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Synthesis of protoberberines using a silyl-directed Pictet–Spengler cyclization

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Abstract—Five naturally-occurring protoberberines have been synthesized in enantioenriched form by alkylation by two different 2-trimethylsilylbenzyl chlorides of four tetrahydroisoquinolines, derivatized with Meyers' formamidine valinol methyl ether chiral auxiliary. Silyl-directed Pictet–Spengler cyclization of the ensuing 3,4-dimethoxy-2-trimethylsilylbenzyl tetrahydroisoquinolines leads to four of the target protoberberines in excellent yield and complete regioselectivity. In the fifth case, the 3,4-methylenedioxy analog gives a mixture of protoberberine and a product of ring closure at C6 of the benzyl moiety in a 3:4 ratio. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Protoberberines are naturally occurring tetracyclic isoquinoline alkaloids. Protoberberines commonly bear substituents at positions 2, 3, 9, and 10, and a single stereocenter at carbon 14 with the (*S*) configuration. Examples include sinactine and corypalmine (Fig. 1).[1]

Several approaches exist for the synthesis of protoberberines and other isoquinoline alkaloids, all of which are variants of the Friedel–Crafts reaction. The Pomeranz–Fritsch reaction[2] produces fully aromatic isoquinolines, and the Bischler–Napieralski process[3] affords 1,2-dihydroisoquinolines. The Pictet–Spengler sequence[4] produces the 1,2,3,4-tetrahydroisoquinoline system found within the structure of most natural protoberberines. It involves the addition of formaldehyde to a phenylethylamine to form an iminium ion. This electrophile is suitable for aromatic substitution and ring-closure (Fig. 2).

A complication of the Pictet–Spengler synthesis of protoberberines is regiochemical control in the closure of ring C when activating substituents are present on the D ring. Experimentally, Pictet–Spengler reactions performed on benzylisoquinolines of the 3′,4′-disubstitution type yield predominantly or exclusively the 10,11-disubstitution

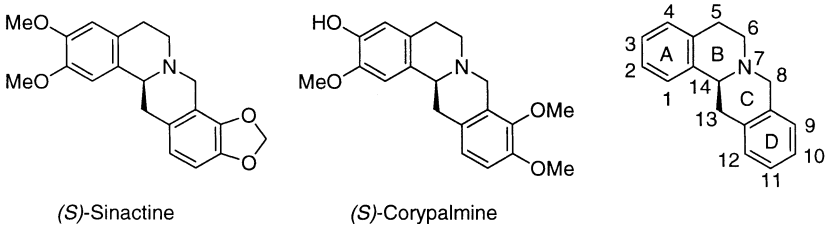

Figure 1. Representative protoberberines and the protoberberine numbering scheme.

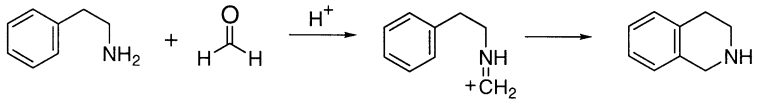

Figure 2. The Pictet–Spengler reaction sequence.

Keywords: enantioselective; *ipso*-substitution; Pictet–Spengler reaction; protoberberine; regioselectivity; silyl-direction.

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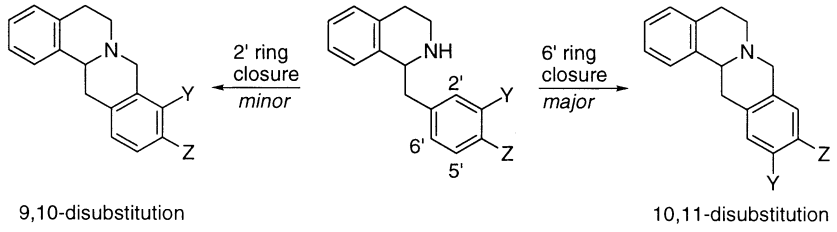


Figure 3. Regiochemistry of the Pictet–Spengler ring-closure.

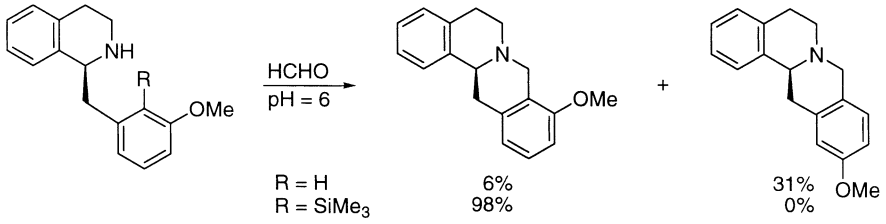


Figure 4. Ring-closure using trimethylsilyl *ipso*-direction.

product, rather than the 9,10-disubstitution pattern present in the majority of naturally occurring protoberberines[5] (Fig. 3).

Several approaches have been used to overcome this problem. One has been to block the 6′ position (*para* to substituent 'Y') with bromine, which is removed after cyclization to give the desired isomer. While this sequence has been used successfully by Kametani,[6] it lowers the yield of the Pictet–Spengler reaction as well as adding two more steps to the synthesis. Our solution was to induce 9,10-disubstitution by *ipso*-direction at the 2′ position using a trimethylsilyl group. Miller and Tsang demonstrated the first successful use of *ipso* direction for protoberberine ring-closure in systems such as the one shown in Fig. 4.[7]

They found that unsubstituted benzylisoquinolines are unreactive under Pictet–Spengler conditions: apparently the ring is insufficiently activated for electrophilic aromatic substitution to occur. However, 2′-trimethylsilylbenzylisoquinoline gives a 27% yield of unsubstituted protoberberine, suggesting that the TMS group is *ipso*-activating. The example in Fig. 4 illustrates the dramatic combined directing and activating effects of trimethylsilyl substitution on reaction of a 3′-methoxybenzylisoquinoline, suggesting that this approach may have general synthetic utility. In this paper we demonstrate that this is indeed the case: we describe syntheses of five naturally-occurring protoberberines, canadine, sinactine, tetrahydropalmatine, corypalmine, and isocorypalmine, evaluating the efficacy of trimethylsilyl direction of ring closure with several substitution patterns. These preparations also make use of an appropriate chiral auxiliary to evaluate the degree to which this methodology affords enantiomerically enriched products.

2. Results and discussion

2.1. Synthesis overview

Our convergent pathway to the construction of protoberberines involved four steps: (1) normal Pictet–Spengler-based construction of appropriately substituted tetrahydroisoquinolines (for rings A and B), (2) preparation of the 2-trimethylsilyl-3,4-dialkoxybenzyl chloride alkylating agents (ring D), (3) enantioselective coupling to give (14*S*)-benzylisoquinolines using Meyers' formamidine methodology,[8–11] and (4) trimethylsilyl-directed Pictet–Spengler reaction to close the C ring and produce the final products (Fig. 5).

2.2. Tetrahydropalmatine, canadine, and sinactine

To begin the syntheses of these protoberberines the appropriate benzaldehyde was subjected to Henry condensation and the resulting nitrostyrene reduced to the corresponding 3,4-dialkoxyphenylethylamine with lithium aluminum hydride.[12] Pictet–Spengler cyclization using paraformaldehyde in formic acid gave the initial

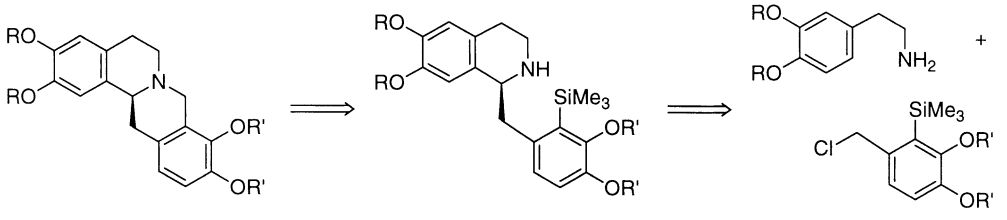
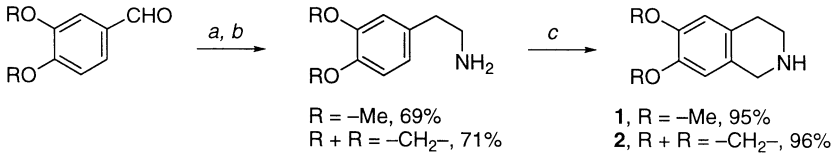
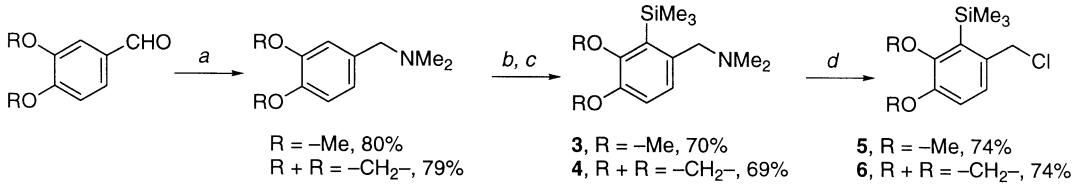


Figure 5. Overview of the synthetic route.



Scheme 1. (a) CH_3NO_2, HOAc, NH_4OAc, Δ, 1.5 h; (b) $LiAlH_4$, THF, Δ, 12 h; (c) $(CH_2O)_n$, HCO_2H, Δ, 12 h.



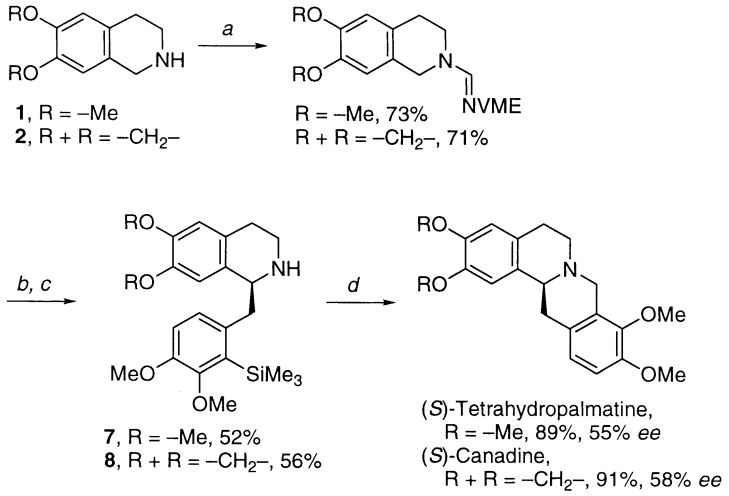
Scheme 2. (a) $(CH_3)_2NH$, $NaBH_3CN$, $ZnCl_2$, 1 h; (b) *n*-BuLi, THF, 0°C, 4 h; (c) $(CH_3)_3SiCl$, −78°C to rt, 4 h, (d) $ClCO_2Et$, −78°C to rt, 12 h.

tetrahydroisoquinolines **1** and **2** in overall yields of nearly 70%. N-Methylation was not observed provided that a 1:1 ratio of phenylethylamine and paraformaldehyde was maintained (Scheme 1).

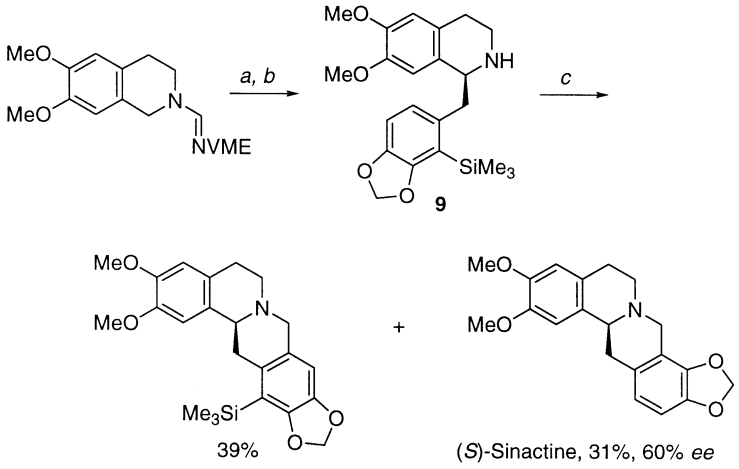
The alkylating agents **5** and **6** were formed from the same starting benzaldehydes, via a sequence of reductive amination using *N*,*N*-dimethylamine, doubly *ortho*-directed lithiation at C2, trimethylsilylation, and replacement of the dimethylamino group by Cl using ethyl chloroformate. Overall yields of about 40% were realized (Scheme 2).

Enantioselective alkylation of the tetrahydroisoquinolines **1** and **2** by the substituted benzyl chlorides **5** and **6** to form predominantly the natural (14*S*) protoberberine precursors utilized the valinol methyl ether-derived formamidine (–CH=NVME) as a chiral auxiliary.[9,13] The formamidine-derivatized precursors were prepared in essentially identical optical purity (≥97%) to that described by Meyers. Finally, each TMS-substituted benzyl tetrahydroisoquinoline was subjected to Pictet–Spengler conditions, giving rise to the corresponding protoberberine. Thus (*S*)-(−)-tetrahydropalmatine was obtained in 46% overall yield from the chiral formamidine derivative of **1** by alkylation with **5** followed by Pictet–Spengler cyclization. The cyclization itself proceeded in excellent yield, with complete *ipso* regioselectivity: no trace of products with any other D-ring substitution pattern was found. However, the optical rotation of the product revealed it to possess an optical purity of only 55%, corresponding to a 77:23 diastereoselectivity in the alkylation step. This is considerably poorer than that obtained using benzyl halides lacking *ortho* substitution, but somewhat better than the 32% ee obtained by Meyers using an analog of **5** containing a carboethoxy group instead of trimethylsilyl. Similarly, alkylation of the formamidine-derivatized tetrahydroisoquinoline **2** with **5** followed by cyclization afforded (*S*)-(−)-canadine in 51% overall yield and 58% optical purity (Scheme 3).

In Meyers' carboethoxy system the lone pairs on the substitutent were positioned to interfere with the desired stereodirecting lithium chelation. The origin of the stereochemical problem in our system is less clear. Perhaps the electron-releasing effect of the silyl substituent increases the Lewis basicity of one of the methoxy groups enough to partially interfere with chelation. This is pure speculation, however, for which we have no independent evidence. The exceptional regioselectivity, however, may be contrasted to the



Scheme 3. (a) (*S*)-*i*-Pr(CH_3OCH_2)CH=CHNMe_2, $(NH_4)_2SO_4$, toluene, 111°C, 18 h; (b) *n*-BuLi, THF, −78°C, 0.5 h; (c) **5**, THF, −105°C, 0.5 h, then HOAc, NH_2NH_2, 0°C to rt, 12 h; (d) HCl, CH_2O, EtOH, 85°C, 12 h.



Scheme 4. (a) *n*-BuLi, THF, −78°C, 0.5 h; (b) **6**, THF, −105°C, 0.5 h, then HOAc, NH_2NH_2, 0°C to rt, 12 h; (c) HCl, CH_2O, EtOH, 85°C, 12 h.

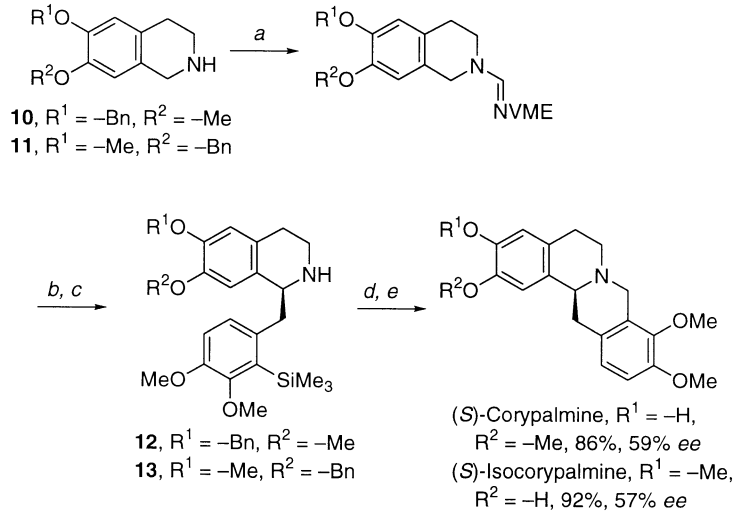
results of Haworth and Perkin.[5b] In an attempt to prepare canadine, they carried out Pictet–Spengler cyclization on the analog of **8** lacking silyl substitution. The sole product obtained was the undesired 10,11-dimethoxy regioisomer, in 60% yield; thus, use of a silyl substitution strategy in this case leads to a significantly improved yield and a complete reversal of regioselectivity.

We next investigated the synthesis of sinactine, a protoberberine with 9,10-methylenedioxy substitution on the D-ring, using the same approach. The required precursor **9** was prepared from formamidine-derivatized **1** by alkylation with **6** in 50% yield. In this case, however, the final cyclization no longer displayed selective trimethylsilyl-directed *ipso*-substitution. We obtained a 31% yield of (*S*)-(−)-sinactine, but 39% of a product that retained the silyl group and was derived from cyclization at C6 (*para* to the oxygen at C3) of the alkylating agent (Scheme 4).

In other, contemporaneous work from our laboratory, Taylor found that the analogous system derived from **2** (2,3-methylenedioxy-substituted A ring) gave a similar mixture containing 40% of a *para*-cyclized silicon-containing product and 29% of the natural product stylopine.[14] Thus it is clear that the stereoelectronic enhancement of the activating and directing power of the methylenedioxy group on the D-ring, relative to two freely rotating methoxy groups, is such that it overcomes the *ipso*-directing capability of the silyl substituent.[15] As a result, we abandoned work with methylenedioxy-substituted D-ring precursors.

2.3. Corypalmine and isocorypalmine

These protoberberines were accessed from the two regioisomeric methoxybenzyloxytetrahydroisoquinolines **10** and **11**, prepared in the manner described in Scheme 1. Both syntheses proceeded uneventfully. After debenzylation using HCl in aqueous EtOH, (*S*)-(−)-corypalmine was obtained in 46% yield and 59% optical purity from the formamidine derivative of **10**, and (*S*)-(−)-isocorypalmine was similarly obtained from derivatized **11** in 57% yield and 57% optical purity (Scheme 5).



Scheme 5. (a) (*S*)-*i*-Pr(CH_3OCH_2)CHN=CHNMe_2, $(NH_4)_2SO_4$, toluene, 111°C, 18 h; (b) *n*-BuLi, THF, −78°C, 0.5 h; (c) **5**, THF, −105°C, 0.5 h, then HOAc, NH_2NH_2, 0°C to rt, 12 h; (d), HCl, CH_2O, EtOH, 85°C, 12 h; (e) conc. HCl, EtOH, 100°C, 2 h.

3. Conclusions

Five protoberberines have been synthesized via a silyl-mediated Pictet–Spengler reactions. Cyclizations to give 9,10-dimethoxy-substituted systems proceed with complete silyl-directed *ipso*-regioselectivity. However, the analogous 9,10-methylenedioxy system does not form selectively and is not best accessed in this way. Even though the optical purities of the formamidine precursors matched those in the literature, the optical purities of the final alkaloids measured only in the 55–60% range, apparently a consequence of low stereoselectivity in the chiral-auxiliary-mediated alkylation step.

4. Experimental

4.1. General

Solvents were purified and dried according to standard procedures. All reactions were carried out under an atmosphere of dry N_2, unless indicated otherwise. All NMR spectra were recorded at 298 K in $CDCl_3$ at 300 MHz (^1H) or 75 MHz (^{13}C). High-resolution mass spectra were obtained on a VG 7070 mass spectrometer at the UC Riverside mass spectrometry lab in Riverside, CA and were performed by Mary Young. Optical rotations were measured on a Jasco DIP-370 digital polarimeter at UC Davis. Preparations of known compounds are detailed in Supplementary Materials.

4.1.1. 3,4-Dimethoxy-1-(dimethylamino)methyl-2-trimethylsilylbenzene (3). To a solution of 3,4-dimethoxy-1-(dimethylamino)methylbenzene (α-dimethylamino-3,4-dimethoxytoluene) (4.96 g, 25.40 mmol) in THF (30 mL) at −78°C was added *n*-butyllithium (2.37 M, 17.17 mL, 39.07 mmol) dropwise. The mixture was than warmed to 0°C, stirred 4 h, and recooled to −78°C. Chlorotrimethylsilane (5.17 mL, 40.67 mmol) was cooled to −78°C, diluted with 6 mL of tetrahydrofuran and then added to the amine via cannula. The mixture was then warmed to rt and stirred an additional 4 h. The reaction mixture was quenched with water and extracted 3× with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), evaporated, and the residue chromatographed (SiO_2, 9:1:1 hexane/EtOAc/Et_3N) to give **3** as a light yellow oil (4.78 g, 70% yield). ^1H NMR δ 7.04 (d, 1H, J=8.1 Hz), 6.84 (d, 1H, J=7.8 Hz), 3.84 (s, 3H), 3.81 (s, 3H), 2.13 (s, 6H), 0.35 (s, 9H). ^{13}C NMR δ 162.7, 159.0, 138.2, 122.9, 118.9, 108.2, 74.3, 72.8, 63.3, 45.7, 1.2. IR (film): 1583, 1412, 1367, 1279, 1228, 1147, 1057, 1024, 897, 843, 767 cm^{-1}. HRMS for $C_{14}H_{25}NO_2Si$ (M^+): calcd 267.1648, found 267.1660.

4.1.2. 1-Chloromethyl-3,4-dimethoxy-2-trimethylsilylbenzene (5). To a slurry of **3** (4.08 g, 15.26 mmol) and K_2CO_3 (3.36 g, 24.35 mmol) in THF (33 mL) at −78°C was added ethyl chloroformate (2.33 mL, 24.35 mmol). The reaction was warmed to rt and stirred for 12 h. The resulting slurry was quenched with water and extracted 3× with EtOAc. The combined organic layers were dried (Na_2SO_4), evaporated, and the residue chromatographed (SiO_2, 19:1 hexane/EtOAc) to give **5** as a pale yellow liquid (2.93 g, 74% yield). ^1H NMR δ 7.08 (d, 1H, J=8.1 Hz), 6.89 (d, 1H, J=7.8 Hz), 4.65 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 0.42 (s, 9H). ^{13}C NMR δ 153.2, 146.2, 139.5, 130.2, 121.9, 111.5, 89.2, 81.1, 46.3, 0.7. IR (film): 2081, 1982, 1857, 1589, 1568, 1468, 1388, 1296, 1246, 1159, 1047, 858 cm^{-1}. HRMS for $C_{12}H_{19}ClO_2Si$ (M^+): calcd 258.0838, found 258.0844.

4.1.3. 1-(Dimethylamino)methyl-3,4-methylenedioxy-2-trimethylsilylbenzene (4). In a manner similar to the preparation of **3**, 1-(dimethylamino)methyl-3,4-methylenedioxybenzene (α-dimethylamino-3,4-methylenedioxytoluene) (3.10 g, 17.29 mmol) was converted into **4** by successive treatment with *n*-butyllithium (2.37 M, 10.73 mL, 24.42 mmol) and chlorotrimethylsilane (3.23 mL, 25.42 mmol) in THF. After work-up and purification **4** was isolated as a light yellow oil (2.99 g, 69% yield). ^1H NMR δ 6.80 (d, 1H, J=8.1 Hz), 6.72 (d, 1H, J=7.8 Hz), 5.89 (s, 2H), 3.35 (s, 2H), 2.14 (s, 6H), 0.35 (s, 9H). ^{13}C NMR δ 153.2, 145.0, 138.2, 122.9, 118.9, 108.2, 99.8, 64.4, 45.0, 1.2. IR (film): 1583, 1412, 1367, 1279, 1228, 1147, 1057, 1024, 897, 843, 767 cm^{-1}. HRMS for $C_{13}H_{22}NO_2Si$ (MH^+): calcd 252.1419, found 252.1414.

4.1.4. 1-Chloromethyl-3,4-methylenedioxy-2-trimethylsilylbenzene (6). In a manner similar to the preparation of **5**, amine **4** (2.72 g, 10.82 mmol) was converted into **6** by reaction with K_2CO_3 (2.24 g, 16.23 mmol) and ethyl chloroformate (1.55 mL, 16.23 mmol) in THF. Work-up and purification produced **6** as a pale yellow liquid (1.95 g, 74% yield). ^1H NMR δ 6.88 (d, 1H, J=8.1 Hz), 6.76 (d, 1H, J=7.8 Hz), 5.93 (s, 2H), 4.62 (s, 2H), 0.42 (s, 9H). ^{13}C NMR δ 153.2, 146.2, 135.7, 124.8, 119.2, 109.1, 100.3, 47.7, 0.8. IR (film): 2081, 1982, 1857, 1589, 1568, 1468, 1388, 1296, 1246, 1159, 1047, 858 cm^{-1}. HRMS for $C_{11}H_{15}ClO_2Si$ (M^+): calcd 242.0526, found 242.0522.

4.1.5. (*S*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[[(1-(methoxymethyl)-2-methylpropyl)imino]methyl]isoquinoline (1-formamidine).[13] To a solution of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **1** (1.44 g, 7.45 mmol) and Meyers' (*S*)-(−)-formamidine chiral auxiliary (1.93 g, 11.18 mmol) in toluene (10 mL) was added $(NH_4)_2SO_4$ (0.10 g, 0.77 mmol), and the mixture was heated to reflux for 18 h open to the air. After cooling to rt and evaporation of the solvent the crude product was chromatographed (SiO_2, 6:3:1 EtOAc/hexane/Et_3N) to give the formamidine-derivatized isoquinoline (**1**-formamidine) as a yellow oil (1.74 g, 73% yield); $[\alpha]_D^{25}=-7.48$ (c 2.46, THF), lit[13]: $[\alpha]_D^{25}=-7.46$ (c 2.59, THF). ^1H NMR δ 7.40 (s, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 4.50 (d, 1H, J=16.5 Hz), 4.40 (d, 1H, J=16.8 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.53–3.49 (m, 4H), 3.34 (s, 3H), 2.78 (m, 3H), 1.74 (sept, 1H, J=6.6 Hz), 0.85 (t, 6H, J=6.3 Hz). ^{13}C NMR δ 153.6, 147.6, 147.4, 126.5, 125.5, 111.5, 109.2, 76.1, 71.4, 59.0, 55.9, 46.4, 44.4, 30.8, 28.7, 20.1, 18.7. IR (film): 1662, 1488, 1382, 1380, 1252, 1105 cm^{-1}.

4.1.6. (*S*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[(3,4-dimethoxy-2-trimethylsilylphenyl)methyl]isoquinoline (7). The **1**-formamidine (0.850 g, 2.65 mmol) was weighed into a flame-dried flask, placed under high vacuum, and gently warmed with a heat gun while N_2 was introduced. The evacuation-warming cycle was repeated five times.

THF (30 mL) was introduced under N_2 and the solution cooled to −78°C. *N*-Butyllithium (1.25 M in hexanes, 3.08 mL, 3.83 mmol) was added until a yellow color persisted, whereupon the remainder was added dropwise. After 0.5 h, the deep red solution was cooled to −105°C, and a solution of **5** (0.720 g, 2.78 mmol) in THF (30 mL) was added dropwise. After 0.5 h, the light yellow mixture was warmed to rt, quenched with 4 mL sat'd NH_4Cl, followed by the addition of water and EtOAc. The aqueous layer was extracted 2× with CH_2Cl_2, and then the combined organic layers dried (Na_2SO_4) and evaporated to yield crude alkylated formamidine derivative as a yellow oil. This material was directly subjected to hydrazinolysis in order to remove the auxiliary, as follows.

Crude alkylated formamidine (1.44 g, based on 2.65 mmol of precursor) was taken up in EtOH (95%, 3.5 mL), cooled to 0°C, and treated with HOAc (0.43 mL) followed by hydrazine monohydrate (0.86 mL). The solution was then warmed to rt, stirred for 12 h, and then partitioned between water and CH_2Cl_2. The aqueous layer was extracted 2× with CH_2Cl_2. The organic layers were then dried (Na_2SO_4) and evaporated. The residue was chromatographed (SiO_2, 6:2:1 hexane/EtOAc/Et_3N) to give **7** as a yellow oil (0.573 g, 52% yield); $[\alpha]_D^{25}=-51.7$ (*c* 3.17, $CDCl_3$). ^{1}H NMR δ 6.90 (d, 1H, *J*=8.1 Hz), 6.89 (d, 1H, *J*=8.4 Hz), 6.58 (s, 1H), 6.42 (s, 1H), 4.10 (m, 1H), 3.86 (s, 6H), 3.81 (s, 3H), 3.70 (s, 3H), 3.37 (dd, 1H, *J*=13.5, 5.1 Hz), 3.21 (m, 1H), 2.98–2.80 (m, 4H), 1.62 (bs, 1H), 0.36 (s, 9H). ^{13}C NMR δ 155.0, 150.3, 147.3, 146.6, 136.9, 132.3, 130.4, 127.2, 126.7, 113.5, 111.8, 109.5, 60.7, 57.2, 56.1, 55.8, 55.5, 41.7, 41.3, 29.5, 2.9. IR (nujol): 1510, 1463, 1381, 1258, 1220 cm^{-1}. HRMS for $C_{23}H_{34}NO_4Si$ (MH^+): calcd 416.2258, found 416.2263.

4.1.7. (*S*)-(−)-Tetrahydropalmatine. A mixture of EtOH (2.1 mL) and aq. formaldehyde (0.9 mL, 37%), which had been acidified with 10% HCl, was added to **7** (0.235 g, 0.565 mmol), and sufficient additional dilute HCl was added after dissolution to adjust the mixture to pH 6. The mixture was heated to 85°C overnight, open to the air, then cooled and basified with 1N aq. NaOH. The mixture was extracted with CH_2Cl_2. The organic layer was washed successively with water and brine, dried (Na_2SO_4), and evaporated. The resulting yellow solid was chromatographed (SiO_2, 9:1 hexane/EtOAc) to give (*S*)-(−)-tetrahydropalmatine as a yellow solid (0.179 g, 89% yield); synthetic mp=142–145°C; natural[16] mp=143°C. Synthetic $[\alpha]_D^{25}=-160$ (*c* 2.73, $CDCl_3$). Natural $[\alpha]_D^{20}=-291$ (EtOH). ^{1}H NMR[17] δ 6.88 (d, 1H, *J*=8.0 Hz), 6.80 (d, 1H, *J*=8.0 Hz), 6.74 (s, 1H), 6.63 (s, 1H), 4.25 (d 1H, *J*=15.7 Hz), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 6H), 3.54 (d, 1H, *J*=15.7 Hz), 3.49 (dd, 1H, *J*=12.2, 4.0 Hz), 3.27 (dd, 1H, *J*=15.8, 4.0 Hz), 3.23 (m, 1H), 3.10 (m, 1H), 2.91 (dd, 1H, *J*=15.8, 12.2 Hz), 2.68 (m, 1H), 2.65 (m, 1H). ^{13}C NMR[18] δ 150.2, 147.5, 147.3, 145.0, 129.6, 128.6, 127.7, 126.7, 123.8, 111.2, 110.8, 108.5, 60.1, 59.3, 56.0, 55.8, 55.7, 54.0, 51.5, 36.3, 29.1.

4.1.8. (*S*)-1,2,3,4-Tetrahydro-2-[[(1-(methoxymethyl)-2-methylpropyl)imino]methyl]-6,7-methylenedioxyisoquinoline (2-formamidine).[13] In manner similar to that used for the preparation of **1**-formamidine, 1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline **2** (1.87 g, 10.55 mmol) was converted into **2**-formamidine by reaction with the Meyers auxiliary (2.81 g, 15.83 mmol). The product was obtained as a yellow oil (2.28 g, 71%); $[\alpha]_D^{25}=-54.2$ (*c* 3.07, $CDCl_3$), lit[13] $[\alpha]_D^{25}=-55.6$ (*c* 1.21, $CDCl_3$). ^{1}H NMR δ 7.38 (s, 1H), 6.59 (s, 1H), 6.57 (s, 1H), 5.89 (s, 2H), 4.45 (d, 1H, *J*=16.5 Hz), 4.36 (d, 1H, *J*=16.8 Hz), 3.54–3.35 (m, 4H), 3.33 (s, 3H), 2.82 (m, 1H), 2.75 (t, 2H, *J*=6.0 Hz), 1.74 (sept, 1H, *J*=6.6 Hz), 0.85 (t, 6H, *J*=6.3 Hz). ^{13}C NMR δ 153.6, 146.00, 145.98, 127.7, 126.6, 108.6, 106.3, 100.7, 76.3, 71.5, 59.0, 46.8, 44.4, 30.9, 29.2, 20.1, 18.7. IR (film): 1653, 1487, 1387, 1248, 1200, 1113, 1039, 928, 856, 756 cm^{-1}.

4.1.9. (*S*)-1,2,3,4-Tetrahydro-1-[(3,4-dimethoxy-2-trimethylsilylphenyl)methyl]-6,7-methylenedioxyisoquinoline (8). In a manner similar to that described for **7**, **2**-formamidine (1.78 g, 5.82 mmol) was alkylated with **5** to produce 3.08 g of crude benzyl tetrahydroisoquinoline formamidine derivative as a yellow oil. This material was directly subjected to hydrazinolysis to yield after purification the benzyl tetrahydroisoquinoline **8** as a yellow oil (1.31 g, 56% yield); $[\alpha]_D^{25}=-51.7$ (*c* 3.17, $CDCl_3$). ^{1}H NMR δ 6.96 (d, 1H, *J*=8.1 Hz), 6.89 (d, 1H, *J*=8.4 Hz), 6.57 (s, 1H), 6.56 (s, 1H), 5.88 (s, 2H), 3.96 (m, 1H), 3.85 (s, 6H), 3.39 (dd, 1H, *J*=13.5, 5.1 Hz), 3.19–3.11 (m, 1H), 2.87–2.68 (m, 4H), 1.68 (bs, 1H), 0.35 (s, 9H). ^{13}C NMR δ 154.5, 150.2, 145.7, 145.4, 136.6, 132.3, 131.7, 128.3, 126.4, 113.5, 108.8, 106.1, 100.5, 60.6, 57.5, 55.4, 41.5, 41.4, 30.1, 2.9. IR (nujol): 1485, 1246, 1156, 1046, 860 cm^{-1}. HRMS for $C_{22}H_{30}NO_4Si$ (MH^+): calcd 400.1944, found 400.1941.

4.1.10. (*S*)-(−)-Canadine. Pictet–Spengler cyclization was carried out as described for the preparation of tetrahydropalmatine earlier, to convert benzyl tetrahydroisoquinoline **8** (0.188 g, 0.471 mmol) into (*S*)-(−)-canadine, isolated after purification as a yellow solid (0.146 g, 91% yield); synthetic mp=142–145°C; natural[19] mp=132°C. Synthetic $[\alpha]_D^{25}=-174$ (*c* 2.88, $CDCl_3$). Natural $[\alpha]_D^{15}=-299$ ($CDCl_3$). ^{1}H NMR[17] δ 6.87 (d, 1H, *J*=8.4 Hz), 6.78 (d, 1H, *J*=8.1 Hz), 6.73 (s, 1H), 6.59 (s, 1H), 5.92 (s 2H), 4.24 (d, 1H, *J*=15.9 Hz), 3.85 (s, 6H), 3.53 (d, 1H, *J*=15.6 Hz), 3.53 (m, 1H), 3.26–3.07 (m, 3H), 2.81 (dd, 1H, *J*=15.9, 11.4 Hz), 2.70–2.59 (m, 2H). ^{13}C NMR[18] δ 150.3, 146.1, 145.9, 145.0, 130.8, 128.6, 127.8, 127.7, 123.9, 110.9, 108.4, 105.5, 100.8, 60.2, 59.6, 55.9, 53.9, 51.4, 36.5, 29.6.

4.1.11. (*S*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[(3,4-methylenedioxy-2-trimethylsilylphenyl)methyl]isoquinoline (9). In a manner similar to that described for **7**, **1**-formamidine (0.876 g, 2.73 mmol) was alkylated with **6** to produce 1.43 g of crude benzyl tetrahydroisoquinoline formamidine derivative as a yellow oil. This material was directly subjected to hydrazinolysis to yield after purification the benzyl tetrahydroisoquinoline **9** as a yellow oil (0.546 g, 50% yield); $[\alpha]_D^{25}=-46.8$ (*c* 2.84, $CHCl_3$). ^{1}H NMR δ 6.77 (d, 1H, *J*=8.1 Hz), 6.71 (d, 1H, *J*=8.1 Hz), 6.60 (s, 1H), 6.56 (s, 1H), 5.93 (s, 2H), 4.01 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.31 (dd, 1H, *J*=13.5, 5.1 Hz), 3.16 (m, 1H), 2.86–2.66 (m, 4H), 1.74 (bs, 1H), 0.36 (s, 9H). ^{13}C NMR δ 154.2, 149.8, 149.7, 147.1, 136.9, 129.2, 128.9, 126.0, 119.3, 114.7, 111.6, 100.6, 59.5, 59.4, 56.4, 45.8,

44.2, 31.5, 2.9. IR (nujol): 1493, 1454, 1331, 1275 cm^{-1}. HRMS for $C_{22}H_{30}NO_4Si$ (MH^+): calcd 400.1944, found 400.1951.

4.1.12. (*S*)-(−)-Sinactine and (*S*)-(−)-2,3-dimethoxy-10,11-methylenedioxy-12-trimethylsilylprotoberberine. Pictet–Spengler cyclization was carried out as described for the preparations of tetrahydropalmatine and canadine earlier, on benzyl tetrahydroisoquinoline **9** (0.181 g, 0.236 mmol). After separation and purification of the resulting crude product mixture as previously described, two products were obtained: the 6′ ring-closure product, (*S*)-(−)-2,3-dimethoxy-10,11-methylenedioxy-12-trimethylsilylprotoberberine, a yellow solid (0.073 g, 39% yield), and the 2′ ring-closure product, (*S*)-(−)-sinactine, also a yellow solid (0.048 g, 31% yield).

(S)-(−)-2,3-Dimethoxy-10,11-methylenedioxy-12-trimethylsilylprotoberberine: mp=81–84°C; $[\alpha]_D^{25}=-99.6$ (*c* 0.45 $CHCl_3$). ^1H NMR δ 6.68 (s, 1H), 6.59 (s, 1H), 6.52 (s, 1H), 5.93 (s, 2H), 3.89 (d, 1H, *J*=14.4 Hz), 3.85 (s, 3H), 3.79 (s, 3H), 3.63 (d, 1H, *J*=14.4 Hz), 3.47 (dd, 1H, *J*=10.8, 3.3 Hz), 3.31 (dd, 1H, *J*=15.6, 3.0 Hz), 3.16–3.08 (m, 2H), 2.78 (dd, 1H, *J*=15.0, 11.1 Hz), 2.67–2.50 (m, 2H), 0.36 (s, 9H). ^{13}C NMR δ 151.6, 146.2, 145.9, 144.5, 142.2, 131.6, 130.9, 127.8, 127.0, 117.7, 108.5, 107.0, 105.1, 100.7, 99.7, 60.1, 59.3, 51.2, 38.5, 29.5, 1.4. HRMS for $C_{23}H_{30}NO_4Si$ (MH^+): calcd 412.1945, found 412.1954.

(S)-(−)-Sinactine: synthetic mp=170–173°C; natural[20] mp=175°C. Synthetic $[\alpha]_D^{25}=-187$ (*c* 3.17, $CHCl_3$). Natural $[\alpha]_D^{25}=-312$ (0.37 $CHCl_3$). ^1H NMR δ 6.73 (s, 1H), 6.67 (AB pattern, 2H), 6.62 (s, 1H), 5.90 (s, 2H), 4.08 (d, 1H, *J*=16.0 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.52 (d, 1H, *J*=16.0 Hz), 2.42–3.24 (m, 7H). ^{13}C NMR δ 150.3, 146.1, 145.9, 145.0, 130.8, 128.6, 127.8, 127.7, 123.9, 110.9, 108.4, 105.5, 100.8, 60.7, 59.6, 55.9, 53.9, 51.4, 36.5, 29.6.

4.1.13. (*S*)-6-Benzyloxy-1,2,3,4-tetrahydro-7-methoxy-1-[(3,4-dimethoxy-2-trimethylsilylphenyl)methyl]isoquinoline (12). Reaction of 6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**10**) (1.49 g, 5.03 mmol) and the Meyers auxiliary (1.34 g, 7.55 mmol) was carried out in the manner described for **1**-formamidine. After workup and silica gel chromatography the corresponding formamidine was obtained as a yellow oil (1.24 g, 62% yield); $[\alpha]_D^{25}=-45.2$ (*c* 3.04, $CDCl_3$). ^1H NMR δ 7.43–7.26 (m, 5H), 6.63 (s, 1H), 6.62 (s, 1H), 5.11 (s, 2H), 4.41 (d, 1H, *J*=16.5 Hz), 4.32 (d, 1H, *J*=16.8 Hz), 3.86 (s, 3H), 3.54–3.41 (m, 4H), 3.33 (s, 3H), 2.78 (t, 2H, *J*=6.0 Hz), 2.51 (m, 1H), 1.74 (sept, 1H, *J*=6.6 Hz), 0.86 (t, 6H, *J*=6.3 Hz). ^{13}C NMR δ 154.0, 148.5, 147.1, 137.5, 128.9, 128.1, 127.5, 125.9, 112.6, 112.0, 76.7, 71.8, 71.5, 59.3, 56.4, 46.7, 44.9, 31.2, 29.1, 20.4, 19.1. IR (film): 1642, 1514, 1454, 1381, 1255 cm^{-1}.

Without further purification this formamidine (1.22 g, 3.08 mmol) was subjected to alkylation by **5** (1.04 g, 4.00 mmol) in the manner described for the preparation of **7**. The crude alkylated material (1.90 g, based on 0.685 mmol of precursor) was directly subjected to hydrazinolysis to yield after purification the benzyl tetrahydroisoquinoline **12** as a yellow oil (0.802 g, 53% yield overall from the corresponding formamidine); $[\alpha]_D^{25}=-44.3$ (*c* 2.32, $CDCl_3$). ^1H NMR δ 6.96 (d, 1H, *J*=8.1 Hz), 6.89 (d, 1H, *J*=8.4 Hz), 6.57 (s, 1H), 6.56 (s, 1H), 5.88 (s, 2H), 3.95 (m, 1H), 3.86 (s, 6H), 3.80 (s, 3H), 3.39 (dd, 1H, *J*=13.5, 5.1 Hz), 1.35–3.18 (m, 1H), 2.91–2.70 (m, 4H), 1.67 (bs, 1H), 0.32 (s, 9H). ^{13}C NMR δ 156.4, 152.2, 143.7, 142.5, 138.7, 135.2, 134.8, 134.4, 128.0, 125.9, 123.8, 123.1, 121.2, 119.5, 117.5, 117.8, 72.7, 64.2, 58.7, 54.3, 53.8, 46.2, 27.7, 2.6. IR (nujol): 1490, 1466, 1326, 1280 cm^{-1}. HRMS for $C_{29}H_{38}NO_4Si$ (MH^+): calcd 492.2571, found 492.2563.

4.1.14. (*S*)-(−)-Corypalmine. Pictet–Spengler cyclization was carried out as described for the preparation of tetrahydropalmatine earlier, to convert benzyl tetraisoquinoline **12** (0.225 g, 0.458 mmol) into (*S*)-(−)-corypalmine, a yellow solid (0.145 g, 86% yield); synthetic mp=210–215°C; natural[21] mp=235–236°C. Synthetic $[\alpha]_D^{25}=-166$ (*c* 2.13, $CDCl_3$). Natural $[\alpha]_D^{16}=-280$ ($CHCl_3$). ^1H NMR δ 6.86 (d, 1H, *J*=8.4 Hz), 6.78 (d, 1H, *J*=8.4 Hz), 6.70 (s, 1H), 6.65 (s, 1H), 6.14 (1H, bs), 4.27 (d, 1H, *J*=15.6), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.55 (d, 1H, *J*=15.6 Hz), 3.46 (dd, 1H, *J*=12.0, 4.0 Hz), 3.25 (dd, 1H, *J*=15.6, 4.0 Hz), 3.18 (m, 1H), 3.10 (m, 1H), 2.88 (dd, 1H, *J*=15.6, 11.8 Hz), 2.66 (m, 1H), 2.64 (m, 1H). ^{13}C NMR δ 150.2, 147.1, 147.0, 145.0, 129.1, 128.6, 127.6, 127.4, 123.8, 114.2, 110.8, 107.7, 60.2, 59.3, 56.0, 55.8, 53.9, 51.5, 36.4, 28.8.

4.1.15. (*S*)-7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-[(3,4-dimethoxy-2-trimethylsilylphenyl)methyl]isoquinoline (13). Reaction of 7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**11**) (1.20 g, 4.46 mmol) and the Meyers auxiliary (1.19 g, 6.69 mmol) was carried out in the manner described for **1**-formamidine. After workup and silica gel chromatography the corresponding formamidine was obtained as a yellow oil (1.05 g, 59% yield); $[\alpha]_D^{25}=-47.2$ (*c* 2.12, $CDCl_3$). ^1H NMR δ 7.43–7.28 (m, 5H), 6.63 (s, 1H), 6.62 (s, 1H), 5.11 (s, 2H), 4.41 (d, 1H, *J*=16.5 Hz), 4.32 (d, 1H, *J*=16.8 Hz), 3.86 (s, 2H), 3.54–3.45 (m, 4H), 3.33 (s, 3H), 2.79 (m, 1H), 2.77 (t, 2H, *J*=6.0 Hz), 1.76 (sept, 1H, *J*=6.6 Hz), 0.85 (t, 6H, *J*=6.3 Hz). ^{13}C NMR δ 157.6, 154.2, 146.2, 137.9, 128.4, 127.5, 126.3, 125.8, 114.0, 104.3, 103.6, 76.6, 72.1, 59.6, 56.3, 47.6, 45.9, 32.9, 28.7, 20.4, 18.1. IR (film): 1650, 1509, 1387, 1251 cm^{-1}.

Without further purification this formamidine (1.05 g, 2.65 mmol) was subjected to alkylation by **5** (0.892 g, 3.45 mmol) in the manner described for the preparation of **7**. The crude alkylated material (1.64 g, based on 2.65 mmol of precursor) was directly subjected to hydrazinolysis to yield after purification the benzyl tetrahydroisoquinoline **13** as a yellow oil (0.807 g, 62% yield overall from the corresponding formamidine); $[\alpha]_D^{25}=-49.6$ (*c* 2.14, $CDCl_3$). ^1H NMR δ 7.41 (m, 5H), 6.91 (d, 1H, *J*=8.0 Hz), 6.89 (d, 1H, *J*=8.0 Hz), 6.62 (s, 1H), 6.45 (s, 1H), 5.10 (s, 2H), 4.10 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.41 (dd, 1H, *J*=13.5, 5.1 Hz), 3.18 (m, 1H), 2.89–2.64 (m, 4H), 1.51 (bs, 1H), 0.37 (s, 9H). ^{13}C NMR δ 154.5, 150.1, 147.2, 146.5, 137.2, 136.9, 132.1, 131.6, 128.3, 127.3, 127.6, 126.8, 126.3, 114.7, 113.5, 110.2, 71.0, 60.5, 57.2,

55.7, 55.4, 41.6, 41.2, 29.4, 2.8. IR (nujol): 1494, 1470, 1332, 1290 cm^{-1}. HRMS for $C_{29}H_{38}NO_4Si$ (MH^+): calcd 492.2571, found 492.2567.

4.1.16. (*S*)-(−)-Isocorypalmine. Pictet–Spengler cyclization was carried out as described for the preparation of tetrahydropalmatine earlier, to convert benzyl tetraisoquinoline **13** (0.201 g, 0.409 mmol) into (*S*)-(−)-isocorypalmine, a yellow solid (0.128 g, 92% yield); synthetic mp=228–235°C; natural[22] mp=241–242°C. Synthetic $[\alpha]_D^{25}=-173$ (*c* 2.44, $CDCl_3$). Natural $[\alpha]_D^{25}=-303$ ($CHCl_3$). ^1H NMR δ 6.87 (d, 1H, *J*=8.4 Hz), 6.78 (d, 1H, *J*=8.1 Hz), 6.71 (s, 1H), 6.68 (s, 1H), 5.88 (bs, 1H), 4.24 (d, 1H, *J*=15.9 Hz), 3.90 (s, 3H), 3.87 (s, 6H), 3.53 (d, 1H, *J*=15.6 Hz), 3.53 (m, 1H), 3.26–3.07 (m, 3H), 2.81 (dd, 1H, *J*=15.9, 11.4 Hz), 2.70–2.59 (m, 2H). ^{13}C NMR δ 150.4, 145.9, 145.3, 144.2, 129.4, 128.7, 124.3, 124.0, 123.7, 114.3, 111.3, 108.1, 60.1, 59.4, 56.9, 56.0, 54.0, 51.5, 36.5, 29.0.

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