O-isop, 72161-10-5; **15**, 72161-11-6; **17**, 72161-12-7; **17** 2',3'-O-isop, 72161-13-8; **18**, 72161-14-9; **20**, 72161-15-0; **22**, 62404-67-5; **23**, 72161-16-1; **24**, 72161-17-2; oxamidohydrazide, 515-96-8; benzoylhydrazine, 613-94-5; acetylhydrazide, 1068-57-1; semicarbazide hydrochloride, 563-41-7; aminoguanidine dihydrochloride, 55457-88-0; hydrazine, 302-01-2; thiosemicarbazide, 79-19-6; aminomalonamide hydrochloride, 57471-66-6; diethyl aminomalonate hydrochloride, 13433-00-6.

The Structure of Thalibrunine, a Reinvestigation and Revision[1]

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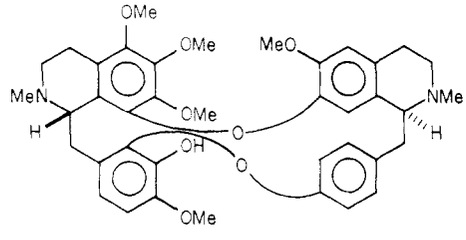
Evidence is presented that thalibrunine has structure **2** and is the 2'-hydroxy derivative of hernandezine. Ceric ammonium nitrate oxidation of thalibrunine acetate (**3**) gave 2-methoxy-4-acetoxy-4',5-diformyldiphenyl ether (**6**), which was also prepared synthetically from 2-methoxy-4-(benzyloxy)phenol and 4-bromobenzaldehyde in four steps, thereby firmly establishing the tail-to-tail diphenyl ether unit. Anomalous products, *o*-cresol **14** and methyl ether **15**, obtained on $NaBH_4$ reduction of the neutral fraction from the ceric ammonium nitrate oxidation of thalibrunine acetate (**3**), were characterized from studies on model compounds. The cryptophenolic nature of thalibrunine (**2**) is due to the strong hydrogen bond between the phenolic group and the unshared electron pair of the tertiary nitrogen. The hydrogen-bonded structure persists in the Na/NH_3 cleavage products (e.g., **17**), lacking the head-to-head diphenyl ether group. The H bond in these products can be broken by protonation, a feature not observed for thalibrunine. CD spectral data reflecting those changes and supporting the *S,S* configuration are presented. Thalibrunimine should have its structure revised to **18**.

Thalibrunine, a bis(benzyltetrahydroisoquinoline) alkaloid from *Thalictrum rochebrunianum* Franc. and Sav. (family Ranunculaceae) was first reported[2] in 1966, and structure **1** was proposed[3] for it in 1974. The head-to-head



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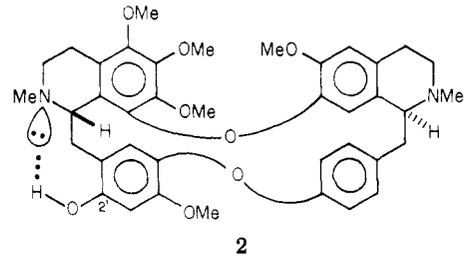

2

or bis(tetrahydroisoquinoline) ether-linked portion was firmly established by direct comparison of the reduced photooxidized product from thalibrunine with synthetically prepared material. The tail-to-tail, or ether-linked bis(benzyl), portion, on the other hand, rests only on biogenetic consideration and the Gibbs test for para-unsubstituted phenols.[4] Availability of additional plant material gave a supply of thalibrunine that made possible a further study of this alkaloid and also provided a mixture of crude bases from which four new thalibrunine-related alkaloids were isolated. These are reported in the following paper.[5]

The first piece of information placing structure **1** in doubt was the ^1H NMR spectrum taken in acetone-d_6 under pulsed-signal Fourier transform conditions.[6] The aromatic region which was resolved more clearly and contained virtually no background noise did not show the outer less intense peaks of a typical AB quartet expected for the ortho protons of the trioxygenated benzylic ring. Also, an ABXY pattern for the monooxygenated benzylic ring was observed as a double set of AB quartets with additional splitting. The remaining peaks were four distinct one-proton singlets. This would require para protons in the trioxygenated benzylic ring, for which six structures can be theoretically considered. Two structures each are possible for three different ring systems, 17-, 18-, and 19-membered. The latter possibility is biogenetically least likely, since the diphenyl ether would involve the para position of each benzylic ring, and none of the six structures would possess an unsubstituted position para to the phenolic hydroxyl. Rechecking the Gibbs test on a scrupulously purified sample of thalibrunine produced a negative result,[7] invalidating the earlier evidence that led to proposal of structure **1**.

The ^1H NMR spectrum of thalibrunine taken in $CDCl_3$ or acetone-d_6 shows a broad one-proton signal considerably downfield (δ 12.4 and 11.9, respectively) that is characteristic of hydrogen-bonded phenolic hydroxyls.[8] These signals do not readily exchange with D_2O, as was observed.

(1) Alkaloids of Thalictrum. 28. For part 27, see W.-T. Liao, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, **41**, 271 (1978).
(2) H. H. S. Fong, J. L. Beal, and M. P. Cava, *Lloydia*, **29**, 94 (1966).
(3) M. P. Cava, J. M. Saá, M. V. Lakshmikantham, M. J. Mitchell, J. L. Beal, R. W. Doskotch, A. Ray, D. C. DeJongh, and S. R. Shrader, *Tetrahedron Lett.*, 4259 (1974).
(4) The reliability of the test can be improved by the procedure of F. E. King, T. J. King, and L. C. Manning [*J. Chem. Soc.*, 563 (1957)] over that of H. D. Gibbs [*J. Biol. Chem.*, **72**, 653 (1927)]. A referee has requested that a statement be included suggesting strongly that the Gibbs test in any form be abandoned. Our experience would suggest that positive results should not be accepted without other corroborating evidence.
(5) J. Wu, J. L. Beal and R. W. Doskotch, *J. Org. Chem.* following paper in this issue.
(6) In acetone-d_6 or methanol-d_4—but not in $CDCl_3$—the aromatic region is composed of almost total first-order patterns, and because it is more spread out, it is readily analyzable. Double-resonance experiments substantiated the pattern relationships.
(7) The earlier positive test must have been due to a very minor contaminant whose presence was not indicated by spectral or TLC examination.
(8) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, New York, 1969, Chapters 3-7.

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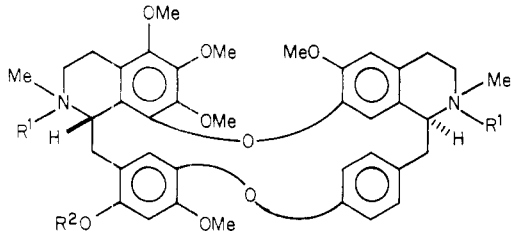
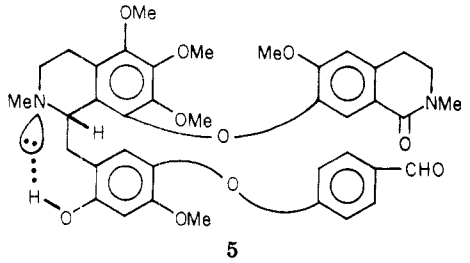
Examination of Dreiding models showed that an intramolecular hydrogen bond could be formed with the electron pair of the tertiary nitrogen to give an unstrained seven-membered ring only when the phenolic group was located ortho to the benzylic carbon. The diphenyl ether must then be placed para to the phenolic hydroxyl, resulting in structure **2** as the best fit for the available data. To confirm this, we subjected thalibrunine to degradations that would provide the tail-to-tail diphenyl ether unit with the substitution pattern intact, but the phenolic group required protection.

O-Methylation of thalibrunine with diazomethane does not occur,[3] while with methyl iodide and base a mixture of products forms, with N-methylation being the main reaction. Contrary to the literature report,[3] thalibrunine acetate (**3**), mp 236–7 °C, can be prepared from acetic



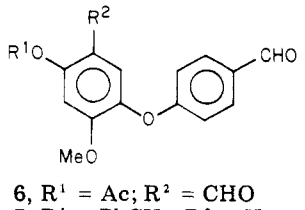
3, R^1 = no substituent, R^2 = Ac
4, R^1 = Me, R^2 = Ac, plus $2I^-$ and nitrogens with positive charge

anhydride and pyridine but cannot be exposed to hydroxylic solvents, which rapidly cause its hydrolysis. The acetate **3** gives cleanly the dimethiodide salt **4**. Oxidation of acetate **3** with $KMnO_4$ in acetone[9] produced secothalibrunine aldehydo lactam **5**, characterized from spectral



5

data. The acetate was hydrolyzed, undoubtedly, upon workup. More vigorous conditions gave complex mixtures. The desired cleavage at both benzylic positions was accomplished by oxidation with ceric ammonium nitrate, a reagent recently described for degrading bis(benzyltetrahydroisoquinoline) alkaloids.[10] However, in order to obtain the tail-to-tail fragment **6**, the acetate buffer had to



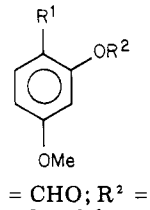
6, R^1 = Ac; R^2 = CHO
7, R^1 = $PhCH_2$; R^2 = H
8, R^1 = $PhCH_2$; R^2 = CHO
9, R^1 = H; R^2 = CHO

be eliminated and acetone used as solvent. At that, the yield was only 6%. Higher yields of the comparable fragment were obtained from other alkaloids,[10] e.g., 94% from hernandezine, but sodium borohydride reduction is required to convert the mixture of oxidation products to a single bis(benzyl) alcohol. This reduction step had to be omitted, in our case, as anomalous products, to be dealt with later, were formed.

Examination of the ^1H NMR spectrum of dialdehyde **6** supported the proposed substitution pattern; the aromatic region showed two one-proton singlets at δ 6.83 and 7.60, and a four-proton AA'BB' pattern that appeared as a further split AB quartet with δ_A 7.02 and δ_B 7.84, as assigned by a first-order approximation with major peaks separated by 8.5 Hz. The synthesis of dialdehyde **6** by a short route was not realized because the Ullmann reaction of the benzyl ether of 2-hydroxy-4-methoxy-5-bromobenzaldehyde[11] with *p*-hydroxybenzaldehyde failed under a variety of conditions, but an alternate pathway was successful.

The Ullmann reaction[12] of 2-methoxy-4-(benzyloxy)-phenol (prepared from methoxyhydroquinone) with *p*-bromobenzaldehyde gave 2-methoxy-4-(benzyloxy)-4'-formyldiphenyl ether (**7**), which underwent the Vilsmeier formylation[13] to dialdehyde **8**, but removal of the benzylic group was not successful with the usual acidic reagents. Cleavage was accomplished with trimethylsilyl iodide,[14] and acetylation of phenol **9** gave a product identical with the dialdehyde acetate **6** obtained from thalibrunine acetate (**3**). Thalibrunine is therefore 2'-hydroxyhernandezine and has structure **2**. A similar change in structure is required for thalibrunimine (**18**) which was directly related to thalibrunine.[15]

When sodium borohydride reduction was applied to the ceric ammonium nitrate products from thalibrunine acetate (**3**), one of the major components lacking nitrogen gave spectra at variance with the expected bis(benzyl) alcohol structure. For example, the ^1H NMR spectrum contained only a single two-proton singlet for the benzylic protons at δ 4.63, yet the aromatic region showed the required AA'BB' "quartet" and two one-proton singlets. In addition, two three-proton peaks at δ 3.72 and 2.14 could be assigned to a methoxy and an acetate, respectively, but the IR spectrum lacked carbonyl absorption. The peak at δ 2.14 was clearly not from an acetate but could be from an aryl methyl. Additional work was not possible with the small amount of material available, thus requiring studies with model compounds. 2-Acetoxy-4-methoxybenzaldehyde (**10**), for example, on treatment with sodium

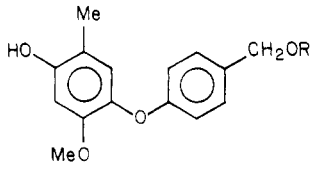


10, R^1 = CHO; R^2 = Ac
11, R^1 = Me; R^2 = H
12, R^1 = CHO; R^2 = H
13, R^1 = CH_2OMe; R^2 = H

borohydride gave a good yield of 2-hydroxy-4-methoxytoluene (**11**), while 2-hydroxy-4-methoxybenzaldehyde (**12**) was converted to 2-hydroxy-4-methoxybenzyl methyl ether (**13**). Consequently, the anomalous products from thalibrunine acetate (**3**) could be formulated as the substituted

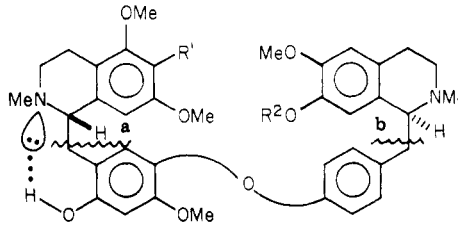
(9) M. Shamma and J. E. Foy, *Tetrahedron Lett.*, 2249 (1975).
(10) I. R. C. Bick, J. B. Bremner, M. P. Cava, and P. Wiriyachitra, *Aust. J. Chem.*, 31, 321 (1978).
(11) P. B. M. Murti and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect A*, 16, 135 (1942).
(12) Reaction conditions were adapted from T. Kametani and K. Fukumoto, *J. Chem. Soc.*, 6141 (1964).
(13) M. R. de Maheas, *Bull. Soc. Chim. Fr.*, 1989 (1962).
(14) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, 42, 3761 (1977).
(15) J. M. Saá, M. V. Lakshmikanthan, M. J. Mitchell, M. P. Cava, and J. L. Beal, *Tetrahedron Lett.*, 513 (1976).

o-cresol **14** and its methyl ether **15**.

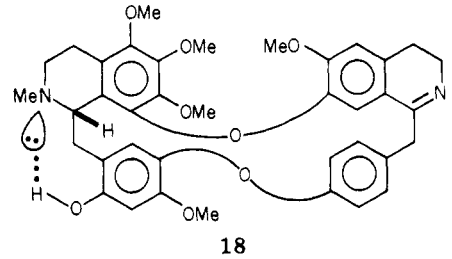


14, R = H
15, R = Me

The *S,S* stereochemistry for thalibrunine (**2**) rests on the identification of (*S*)-*N*-methylcoclaurine as a sodium–ammonia cleavage product corresponding to the right-hand benzyltetrahydroisoquinoline unit (as in **2**) and the very similar circular dichroism (CD) spectra of thalibrunine (**2**) and hernandezine, the latter with known stereochemistry.[3,16] The left-hand benzyltetrahydroisoquinoline unit, unfortunately, had not given an isolatable fragment. Sodium–ammonia cleavage of thalibrunine (**2**) was repeated, and study of one of the cleavage products provided further evidence for the *S,S* configuration. In addition to the already reported dihydrothalibrunine,[3] now to be formulated as **16**, another compound was isolated that was assigned the structure of 6-demethoxydihydrothalibrunine (**17**) on the basis of spectral data. The ^{1}H NMR spectrum showed only four methoxyls and an additional aromatic proton as part of a tightly coupled AB quartet ($J \approx 2.5$ Hz) characteristic of meta protons. The mass spectral peak at *m/e* 206 was in accord with fragment **17a** bearing those protons. Loss of the 6-methoxy group during sodium–ammonia reduction is well documented for 5,6,7-trialkoxytetrahydroisoquinolines.[17]



16, R^1 = OMe; R^2 = H
17, R^1 = R^2 = H



18

The CD spectrum of 6-demethoxydihydrothalibrunine (**17**) taken under neutral conditions exhibits three maxima, two negative at 298 and 276 nm and one positive at 240 nm, yet related compounds with one tail-to-tail diphenyl ether bridge and *S,S* configuration such as thalibrine,[18] thalirugidine,[19] and thalistyline[18b] show generally two positive maxima, one near 285 nm and the other around 230 nm. The *R,R* alkaloids show the opposite pattern, and the conversion of the tertiary uncharged nitrogen to a quaternary charged nitrogen does not change the sign of the Cotton effects, e.g., dauricine and dauricine dimethiodide.[20] However, the CD spectrum of 6-demethoxydihydrothalibrunine (**17**) in 0.02 N methanolic HCl reverted to the expected *S,S* pattern with $[\theta]_{288}$ +19 500 and $[\theta]_{227}$ +77 500. Apparently protonation of the tertiary nitrogen results in elimination of the strong H bond between the phenolic group and the isoquinoline unit, thereby causing the molecule to assume the conformation typical of the more normal tail-to-tail ether-linked alkaloids.

Although the evidence is supportive of thalibrunine (**2**) and hernandezine (2′-deoxythalibrunine) possessing the *S,S* configuration, the CD spectra are not identical.[16] Protonation of thalibrunine does not alter the relative signs of the maxima, yet thalibrunine acetate (**3**) does have a CD curve more like that of hernandezine with the Cotton-effect peak at 274 nm now positive. Apparently, acetylation does allow for alteration of the conformation of thalibrunine to more closely resemble hernandezine, yet acid conditions fail to disrupt the H-bonded structure when two diphenyl ether linkages are present.

Experimenal Section[21]

Extraction of *T. rochebrunianum* Roots and Initial Partitioning. The dried and powdered roots of plant material (10.9 kg), grown in the College of Pharmacy Medicinal Plant Garden, were percolated to exhaustion with 140 L of EtOH. The residue, after evaporation of solvent under reduced pressure, was divided into the various alkaloid fractions as reported.[22] The crude tertiary Et_2O-soluble nonphenolic alkaloid fraction weighed 85.7 g.

Isolation of Thalibrunine (2). A 50-g sample of the nonphenolic alkaloid fraction was chromatographed on 1.5 kg of silica gel (E. Merck) with $CHCl_3$ as initial eluant followed by $CHCl_3$ with increasing amounts of MeOH. The 6% MeOH in $CHCl_3$ effluent gave 6.7 g of thalibrunine (**2**), mp 172–174 °C from MeOH. The IR, UV, ^{1}H NMR (in $CDCl_3$), and CD spectra were previously reported.[2,3] The ^{1}H NMR peaks (in acetone-d_6) are at δ 2.46 and 2.56 (2 s, 2 NMe), 3.15, 3.38, 3.73, 3.79, and 3.82 (5 s, 5 OMe), 5.89, 6.37, 6.46, and 6.64 (4 s, 4 ArH), the split ABXY pattern of the disubstituted phenyl ring, each a one-proton doublet of doublets at 6.16 (J = 2.0, 8.3 Hz), 6.36 (J = 2.4, 8.3 Hz), 7.16 (J = 2.4, 8.1 Hz), and 7.37 (J = 2.0, 8.1 Hz), and 11.9 (br s, OH).

Thalibrunine Acetate (3). Thalibrunine (**2**, 100 mg) was stirred with 2 mL of pyr and 0.5 mL of Ac_2O at ambient temperature for 3 h. The mixture was evaporated to dryness under reduced pressure and the residue partitioned between $CHCl_3$ and H_2O. The dried (Na_2SO_4) $CHCl_3$ layer gave a residue (102 mg) on evaporation that crystallized from EtOAc as colorless needles of **3** (85 mg, 80%): mp 236–237 °C; $[\alpha]^{22}_D$ +161° (*c* 0.26, CH_3CN); CD (concentration 1.0 × 10^{-3} M, CH_3CN) $[\theta]_{287}$ + 46 000, $[\theta]_{266}$ +8000, $[\theta]_{245}$ −77 000, and $[\theta]_{216}$ +380 000; IR ($CHCl_3$) ν_{max} 1742 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.26 (s, OAc), 2.30 and 2.63 (2 s, 2 NMe), 3.17, 3.33, 3.77, 3.80, and 3.90 (5 s, 5 OMe), 5.96, 6.48,

(16) The CD spectra of thalibrunine and hernandezine were redetermined on an upgraded instrument and found to have values $[\theta]_{293}$ +62 000, $[\theta]_{273}$ −28 000, $[\theta]_{245}$ −124 000, and $[\theta]_{222}$ +244 000 for the former and $[\theta]_{288}$ +28 000, $[\theta]_{265}$ +6700, $[\theta]_{246}$ −52 000, and $[\theta]_{222}$ +300 000 for the latter. The earlier reported negative maximum at about 265 nm is correctly positive; thus the absorption in that region differs in sign for the two alkaloids.

(17) M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh, and S. R. Shrader, *J. Chem. Soc., Chem. Commun.*, 7 (1966); M. Shamma, R. J. Shine, and B. S. Dudock, *Tetrahedron*, **23**, 2887 (1967); W.-N. Wu, J. L. Beal, R.-P. Leu, and R. W. Doskotch, *Lloydia*, **40**, 384 (1977).

(18) (a) J. M. Saá, M. J. Mitchell, M. P. Cava, and J. L. Beal, *Heterocycles*, **4**, 753 (1976); (b) W.-N. Wu, J. L. Beal, R.-P. Leu, and R. W. Doskotch, *Lloydia*, **40**, 281 (1977). The CD curve in MeOH showed $[\theta]_{285}$ +17 400, $[\theta]_{248}$ −2600, and $[\theta]_{223}$ +90 000; the weakest maximum appearing at ~250 nm is not always observed; see the examples in ref 19.

(19) W.-N. Wu, J. L. Beal, E. H. Fairchild, and R. W. Doskotch, *J. Org. Chem.*, **43**, 580 (1978).

(20) *R,R*-Dauricine has ellipticities at $[\theta]_{285}$ −14 800 and $[\theta]_{225}$ −70 200 and the dimethiodide at $[\theta]_{280}$ −15 400 and $[\theta]_{226}$ −131 000. Note that no maximum is observed near 250 nm for these compounds.

(21) The instruments and conditions used for collecting data are given in ref 19. Herbarium specimens are on file. ^{1}H NMR spectra were taken at 90 MHz unless stated otherwise.

(22) J. Wu, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, **40**, 294 (1977).

6.60, and 6.63 (4 s, 4 ArH), split ABXY pattern at 6.27 (J = 1.9, 8.3 Hz), 6.78 (J = 2.5, 8.3 Hz), 7.13 (J = 2.5, 8.0 Hz), and 7.35 (J = 1.9, 8.0 Hz).

Anal. Calcd for $C_{41}H_{46}N_2O_9$: C, 69.28; H, 6.52; N, 3.94. Found: C, 69.00; H, 6.53; N, 3.49.

***N,N'*-Dimethylthalibrunine Acetate Diiodide (4).** Thalibrunine acetate (**3**, 100 mg) was treated with 2 mL of MeI in 20 mL of Me_2CO for 24 h. The crystalline precipitate of product **4** as colorless cubes (131 mg, 85%) was collected by filtration: mp 232–234 °C, $[\alpha]^{22}_D$ +210° (c 0.55, MeOH); IR (Nujol) ν_{max} 1763 cm^{-1} (C=O); ^{1}H NMR (Me_2SO-d_6, 370 K) δ 2.35 (s, Ac), 2.98, 3.08, 3.16, and 3.46 (4 s, 4 Me), 3.18, 3.43, 3.73, 3.82, and 3.84 (5 s, 5 OMe), 6.05, 6.70 and 6.90 (double intensity) (3 s, 4 ArH), split ABXY pattern with multiplets centered at 6.48, 6.98, 7.03, and 7.53.

Anal. Calcd for $C_{43}H_{52}N_2O_9I_2 \cdot CH_3COCH_3 \cdot 2H_2O$: C, 50.75; H, 5.73; N, 2.57; I, 23.26. Found: C, 50.39; H, 5.67; N, 2.30; I, 23.25.

$KMnO_4$ Oxidation of Thalibrunine Acetate (3). Acetate **3** (100 mg) dissolved in 20 mL of Me_2CO was treated with 100 mg of $KMnO_4$, portionwise over 1 h, while being stirred. After an additional 6 h, 10 mL of MeOH was added and the MnO_2 removed by filtration. The filtrate was concentrated to a few milliliters and partitioned between 0.1 N HCl and $CHCl_3$. The $CHCl_3$-soluble residue (55 mg) was chromatographed on 2 g of silica gel with $CHCl_3$ and increasing amounts of MeOH in $CHCl_3$ as eluants. The 5% MeOH in $CHCl_3$ eluate yielded 23 mg of the aldehydo lactam **5** as an amorphous solid: $[\alpha]^{22}_D$ −33° (c 0.38, MeOH); IR ($CHCl_3$) ν_{max} 1640 (lactam), 1695 cm^{-1} (CHO); ^{1}H NMR ($CDCl_3$) δ 2.47 and 3.03 (2 s, 2 NMe), 3.66, 3.68 (double intensity), 3.88, and 3.91 (4 s, 5 OMe), 6.44, 6.49, 6.54, and 7.18 (4 s, 4 ArH), AA'BB' quartet at 6.88 and 7.78 (2 H each, J_{AB} = 8.9 Hz), 9.90 (s, CHO); mass spectrum (relative intensity) m/e 698.2854 (0.6, M$^+$, $C_{39}H_{42}N_2O_{10}$ requires m/e 698.2839), 441 (100, $C_{24}H_{29}N_2O_6$), 257 (4), 235 (0.9), 206 (3).

Ceric Ammonium Nitrate Oxidation of Thalibrunine Acetate (3). A. Without Reduction of Neutral Products. Acetate **3** (200 mg) in 100 mL of Me_2CO was treated with 1.2 g of ceric ammonium nitrate, added portionwise over 30 min with stirring at ambient temperature. After 1 h the reaction mixture was filtered, and the filtrate was concentrated to a few milliliters and then partitioned between $CHCl_3$ and 0.1 N HCl. The dried (Na_2SO_4) $CHCl_3$ extract on evaporation to dryness left a residue (91 mg) that was separated by preparative TLC [silica gel HF 254, 0.6 mm, $CHCl_3$–MeOH (98:2), developed twice]. The band with R_f 0.34 was removed, extracted with $CHCl_3$, and rechromatographed with hexane–Et_2O (1:1) (developed twice) as solvent. The band with R_f 0.53 yielded 5 mg of the diphenyl ether dialdehyde **6**, identical by TLC and IR and ^{1}H NMR spectra with the synthetically prepared material (vide infra).

The 0.1 N HCl extract (100 mL) was basified with NH_4OH, diluted with 10 mL of MeOH, treated portionwise with 100 mg of $NaBH_4$ over 30 min, and then refluxed on a steam bath after another 30 min. The cooled reaction mixture was diluted with 40 mL of H_2O and extracted with $CHCl_3$ from which 89 mg of residue was recovered. Chromatography on silica gel (6 g) with $CHCl_3$ and mixtures of MeOH and $CHCl_3$ gave from the 4% MeOH in $CHCl_3$ effluent 75 mg of the diamine from the head-to-head-linked tetrahydroisoquinoline portion, identical in physical properties with those reported[10] and on direct comparison with the diamine obtained in like manner from hernandezine.

B. With Reduction of Neutral Products. Oxidation of 79 mg of thalibrunine acetate (**3**) as stated above and separation of the products gave a neutral fraction that was dissolved in 8 mL of MeOH and treated portionwise with 200 mg of $NaBH_4$ over 30 min. After an additional 30 min, 10 mL of H_2O was added, and the solution was refluxed 15 min on the steam bath. Removal of the solvent by evaporation gave a residue that was triturated with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ residue (19 mg) showed on TLC (silica gel G, $CHCl_3$) two major spots, R_f 0.15 and 0.03. Chromatography on 2 g of silica gel with $CHCl_3$ gave 5.3 mg (yield 19%) of first-eluted product **15**: IR ($CHCl_3$) ν_{max} 3600 (OH), 3350 (associated OH), 1100 cm^{-1} (double intensity, C–O–C sym stretching); ^{1}H NMR ($CDCl_3$) δ 2.14 (s, $ArCH_3$), 3.38 (s, CH_2OCH_3), 3.72 (s, OMe), 4.40 (s, CH_2OCH_3), 6.48 and 6.80 (2 s, 2 ArH), AA'BB' "quartet" at 6.82 and 7.26 (J_{AB} = 8.9 Hz), 5.0 (s, OH, D_2O exchangeable); mass spectrum (relative intensity) m/e 274.1213 (100, $C_{16}H_{18}O_4$ requires m/e 274.1205), 258 (17), 243 (53), 227 (5), 137 (3), 122 (3), 121 (10), 107 (5), 91 (3), 90 (3), 89 (5), 77 (5).

The second-eluted material was the benzyl alcohol **14** (6 mg, yield 20%): IR ($CHCl_3$) ν_{max} 3600 (OH), 3370 (associated OH), 1105 cm^{-1} (single intensity, C–O–C sym stretching); ^{1}H NMR ($CDCl_3$) δ 2.15 (s, $ArCH_3$), 3.72 (s, OMe), 4.63 (s, CH_2OH), 6.50 and 6.79 (2 s, ArH), AA'BB' "quartet" at 6.87 and 7.26 (J_{AB} = 8.9 Hz), 1.9 (br, OH, D_2O exchangeable); mass spectrum (relative intensity) m/e 260.1052 (100, $C_{15}H_{16}O_4$ requires m/e 260.1048), 243 (7), 227 (5), 215 (8), 200 (5), 153 (5), 142 (5), 125 (2), 123 (2), 122 (2), 107 (5), 89 (4), 77 (9), 65 (3).

4-(Benzyloxy)-2-methoxyphenol. Methoxyhydroquinone (15 g), benzyl chloride (12 mL), anhydrous K_2CO_3 (30 g), and anhydrous Me_2NCHO were heated at 160–165 °C for 1.5 h, diluted with 500 mL of H_2O, and neutralized with 2 N HCl. Extraction with $CHCl_3$ (6 × 400 mL) gave an extract that after being washed with H_2O and dried (Na_2SO_4) left a 28.2-g brown residue that was chromatographed on silica gel (500 g) with benzene. Eluted first was 10.7 g of 2,5-bis(benzyloxy)anisole, mp 69–70 °C (benzene), followed by 6.2 g of 4-(benzyloxy)-2-methoxyphenol as a buff solid: mp 35–37 °C; TLC R_f 0.76 on a silica gel G with benzene; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.80 (s, OMe), 4.98 (s, $C_6H_5CH_2$), 5.28 (s, OH, lost in D_2O), 6.3–6.9 (3 H, ABX pattern), 7.2–7.6 (m, 5 H, $C_6H_5CH_2$).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.06; H, 6.18.

Treatment of the phenolic product with diazomethane gave a material identical (TLC, IR, NMR, and melting point) with authentic 1,2-dimethoxy-4-(benzyloxy)benzene prepared from 3,4-dimethoxyphenol (Aldrich), mp 52–53 °C from petroleum ether (lit.[23] mp 53–54 °C).

Ullmann Reaction of 4-(Benzyloxy)-2-methoxyphenol with 4-Bromobenzaldehyde. 2-Methoxy-4-(benzyloxy)phenol (1.12 g), 4-bromobenzaldehyde (0.925 g), Cu powder (0.32 g), anhydrous K_2CO_3 (0.35 g), and pyr (5 mL) were heated for 3 h at 160–170 °C. The cooled mixture was triturated with benzene, the extract filtered, and the filtrate washed with 10% aqueous NaOH and H_2O. The dried (Na_2SO_4) benzene layer gave a yellow-brown solid that on repeated crystallization from absolute EtOH afforded 0.54 g (yield 38%) of 2-methoxy-4-(benzyloxy)-4'-formyldiphenyl ether (**7**) as needles: mp 108–109 °C; IR ($CHCl_3$) ν_{max} 1693 cm^{-1} (CHO); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, OMe), 5.05 (s, CH_2), 6.55 (dd, J = 2.7, 8.5 Hz, A of ABX), 6.68 (d, J = 2.7 Hz, B of ABX), 7.00 (d, J = 8.5 Hz, X of ABX), AA'BB' "quartet" at 6.95 and 7.78 (J_{AB} = 8.9 Hz), 7.3–7.5 (m, 5 H, C_6H_5), 9.87 (CHO).

Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.01; H, 5.47.

2-Methoxy-4-(benzyloxy)-4',5-diformyldiphenyl Ether (8). To a mixture of $POCl_3$ (16 mg) and *N*-methylformanilide (30 mg) previously stirred for 45 min was added 33.4 mg of 2-methoxy-4-(benzyloxy)-4'-formyldiphenyl ether (**7**) over 30 min at ambient temperature. After being stirred an additional 2 h, the mixture was heated for 2 h at 80–85 °C, and then 10 mL of H_2O was added and stirring continued for 4 h. The mixture was taken up in Et_2O and the extract washed with H_2O and dried (Na_2SO_4). The extract residue (31 mg) was separated by preparative TLC (silica gel, 0.6 mm, $CHCl_3$, R_f 0.34) to give 27 mg (yield 75%) of diphenyl ether **8** that crystallized from absolute EtOH: mp 156–157 °C; IR ($CHCl_3$), ν_{max} 1687 cm^{-1} (CHO); ^{1}H NMR ($CDCl_3$) δ 3.82 (s, OMe), 5.24 (s, CH_2), 6.67 (s, H-3), AA'BB' "quartet" at 6.95 and 7.80 (J_{AB} = 8.9 Hz), 7.2–7.5 (m, 5 H, C_6H_5), 7.62 (s, H-6), 9.88 and 10.38 (2 s, 2 CHO).

Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01. Found: C, 72.79; H, 5.05.

2-Methoxy-4-hydroxy-4',5-diformyldiphenyl Ether (9). Diphenyl ether **8** (100 mg) in 5 mL of $CHCl_3$ was treated with 0.5 mL of Me_3SiI under N_2 at 55–65 °C (oil bath) for 2 h, and then 10 mL of MeOH was added. The residue remaining after evaporation of volatiles under reduced pressure was dissolved in Et_2O (100 mL) and extracted with H_2O, and the extract was dried (Na_2SO_4). Chromatography of the Et_2O residue on 3 g of silica gel with $CHCl_3$ gave 61 mg (yield 80%) of the phenolic diphenyl

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ether **9** as colorless crystals from absolute EtOH: mp 127–128 °C; IR ($CHCl_3$) ν_{max} 2900–3400 (intramolecular H-bonded OH), 1700 (CHO), 1655 cm^{-1} (CHO, H bonded); ^1H NMR ($CDCl_3$) δ 3.84 (s, OMe), 6.59 (s, H-3), 7.29 (s, H-6), AA'BB' "quartet" at 6.98 and 7.84 (J_{AB} = 8.9 Hz), 9.70 and 9.92 (2 s, 2 CHO), 11.53 (s, OH, lost in D_2O); mass spectrum (relative intensity) *m/e* 272.0693 (100), $C_{15}H_{12}O_5$ requires *m/e* 272.0685.

2-Methoxy-4-acetoxy-4',5-diformyldiphenyl Ether (6). Phenolic diphenyl ether **9** (15 mg) was stirred at ambient temperature for 24 h with 1 mL of pyr and 0.5 mL of Ac_2O. The mixture was evaporated to dryness at reduced pressure, the residue dissolved in 30 mL of $CHCl_3$, the solution extracted with H_2O (2 × 20 mL) and the extract dried (Na_2SO_4). The amorphous solid (15 mg) remaining after removal of solvent had the same mobility on TLC as the product from thalibrunine acetate (**3**) and had spectral properties consistent with structure **6**: IR ($CHCl_3$) ν_{max} 1775 (Ac C=O), 1694 cm^{-1} (CHO); ^1H NMR ($CDCl_3$) δ 2.41 (s, Ac), 3.86 (s, OMe), 6.83 (s, H-3), 7.59 (s, H-6), AA'BB' "quartet" at 7.01 and 7.84 (J_{AB} = 8.6 Hz), 9.92 and 9.96 (2 s, 2 CHO); mass spectrum (relative intensity) *m/e* 314 (1, M^+), 272.0691 (52, M – CH_2CO or $C_{15}H_{12}O_5$ which requires *m/e* 272.0685), 177 (9), 167 (12, $C_8H_7O_4$), 150 (12), 129 (10), 121 (12, $C_7H_5O_2$), 120 (54, $C_7H_4O_2$), 105 (100, C_7H_5O), 91 (40), 77 (60), 43 (73, CH_3CO).

2-Acetoxy-4-methoxybenzaldehyde (10). 2-Hydroxy-4-methoxybenzaldehyde (1.0 g) was stirred for 17 h with 8 mL each of pyr and Ac_2O and then quenched with 30 mL of H_2O. The mixture was extracted with $CHCl_3$ (3 × 40 mL) and the extract washed with H_2O and dried (Na_2SO_4). Removal of solvent and purification of the residue by preparative TLC (1.0 mm, silica gel GF, $CHCl_3$, developed twice, R_f 0.2) gave 897 mg (yield 70%) of an oil: IR ($CHCl_3$) ν_{max} 1694 (CHO), 1773 cm^{-1} (Ac); ^1H NMR ($CDCl_3$, 90 MHz) δ 2.33 (s, Ac), 3.79 (s, OMe), 6.57 (d, J = 2.5 Hz, H-3), 6.76 (dd, J = 2.5, 8.5 Hz, H-5), 7.66 (d, J = 8.5 Hz, H-6), 9.83 (s, CHO); ^{13}C NMR ($CDCl_3$) exactly as reported.[24]

$NaBH_4$ Reduction of 2-Acetoxy-4-methoxybenzaldehyde (10). To a solution of 0.8 g of $NaBH_4$ in 20 mL of MeOH at ambient temperature was added 160 mg of 2-acetoxy-4-methoxybenzaldehyde in 4 mL of MeOH. After 5 min, 25 mL of H_2O was added and the mixture extracted with $CHCl_3$ (3 × 40 mL). The dried (Na_2SO_4) extract on evaporation gave, quantitatively, 2-methyl-5-methoxyphenol (**11**): mp 38–40 °C (lit.[25] mp 44 °C); IR ($CHCl_3$) ν_{max} 3600 (OH), 3360 cm^{-1} (OH, associated), no carbonyl bands; ^1H NMR ($CHCl_3$, 60 MHz) δ 2.12 (s, $ArCH_3$), 3.63 (s, OMe), 6.2–6.4 (m, 2 H, H-4 and H-6), 6.89 (d, H-3), 5.72 (br s, OH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 14.8, 55.3, 101.6, 105.9, 116.4, 131.2, 154.5, 158.6.

$NaBH_4$ Reduction of 2-Hydroxy-4-methoxybenzaldehyde (12). Phenol **12** (1.0 g) in 25 mL of MeOH was added to 0.5 g of $NaBH_4$ in 100 mL of MeOH, and after 5 min at ambient temperature, 100 mL of H_2O was added. The aqueous solution, after extraction with $CHCl_3$ (3 × 200 mL), was acidified with HCl and reextracted with $CHCl_3$, and the extract was washed with H_2O and dried (Na_2SO_4). The viscous oil (1.02 g), left after evaporation of solvent, was chromatographed on silica gel with PhH–Et_2O (2:1) to give 0.30 g of 2-(methoxymethyl)-5-methoxyphenol (**13**) as a heavy oil: IR ($CHCl_3$) ν_{max} 3370 cm^{-1} (associated OH), no carbonyl bands; UV (MeOH) λ_{max} 277 nm (log ϵ 4.01), 282 (sh, 3.97) with shift to 293 (4.15) with base; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.37 (s, CH_2OCH_3), 3.72 (s, $ArOCH_3$), 4.53 (s, CH_2OCH_3), 6.2–6.4 (m, 2 H, H-4 and H-6), 6.80 (d, J = 8 Hz, H-3), 7.35 (br s, OH, lost in D_2O); mass spectrum (relative intensity) *m/e* 168 (M^+, 53), 151 (11), 138 (58), 137 (78), 136 (100), 108 (48), 94 (8), 78 (25), 65 (20), 51 (15). The ^1H NMR in $CDCl_3$–C_6D_6 (8:2) and the mass spectrum are recorded;[26] our data is comparable.

Na/NH_3 Cleavage of Thalibrunine (2). A 1.0-g sample of thalibrunine **2** in 20 mL of dry tetrahydrofuran was added over 1 h to 35 mL of liquid NH_3 containing 1.05 g of Na, maintained between –30 and –50 °C under N_2. After an additional 2 h the NH_3 was allowed to evaporate and excess Na removed with MeOH. The mixture was evaporated to a few milliliters, mixed with 50 mL of 5% NaOH, and extracted with Et_2O (5 × 100 mL) to give 92 mg of a nonphenolic residue. The aqueous solution was treated with excess NH_4Cl and extracted with Et_2O as before to yield 0.57 g of phenolic bases, which showed four spots on TLC [silica gel G, PhH–Me_2CO–NH_4OH (10:10:0.6)].

Chromatography of the phenolic bases on 35 g of silica gel with $CHCl_3$ and increasing amounts of MeOH in $CHCl_3$ gave from the 2% MeOH eluates 137 mg of 6-demethoxydihydrothalibrunine (**17**): $[\alpha]^{20}_D$ –75° (*c* 0.16, MeOH), $[\alpha]^{20}_D$ +156° (*c* 0.13, 0.02 N HCl in MeOH); CD (concentration 4.1 × 10^{-3} M, MeOH) $[\theta]_{325}$ 0, $[\theta]_{298}$ –8400, $[\theta]_{289}$ –2000 (min), $[\theta]_{276}$ –10 000, $[\theta]_{262}$ 0, $[\theta]_{240}$ +25 000, $[\theta]_{232}$ 0, $[\theta]_{225}$ –23 000 (end absorbance); under acid conditions (concentration 2.0 × 10^{-3} M, 0.02 M HCl in MeOH) $[\theta]_{330}$ 0, $[\theta]_{288}$ +19 500, $[\theta]_{260}$ (min) +4000, $[\theta]_{227}$ +77 500; ^1H NMR ($CDCl_3$) δ 2.46 and 2.57 (2 s, 2 NMe), 3.69, 3.72, 3.76, and 3.80 (4 s, 4 OMe), 6.19 and 6.27 (AB q, J = 2 Hz, H-6 and H-8), 6.36, 6.49, 6.52, and 6.59 (4 s, 4 ArH), AA'BB' "quartet" at 6.51 and 7.14 (J_{AB} = 8.6 Hz); mass spectrum (relative intensity) *m/e* 640 (0.3, $C_{38}H_{44}N_2O_7$ requires *m/e* 640), 448 (0.3, M – 192), 433 (0.5, M – H – 206), 206 (60, $C_{12}H_{16}NO_2$ fragment **17a**), 192 (100, $C_{11}H_{14}NO_2$ fragment **17b**).

The 5% MeOH eluates gave 15 mg of dihydrothalibrunine (**16**), and the 15% MeOH eluated yielded 80 mg of (*S*)-*N*-methylcoclaurine, both products already reported from this degradation.[3].

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Registry No. **2**, 11021-81-1; **3**, 72204-55-8; **4**, 72204-56-9; **5**, 72187-03-2; **6**, 72187-04-3; **7**, 72187-05-4; **8**, 72187-06-5; **9**, 72187-07-6; **10**, 62536-84-9; **11**, 20734-74-1; **12**, 673-22-3; **13**, 62849-09-6; **14**, 72187-08-7; **15**, 72187-09-8; **16**, 55592-64-8; **17**, 72187-10-1; **18**, 59553-87-6; methoxyhydroquinone, 824-46-4; benzyl chloride, 100-44-7; 2,5-bis(benzyloxy)anisole, 61654-73-7; 4-(benzyloxy)-2-methoxyphenol, 72187-11-2; 1,2-dimethoxy-4-(benzyloxy)benzene, 42138-42-1; 4-bromobenzaldehyde, 1122-91-4; *N*-methylformanilide, 93-61-8; 2-hydroxy-4-methoxybenzaldehyde, 673-22-3.

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