	6.23 dd (8.8, 1.5)	133.0	d		6.23 br d (8.8)	133.1
12′	6.33 dd (8.8, 1.5)	122.1	d		6.34 br d (8.8)	122.3
13′		159.6	s	H-12, H-15′		159.7
14′	7.28 br s	121.5	d		7.28 br s	121.7
15′	7.28 br s	129.2	d		7.28 br s	129.3
MeO-6′	3.46 s	55.6	q		3.48 s	55.6
MeN-2′	2.56 s	42.7	q		2.56 s	42.9

[a] Taken at 300 MHz in $CDCl_3$ with data point resolution of 0.4 Hz for ^{1}H and 1.9 Hz for ^{13}C and chemical shift (δ) in ppm as referenced to TMS with residual solvent peak ($CHCl_3$) taken as internal standard at 7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C. Spin-coupled patterns are designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and h = hidden or overlapped. The spin coupling constant (J) is given in parenthesis in Hz. [b] May be interchanged.

narrow ranges observed for a series of β-positioned C-13 substituted protoberberines.[23] However, in **1**, C-8 (δ 57.1) is downfield 9 ppm units and best fits a trans ring fusion. This is due, undoubtedly, to the absence in **1** of the C-13 pseudoaxial substituent with its upfield γ-shift effect. The C-8 chemical shift does fit the predicted value (δ 57.0) for 10,11-dioxygenated protoberberine.[14] Other data do not agree with the empirical rules in the literature. For example, the H-14 chemical shift of δ 3.51 is less than δ 3.8 and would require a trans orientation, [24] and this anomaly cannot be explained by a shielding from the isoquinoline ring at C-1, as it is positioned away and on the opposite side of ring A. Furthermore, the H-14 pattern (br d, J = 10.9 Hz) does not agree with either the trans or cis forms.[14,23] Clearly, additional studies are warranted before the conformation of the protoberberine ring is settled.

Experimental Section

General Experimental Procedures. The instruments used and general procedures followed have been reported.[7,25]

Plant Material. *T. longistylum* was identified and collected by Mr. Mauricio Pinzon in the region of Macheta, province of Cundinamarca, Colombia, during June and July 1982, and in the region of Zipacon, Colombia, during February and March 1982. Herbarium specimens are on file in the College of Pharmacy, Ohio State University. The air-dried roots when received were dried at 40 °C for 2 days in a force-draft plant-drying oven, then ground in a Wiley Mill.

Extraction and Initial Isolation Procedure. Extraction of the roots and fractionation of the crude extracts to give the alkaloid fractions were performed as recorded for the initial study of *T. longistylum*.[7] The Macheta collection (5.4 kg) gave 1.47 g of the nonphenolic Et_2O-soluble, 4.05 g of the phenolic Et_2O-soluble, and 14.0 g of the $CHCl_3$-soluble alkaloids; while the Zipacon collection (4.7 kg) gave 2.16, 1.34, and 14.7 g of those alkaloids, respectively.

Isolation of Longiberine (1) and *O*-Methyllongiberine (2). The nonphenolic Et_2O-soluble alkaloids (1.9 g) from the Zipacon collection were chromatographed on Si gel (80 g) with MeOH in $CDCl_3$ mixtures of 1, 1.5, 2.5, 3, 4, 5, 7, 10, and 50%. The effluent fractions were monitored by TLC on Si gel with PhMe−Me_2CO−NH_4OH (25:25:1). The 2.5% MeOH in $CHCl_3$ solvent gave a fraction (400 mg) containing **2**, with R_f 0.42 on TLC, which was further separated on 15.6 g of Si gel with PhMe−Me_2CO−NH_4OH (15:5:1) from which 159 mg of residue was purified on 5 g of Si gel with 1% MeOH in $CHCl_3$ to give 100 mg of homogeneous amorphous **2**. A fraction (131 mg) eluted from the first column with 4% MeOH in $CHCl_3$ was crystallized from MeOH−Et_2O to give 50 mg of **1** as white rosettes, with R_f 0.25 on TLC.

Longiberine (1) from the Phenolic Et_2O-Soluble Alkaloid Fraction. The alkaloid fraction (1.3 g) from the Zipacon collection was chromatographed on 100 g of Si gel with 650 mL of $CHCl_3$−MeOH−NH_4OH (96:4:0.2). After 265 mL of effluent, the next 125 mL contained 740 mg of residue that, on recrystallization from MeOH−Et_2O, gave 393 mg of **1**.

Longiberine (1): mp 169−170 °C; $[\alpha]^{25}_D$ +43.8° (*c* 0.56, MeOH); CD (*c* 5 × 10^4 M, MeOH) (deg.) $[\theta]_{305}$ 0, $[\theta]_{289}$ +37 300, $[\theta]_{278}$ 0, $[\theta]_{271}$ −23 400 (sh), $[\theta]_{248}$ −142 000, $[\theta]_{238}$ 0, $[\theta]_{218}$ +221 000 and $[\theta]_{202}$ 0; UV (MeOH) λ_{max} (log ϵ) 283 (4.14), 240 (sh 4.42) and 221 (end absorption 4.77), (0.01 N KOH, MeOH) 288 (4.19), 244 (sh 4.41) and 220 (end absorption 4.88) nm; IR ($CHCl_3$) ν_{max} 3540 (OH), 3100, 2940, 2803, 1610, 1510, 1470, 1203, 1100, 1040, 950, 876, and 857 cm^{-1}; HRMS *m/z* 636.2815 (100%, M^+, $C_{38}H_{40}N_2O_7$, 3.2 ppm error), 462.1873 (7, $C_{27}H_{28}NO_6$, 9.5), 397.1744 (7, $C_{22}H_{25}N_2O_5$, 4.8), 239,1048 (1, $C_{16}H_{15}O_2$, 9.9), 205.073 (18, $C_{11}H_{11}NO_3$, 2.2), 192.1015 (51, $C_{11}H_{14}NO_2$, 5.1), 175.0628 (95, $C_{10}H_9NO_2$, 3.2) 149.0589 (2, $C_9H_9O_2$, 9.1), 107.0512 (22, C_7H_7O, 14.1); ^1H and ^{13}C NMR see Table 1.

***O*-Methyllongiberine (2):** amorphous; $[\alpha]^{24}_D$ +31 ° (*c* 0.21, MeOH); CD (*c* 4.3 × 10^{-3} M, MeOH) (deg) $[\theta]_{304}$ 0, $[\theta]_{285}$ +17 200, $[\theta]_{274}$ 0, $[\theta]_{266}$ −8400 (sh), $[\theta]_{246}$ −66 500, $[\theta]_{237}$ 0, and $[\theta]_{221}$ +77 400; UV (MeOH) λ_{max} (log ϵ) 282 (4.01), 242 (sh, 4.42) and 220 (end 4.82) nm and no change in 0.01 N KOH; IR ($CHCl_3$) ν_{max} 3010, 2940, 2803, 1610, 1510, 1470, 1422, 1202, 1100, 1067, 873 and 857 cm^{-1}; HRMS *m/z* 650.299 (100, $C_{39}H_{42}N_2O_7$, dev 0.7 mmu), 476.2052 (10, $C_{28}H_{30}NO_6$, −2.1), 411.2136 (9, $C_{23}H_{27}N_2O_5$, 21.6), 192.0978 (11, $C_{11}H_{14}NO_2$ −4.7), 174.0885 (39, $C_{11}H_{12}NO$, −3.4) and 106.0443 (17, C_7H_6O, 2.4); ^1H and ^{13}C NMR, see Table 1.

Longiberine acetate (3): Longiberine (**1**) (8 mg) was treated with Ac_2O in pyridine and the product purified as described,[1] with final purification on a Si gel (3 g) column with 1.0 and 1.5% MeOH in $CHCl_3$ to give 7 mg of **3**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (1H, dd, J = 8.0, 1.8 Hz, H-15′), 7.28 (1H, dd, J = 8.0, 2.2 Hz, H-14′), 6.72 (1H, s, H-9), 6.54 (1H, s, H-5′), 6.36 (1H, dd, J = 8.2, 2.2 Hz, H-12′), 6.28 (1H, s, H-12), 6.22 (1H, dd, J = 8.2, 1.8 Hz, H-11′), 5.99 (1H, s, H-8′), 3.92 (3H, s, MeO-10), 3.74 (3H, s, MeO-3), 3.49 (3H, s, MeO-6′), 3.26 (3H, s, MeO-2), 2.62 (3H, s, MeN-2′) and 2.33 (3H, s, AcO-4); NOED δ 2.33 (AcO-4) relaxed to 3.74 (MeO-3, 0.5%).

Methylation of Longiberine (1). Longiberine (**1**) (41 mg) in 5 mL of MeOH was treated with CH_2N_2 in Et_2O prepared from 1.5 g of Diazald (Aldrich) and 0.4 g of KOH. After 1 week, the residue was passed through neutral Al_2O_3 (6 g) with $CHCl_3$ and 1% MeOH in $CHCl_3$ to give 40 mg of a pale yellow solid identical (TLC, UV, $[\alpha]_D$, and ^1H NMR) with **2** isolated from the plant.

***O*-Ethyllongiberine (4):** Longiberine (**1**) (150 mg) in 5 mL of MeOH was treated for 5 days with diazoethane in Et_2O prepared from 2 g of *N*-nitrosoethylurea and 5 mL of 50% aqueous KOH. The mixture was chromatographed on Si gel (50 g) with $CHCl_3$ and 1% MeOH in $CHCl_3$ to give 85 mg of **4**: ^1H NMR (90 MHz; $CDCl_3$) δ 4.05 (2H, CH_3CH_2O) and 1.38 (3H, CH_3CH_2O).

Na/NH_3 Cleavage of *O*-Ethyllongiberine (4). *O*-Ethyllongiberine (**4**) (80 mg) in 6 mL of THF was reacted with Na (180 mg) in liquid NH_3 (20 mL) at −30 to −50 °C, and the products separated as described.[7] The nonphenolic fraction (14 mg) yielded unidentified products, and the phenolic fraction (18 mg) after Si gel chromatography with $CHCl_3$, 2% and 4% MeOH in $CHCl_3$ gave from the last solvent 10 mg of a yellow solid: $[\alpha]^{24}_D$ +86° (*c* 0.76, MeOH); CD (*c* 6.0 × 10^{-3} M, MeOH) (deg) $[\theta]_{290}$ +10 800, $[\theta]_{278}$ 0, $[\theta]_{276}$ −2910, $[\theta]_{262}$ 0, and $[\theta]_{230}$ +44 000; with TLC, IR, and ^1H NMR identical with an authentic sample of (+)−(*S*)-*N*-methylcoclaurine (**5**).[10]

Isolation of Thalidezine (6). The phenolic Et_2O-soluble alkaloid fraction (4.05 g) from the Macheta collection gave from Me_2CO−hexane 1.8 g of crystalline **6**, mp 158 °C. The mother liquor residue was chromatographed on Si gel (50 g) with $CHCl_3$ and MeOH−$CHCl_3$ mixtures of 0.5, 1, 2, 5, 10, and 20% to give 0.76 g of **6**, R_f 0.41 on TLC with PhMe−Me_2CO−NH_4-OH (25:25:1).

Thalidezine acetate (7): Thalidezine (**6**) (200 mg) was treated with Ac_2O (5 mL) and pyridine (2 mL) for 16 h at ambient temperature, evaporated with aid of PhMe, and chromatographed on Si gel (6 g) with $CHCl_3$ (100 mL) and 2% MeOH in $CHCl_3$ (50 mL) to give 190 mg of acetate **7**: HRMS *m/z* 680.3105 (74%, $C_{40}H_{44}N_2O_8$, −0.7 mmu), 453.2012 (100, $C_{25}H_{29}N_2O_6$, 1.4); ^1H NMR (90 MHz, $CDCl_3$) δ 7.36 (1H, dd, J = 8.3, 1.9 Hz, H-11′), 7.14 (1H, dd, J = 8.3, 2.2 Hz, H-12′), 6.85 (2H, br s, H-14 and H-15), 6.79 (1H, dd, J = 8.3, 2.2 Hz, H-14), 6.55 (1H, br s, H-11), 6.52 (1H, s, H-5′), 6.30 (1H, dd, J = 8.3, 1.9 Hz, H-15′), 6.01 (1H, s, H-8′), 3.93 (3H, s, MeO-13), 3.70 (3H, s, MeO-6), 3.36 (3H, s, MeO-6′), 3.24 (3H, s, MeO-7), 2.64 (3H, s, MeN-2′), 2.31 (3H, s, Ac-5), 2.29 (3H, s, MeN-2).[26]

Dinorthalidezine (*N,N′*-didemethylthalidezine) acetate (9): Thalidezine acetate (**7**) (106 mg), PhH (10 mL), and trichloroethyl chloroformate (99 mg, 2.2 equiv.)[17] were refluxed for 1.5 h, another 45 mg of reagent was added and refluxed overnight. The residue, after evaporation under vacuum, was chromatographed on Si gel (5 g) with $CHCl_3$ (30 mL) and 0.5% MeOH in $CHCl_3$ to give 92 mg of the dicarbamate **8** of which 36 mg in 90% HOAc (1 mL) was stirred with activated Zn powder (36 mg) for 2 h. The mixture was filtered and the residue washed with H_2O. The combined filtrate and wash were basified with NH_4OH to pH 9 and extracted with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ residue was purified by preparative TLC on Si gel (20 × 20 cm^2, 0.75 mm) with $CHCl_3$−MeOH−NH_4OH (93:7:1) to give, from the major band, 15 mg of **9**: $[\alpha]^{25}_D$ +200° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600−3200, 3000, 2930, 2830, 1760, 1605, 1582, 1505, 1455, 1420, 1255, 1225−1190, 1123, 1010, 960, 873, and 830 cm^{-1}; HRMS *m/z* 652.2816 (M^+, $C_{38}H_{40}N_2O_8$, −3.1 mmu); FABMS (glycerol) *m/z* 653 (27, MH^+), 611 (45, $M^+ - CH_2CO$), 93 (100); ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, dd, J = 8.2, 2.0 Hz, H-11′), 7.17 (1H, dd, J = 8.2, 2.5 Hz, H-12′), 6.88 (1H, d, J = 8.1 Hz, H-14), 6.85 (1H, dd, J = 8.2, 2.5 Hz, H-14′), 6.75 (1H, dd, J = 8.1, 1.8 Hz, H-15), 6.52 (1H, s, H-5′), 6.423 (1H, d, J = 1.8 Hz, H-11), 6.419 (1H, dd, J = 8.0, 2.0 Hz, H-15′), 6.02 (1H, s, H-8′), 4.27 (1H, dd, J = 11.1, 5.4 Hz, H-1′), 4.03 (1H, d, J = 9.7 Hz, H-1), 3.96 (3H, s, MeO-13), 3.73 (3H, s, MeO-6), 3.40 (3H, s, MeO-6′), 3.34 (3H, s, MeO-7), 3.30 (1H, dd, J = 11.4, 5.0 Hz, H-9β′), 3.04 (1H, dd, J = 11.4, 11.4 Hz, H-9α′) 2.79 (1H, dd, J = 13.6, 10.4 Hz, H-9β), 2.60 (1H, d, J = 13.2 Hz, H-9α), 2.32 (3H, s, Ac-5).[26]

Preparation of Longiberine (1). Compound **9** (15 mg), 37% HCHO (0.5 mL) MeOH (0.8 mL), and conc HCl (0.3 mL) were refluxed for 1 h, then HCHO (0.4 mL) and HCl (0.2 mL) were added and refluxed for 1 h. H_2O (20 mL) was added, then NH_4OH to pH 9 and extracted with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ phase yielded 11 mg of N′-norlongiberine, which was immediately treated with HCHO (0.4 mL), HCO_2H (0.4 mL), and MeOH (0.5 mL) and refluxed for 1 h. The mixture was evaporated under vacuum and the residue diluted with H_2O (20 mL), basified with NH_4OH to pH 9.0, and extracted with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ residue was separated by preparative TLC on Si gel (20 × 20 cm^2, 0.75 mm) with $CHCl_3$−MeOH−NH_4OH (92:8:1). The 4.5 mg of product showed identical physical properties (TLC, IR, ^1H NMR, $[\alpha]_D$, and CD) with natural **1**.

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