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Total Synthesis of New 8-(Arylmethyl)berbines

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Dedicated to Prof. Luis Castedo on the occasion of his 70th birthday

Keywords: Alkaloids / Rearrangement / Diastereoselectivity / Total synthesis / Natural products

The total synthesis of the natural compound (8*S**,14*S**)-8-(4′-hydroxybenzyl)-2,3-dimethoxyberbin-10-ol and its C-8 epimer has been conveniently developed by making use of the diastereoselective Stevens rearrangement of the corresponding *N*-(arylmethyl)berbinium salts as the key step.

Introduction

The isoquinoline moiety is present in a wide variety of pharmacologically active compounds of both natural and synthetic origin; one representative example being protoberberine alkaloids.[1] Tetrahydroprotoberberines (known as berbines) bearing a benzyl group attached to C-8 are rather uncommon protoberberines that are isolated from natural sources. These compounds are interesting from both the chemical and pharmacological points of view because they incorporate the phenylethylamine moiety in their structure, which is an important biological pharmacophore. Typically, the 8-(arylmethyl)berbine alkaloids bear oxygenated substituents (usually methoxy or phenolic groups) on the A and D rings (Figure 1). For instance, javaberine A, which was recently isolated from *Talinum paniculatum*, contains a 3,4-dioxy-substituted benzyl group at C-8 and exhibits strong inhibitory activity on the lipopolysaccharide-induced tumour necrosis factor.[2] This factor is produced from adipose tissue and has been reported to be involved in insuline resistance in adipocytes. Theoneberine is a brominated berbine that was isolated from a marine organism and exhibits antimicrobial and cytotoxic activities; it is the only known example of a halogen-containing 8-(arylmethyl)berbine.[3] Latifolians A and B are 8-(arylmethyl)berbinium salts in which the isoquinolinic nitrogen is additionally linked to C-5 of the benzyl substituent.[4] Other 8-(arylmethyl)berbines have been isolated from plant sources such as *Gnetum parvifolium*[5] and *Aristolochia sp.*[6] A particular example is the 8-substituted berbine (–)-8β-(4′-hydroxybenzyl)-2,3-dimethoxyberbin-10-ol (**1**), which was isolated from the aerial part of *Aristolochia constricta*,[7] a medicinal plant found in Ecuador. This compound displays a peculiar substitution pattern, with two methoxy groups in the A ring (at C-2 and C-3), only one hydroxy group in the D ring (at C-10), and one 4-hydroxy benzyl group at C-8, which has no precedent in the berbine family. The synthesis of **1** has not been reported to date and its biological properties still remain unexplored.

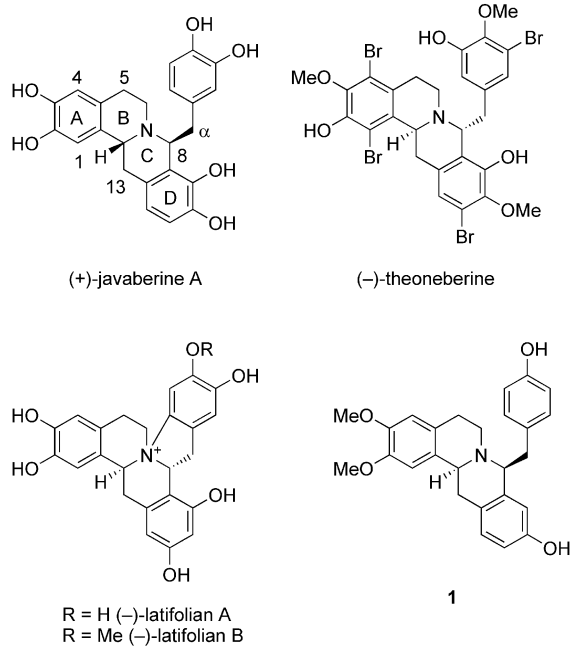

Figure 1. Structures of relevant 8-(arylmethyl)berbine alkaloids.

Synthetic approaches to 8-substituted berbines include a range of strategies. The intramolecular Mannich[8] reaction of 1-benzyltetrahydroisoquinoline with aldehydes under

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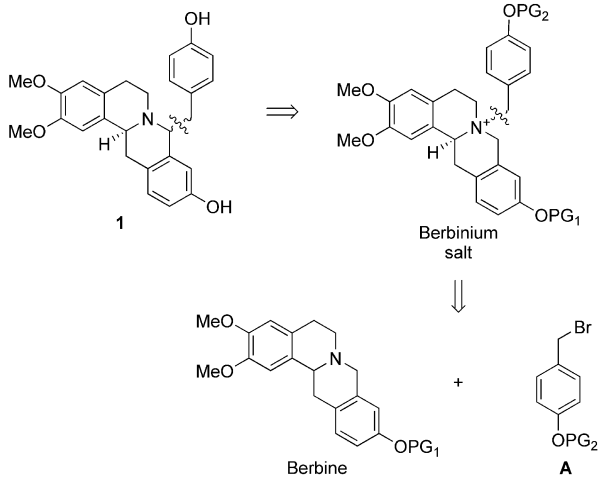
acidic conditions is the classical procedure for the synthesis of systems with an activated C ring, but this reaction is not stereoselective. Alternative routes based on the classical Bischler–Napieralski[9] and Pictet–Spengler[10] cyclizations have been employed with 1-substituted *N*-(phenylethyl)-tetrahydroisoquinoline to yield 8-alkyl- and 8-arylberbines. The C-8 substituent may also be incorporated once the berbine skeleton has been formed. In one method, protoberberinium salts[11] or 8-oxoprotoberberine alkaloids,[12] which are readily available compounds, are treated with organometallic reagents to yield the corresponding 8-substituted berbines. A second method to insert the substituent at C-8 is based on the stereoselective Stevens rearrangement. In previous work, we developed an efficient method for the diastereoselective synthesis of 8-(arylmethyl)-berbines that was based on the Stevens rearrangement of the corresponding *N*-(arylmethyl)berbinium salts with dimsyl sodium in DMSO.[13]

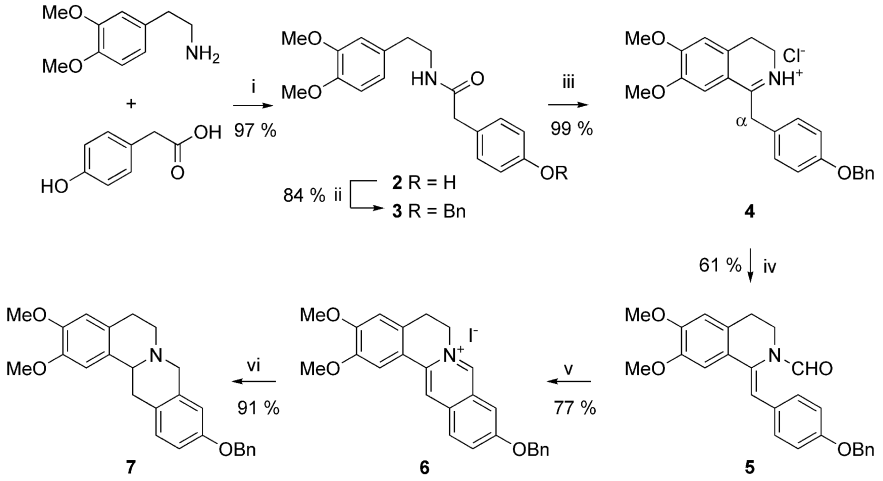
In this paper we describe the full synthesis of compound (±)-**1** and its unknown *cis*-diastereoisomer, as well as three other berbines that are structurally related to **1**, by applying the Stevens rearrangement. Berbinium salts used in this synthesis were prepared from the corresponding berbine and the halo derivative **A** (Scheme 1). The aim was to generate novel variants of compound **1** that could be used to help understand structure–activity relationships in the berbine series.



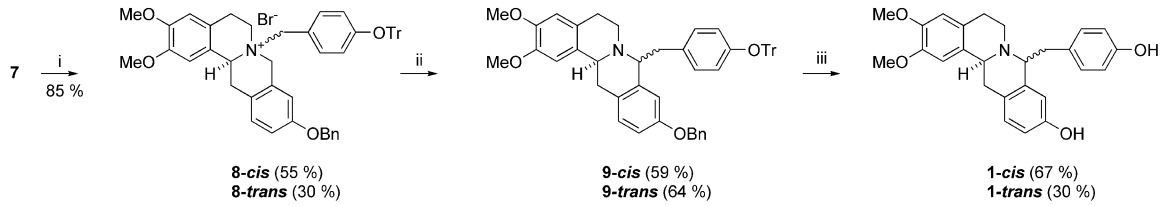
Scheme 1. Retrosynthetic analysis of compound **1**.

Results and Discussion

As shown in Scheme 2, the synthetic route started with the condensation of 2-(3,4-dimethoxyphenyl)ethylamine with (*p*-hydroxyphenyl)acetic acid, which provided the amide **2** in 97% yield. The classical Bischler–Napieralski cyclization reaction was then used to obtain compound **4** from amide **2** after the hydroxy group had been conveniently protected. Because the protecting group used at this stage should be stable under the basic conditions present in the Stevens rearrangement (see below), should be effective in avoiding the generation of by-products along the whole reaction sequence, and should be easily removable at the end of the total synthesis, we tested several protecting groups for their suitability and found the benzyl protecting group to be optimal. Thus, benzyl-protected amide **3** was reacted with $POCl_3$ in acetonitrile to give the corresponding dihydroisoquinoline. Given the high tendency of this compound to undergo spontaneous oxidation to the corresponding α-oxo derivatives, it was isolated as its hydrochloride salt **4**.[14] In a first attempt to build the berbine skeleton, the 1-benzyltetrahydroisoquinoline obtained upon reduction of **4** was subjected to the Mannich reaction.[8a] Unfortunately, no cyclization took place, presumably due to the lack of C-ring activation. As an alternative method, photochemical cyclization of 1-benzylidene-2-formylisoquinoline enamides to protoberberine and subsequent reduction to berbine was considered.[15] Although exactly the same reaction conditions described in the original work were applied to compound **4**, no formylated product was obtained in this case. However, when the reaction was per-



Scheme 2. Synthesis of berbine (**7**): i) Δ, 215 °C; ii) BrBn/K_2CO_3/EtOH; iii) $POCl_3$/CH_3CN, reflux; iv) DEMA, $CHCl_3$, room temp.; v) *hν*/HI, dioxane:*t*BuOH (2:1), room temp.; vi) $NaBH_4$, MeOH, room temp.



Scheme 3. Synthesis of 8-(arylmethyl)berbines **1**-*cis* and **1**-*trans*: i) 1-(bromomethyl)-4-(trityloxy)benzene/K_2CO_3/CH_2Cl_2, room temp.; ii) NaH/DMSO, room temp.; iii) H_2/PtO_2/MeOH, room temp.

formed with diethoxymethyl acetate (DEMA) as formylating agent,[16] the (*Z*)-formyl derivative **5** was obtained in good yield. In the presence of hydriodic acid, enamide **5** furnished the corresponding protoberberine iodide **6**; sodium borohydride reduction of **6** afforded the desired berbine **7** in 91% yield.

According to Scheme 1, the bromobenzyl derivative **A** is the complementary reagent needed for the synthesis of the *N*-(arylmethyl)berbinium salt from berbine. Thus, benzylic bromination of the trityl O-protected *p*-cresol[17] with *N*-bromosuccinimide in CCl_4 led to *p*-(trityloxy)benzyl bromide. The trityl group was chosen for protection because the absence of sensitive hydrogen atoms in this group makes it highly efficient in bromination reactions.

The *N*-(arylmethyl)berbinium salts **8** were prepared according to the standard procedure previously described.[18] Thus, treatment of berbine **7** with *p*-(trityloxy)benzyl bromide and K_2CO_3 in dichloromethane, resulted in the formation of a *cis*/*trans* mixture of diastereoisomers **8** in a 1.5:1 ratio, which was separated by column chromatography (Scheme 3).

Data that discriminated between the two diastereomeric *N*-(arylmethyl)berbinium salts (**8**-*cis* and **8**-*trans*) were provided by ^{13}C NMR spectroscopy (Table 1). Clear differences in the chemical shift of the signals arising from C-6, C-13, and *N*-CH_2Ar were observed for the two diastereomers. Whereas the C-6 signal arising from the *cis* isomer appeared at higher field than for the *trans* isomer, the opposite effect was observed for the second pair of signals. These data are fully consistent with those of other berbinium salts previously reported by us.[13]

Table 1. ^{13}C NMR spectroscopic data for *N*-(arylmethyl)berbinium salts **8** compared to those of previously prepared salts.

	Compound **8**		Berbinium salts[13]	
δ [ppm]	*cis*	*trans*	*cis*	*trans*
C-6	48.8	54.8	49–50	55–56
C-13	34.6	29.0	33–34	29–30
NCH_2Ar	61.6	50.8	62–63	51–52

^1H NMR spectra of the two **8**-*cis* and **8**-*trans* diastereomers contained additional differences, especially for the H-14 and H-8 signals. These two signals both appeared displaced upfield in the spectra of the *cis* and *trans* diastereomers, respectively. A possible explanation for such shielding effects could be given with the aid of molecular modeling.[19] As depicted in Figure 2, the magnetic anisotropy of the *N*-benzyl ring would be responsible for the upfield shifting observed for the two signals.

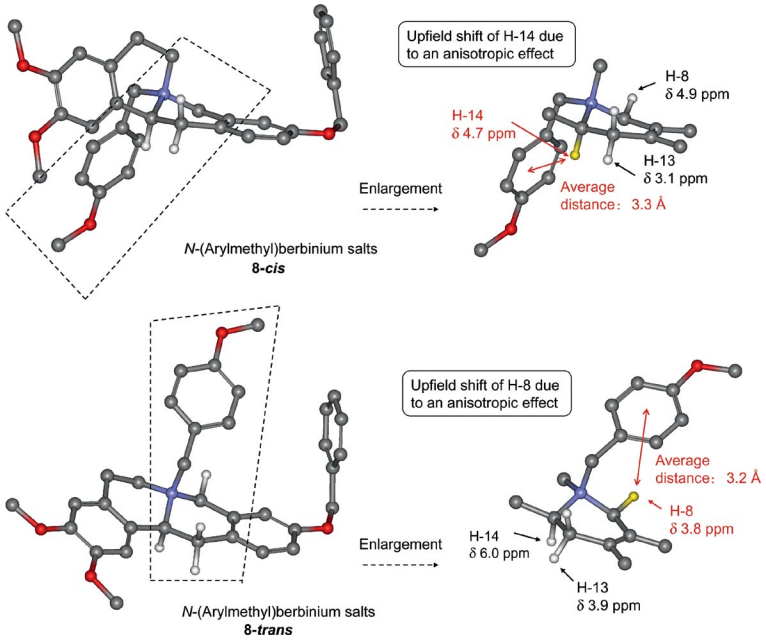


Figure 2. 3D model structures of the most stable conformations of *cis* and *trans* *N*-(arylmethyl)berbinium salts **8**.

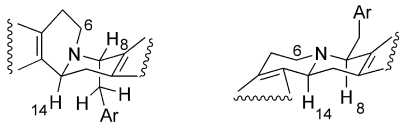
The synthetic strategy applied in this work hinges on the application of the Stevens rearrangement reaction of the *N*-(arylmethyl)berbinium salt, which we described in a previous work.[13] Treatment of the diastereomerically pure berbinium salt **8**-*cis* with dimsyl sodium in DMSO, stereoselectively yielded the 8-(arylmethyl)berbine **9**-*cis*, with the H-14 and the substituent at C-8 in *cis* configuration. Similarly, the same treatment applied to salt **8**-*trans* afforded the diastereomerically pure 8-(arylmethyl)berbine **9**-*trans*.

The relative configuration between H-14 and H-8 in the 8-(arylmethyl)berbines may be ascertained by H,H-NOESY analysis. Berbines that are *cis* 8-substituted exhibit one intense NOE correlation between H-14 and one proton of the benzyl group at C-8, whereas such correlation is observed between H-14 and H-8 in *trans* 8-(arylmethyl)-berbines.

In addition, we have previously established a method, based on differences in configuration and conformation, that allows unequivocal assignment of the *cis* or *trans* configuration of 8-(arylmethyl)berbines using NMR spectroscopic data.[13,20] As can be seen in Table 2, the H-14 signal of the *cis* diastereomer is shifted downfield, whereas signals arising from C-14, C-6 and C-13 are displaced upfield. Comparison of these data with NMR spectroscopic data recorded for compounds **9**-*cis* and **9**-*trans* allow the unequivocal identification of these two stereoisomers. Because the quinolizidine moiety in the berbines can undergo pyramidal inversion at the N-bridgehead, the B/C-rings can be present in different conformations. Thus, the observed shifts reported here are in full accordance with the major contribution of the *cis*-B/C and *trans*-B/C quinolizidine junction in **9**-*cis* and **9**-*trans* berbines, respectively.

It is noteworthy that the ^{1}H NMR spectra show significant differences in the signals arising from protons attached to C-9 and C-13. In fact, the signals arising from H-9 in **9**-*cis* and H-13′ in **9**-*trans* appear displaced upfield. The observed differences can again be explained by molecular modeling.[19] As seen in Figure 3, the upfield shift observed for both H-9 and H-13′ can be due to the anisotropic magnetic effect exerted by the arylmethyl group at C-8.

Table 2. Relevant NMR spectroscopic data for the rearranged product.



cis *trans*

	Compound **9**		8-(Arylmethyl)berbines[13]	
δ [ppm]	*cis*	*trans*	*cis*	*trans*
H-14	4.30	3.53	4.30–4.42	3.45–3.53
C-14	50.9	58.5	50–52	58–59
C-6	46.9	48.7	47–48	48–50
C-13	33.2	36.2	32–34	36–37

In the last step of the synthesis the *O*-benzyl and *O*-trityl protecting groups of **9**-*cis* and **9**-*trans* berbines were removed. No deprotection was observed upon treatment of either **9**-*cis* or **9**-*trans* with H_2 in the presence of Pd/C in ethanol. Treatment of **9**-*cis* with ammonium formate and Pd/C in refluxing ethanol[21] afforded the *O*-trityl-deprotected derivative **10**-*cis* (Scheme 4), whereas no deprotection was observed upon similar treatment of **9**-*trans*. Finally, hydrogenolytic cleavage by pressurized H_2 (3 atm) in the presence of PtO_2 in methanol led to **1**-*cis* and **1**-*trans* berbines in 67% and 30% yield, respectively, after purification. Characterization data for the novel compound **1**-*cis*

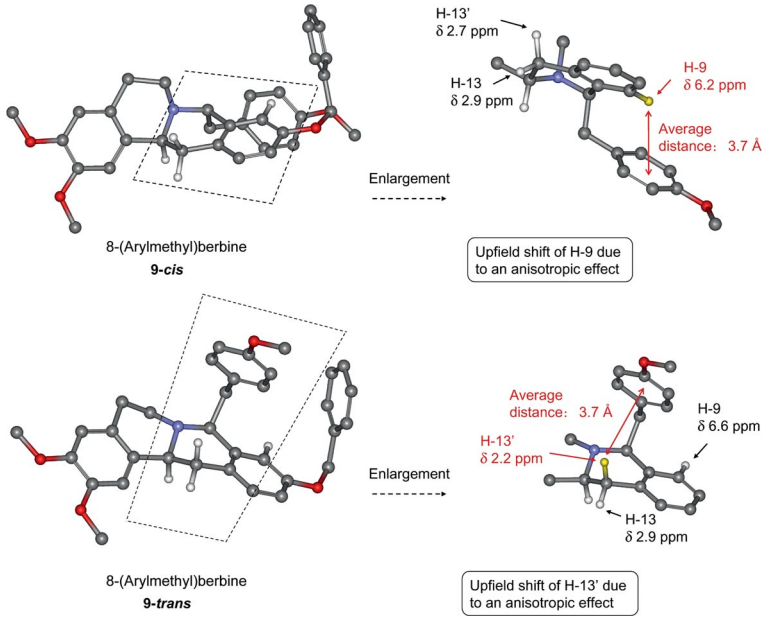
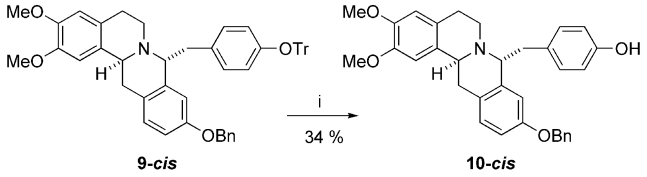


Figure 3. 3D model structures of the more stable conformations of the *cis* and *trans* diastereoisomers **9**.

are given in the Exp. Section and spectroscopic data acquired for the known berbine **1**-*trans* were in full agreement with those previously reported for this compound.[7]



Scheme 4. Synthesis of the 8-(arylmethyl)berbine **10**-*cis*: i) HCO_2NH_4/Pd/C (10%)/EtOH, reflux.

Conclusions

The total synthesis of natural 8-(arylmethyl)berbine **1**-*trans* and its C-8 epimer **1**-*cis*, a non-natural 8-substituted berbine, was attained by following a synthetic route that made use of the diastereoselective Stevens rearrangement as the key step. Application of this methodology to the synthesis of other related natural products and an evaluation of their bioactivity is currently underway.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp instrument and are uncorrected. MS(EI) data were recorded with an HP-MS 5988A spectrometer operating at 70 eV and HRMS data with a VG Autospec spectrometer. EI-HRMS data were recorded by using *m*-nitrobenzyl alcohol as the matrix. Infrared spectra were obtained with an ATR accessory (MIRacle ATR, PIKE Technologies, USA) coupled to an FTIR spectrometer (FT/IR-4100, JASCO). All spectra were recorded in the range from 4000 to 600 cm^{-1} with a resolution of 4 cm^{-1}. NMR spectra were recorded with a Bruker AC 200 instrument operating at 200 MHz for ^1H and 50.3 MHz for ^{13}C NMR, or with a Bruker ARX 400 instrument operating at 400 MHz for ^1H and 100.6 MHz for ^{13}C NMR. Chemical shifts are given relative to residual $CHCl_3$ (δ = 7.24 ppm) or $CDCl_3$ (δ = 77.0 ppm). All solvents were dried and distilled prior to use. Reaction mixtures were magnetically stirred and monitored by TLC with silica gel 60 F_{254} (Merck) or neutral aluminium oxide 60 F_{254} (Merck) plates. Products were purified by column chromatography with either 0.063–0.200 mm silica gel (Merck 7734) or 0.063–0.200 mm neutral aluminium oxide (Merck 1077). 2-(3,4-Dimethoxyphenyl)ethylamine and (*p*-hydroxyphenyl)-acetic acid were purchased from Acros Organics and Aldrich Chemical Co., respectively.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(4-hydroxyphenyl)acetamide (2):** A mixture of (*p*-hydroxyphenyl)acetic acid (6 g, 0.04 mol) and 2-(3,4-dimethoxyphenyl)ethylamine (6.8 mL, 0.04 mol) was stirred at 215 °C for 5 h. The reaction crude was dissolved in $CHCl_3$ and washed with HCl (2.5%, 2 × 200 mL), a saturated solution of $NaHCO_3$ (2 × 200 mL) and water. The organic layers were dried with Na_2SO_4 and the solvent was concentrated under vacuum to yield amide **2** (12.4 g, 97%) as a pale-brown solid; m.p. 139–141 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 8.1 Hz, 2 H, 2′-H, 6′-H), 6.71 (d, *J* = 8.1 Hz, 2 H, 3′-H, 5′-H), 6.67 (d, *J* = 8.1 Hz, 1 H, 5′′-H), 6.54 (s, 1 H, 2′′-H), 6.48 (d, *J* = 8.1 Hz, 1 H, 6′′-H), 5.47 (br. s, 1 H, NH), 3.78, 3.75 (2 × s, 3 H each, 2 × OMe), 3.39 (s, 2 H, CH_2-CO), 3.37 (t, *J* = 7.0 Hz, 2 H, CH_2-CH_2-NH), 2.61 (t, *J* = 7.0 Hz, 2 H, CH_2-CH_2-NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (CO), 155.6 (C-4′), 149.0, 147.6 (C-3′′, C-4′′), 130.9 (C-1′′), 130.6 (C-2′, C-6′), 125.8 (C-1′), 120.6 (C-6′′), 116.0 (C-3′, C-5′), 111.7, 111.3 (C-2′′, C-5′′), 55.9, 55.8 (2 × OMe), 42.8 (*C*H_2-CO), 40.7 (CH_2-*C*H_2-NH), 35.0 (*C*H_2-CH_2-NH) ppm. IR (neat): $\tilde{\nu}$ = 3450, 3308, 3072, 2968, 1640, 1614, 1594, 1545, 1513, 1464, 1293, 1255 cm^{-1}. EI-MS *m*/*z* (%) = 315 (12) $[M]^+$, 164 (100), 151 (22), 107 (20). HRMS: calcd. for $C_{18}H_{21}NO_4$ 315.1470; found 315.1482.

2-(4-Benzyloxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (3): To a solution of **2** (5 g, 15.8 mmol) in EtOH (75 mL), was added K_2CO_3 (2.2 g, 15.8 mmol) and benzyl bromide (1.9 mL, 15.9 mmol). The mixture was refluxed for 12 h and the white solid that was formed was filtered, dissolved in $CHCl_3$ (150 mL) and washed with water. The organic layer was dried with $MgSO_4$ and concentrated under vacuum to obtain amide **3** (5.5 g, 84%) as a white solid; m.p. 110–111 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.24 (m, 5 H, Ph-H), 7.01 (d, *J* = 8.6 Hz, 2 H, 2′-H, 6′-H), 6.85 (d, *J* = 8.6 Hz, 2 H, 3′-H, 5′-H), 6.66 (d, *J* = 8.1 Hz, 1 H, 5′′-H), 6.55 (s, 1 H, 2′′-H), 6.49 (d, *J* = 8.1 Hz, 1 H, 6′′-H), 5.29 (br. s, 1 H, NH), 5.00 (s, 2 H, CH_2Ph), 3.78, 3.77 (2 × s, 3 H each, 2 × OMe), 3.41 (s, 2 H, CH_2-CO), 3.37 (t, *J* = 7.0 Hz, 2 H, CH_2CH_2NH), 2.62 (t, *J* = 7.0 Hz, 2 H, C$H_2$$CH_2$NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (CO), 157.9 (C-4′), 148.8, 147.47 (C-3′′, C-4′′), 136.7 (Ph-C_q), 131.0 (C-1′′), 130.4 (C-2′, C-6′), 128.4, 127.9, 127.3 (Ph-CH), 126.9 (C-1′), 120.4 (C-6′′), 115.1 (C-3′, C-5′), 111.6, 111.1 (C-2′′, C-5′′), 69.8 (*C*H_2Ph), 55.7, 55.6 (2 × OMe), 42.7 (*C*H_2CO), 40.6 (CH_2*C*H_2NH), 34.9 (*C*$H_2$$CH_2$NH) ppm. IR (neat): $\tilde{\nu}$ = 3319, 3067, 2963, 2939, 1639, 1611, 1590, 1541, 1510, 1466, 1438, 1236, 1226 cm^{-1}. EI-MS *m*/*z* (%) = 405 (15) $[M]^+$, 164 (100), 151 (23), 149 (17), 91 (50).

1-(4-Benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Chloride (4): A solution of $POCl_3$ (0.46 mL, 5 mmol) in CH_3CN (5 mL) was added dropwise to a solution of amide **3** (1 g, 2.5 mmol) in CH_3CN (30 mL) under argon. The reaction mixture was refluxed for 2 h and concentrated to dryness. The crude material was dissolved in CH_2Cl_2 (30 mL) and washed with NaOH (5%, 3 × 30 mL) to obtain 1-(4-benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline.[22] The dihydroisoquinoline was dissolved in a HCl-saturated MeOH solution (3 mL) and diethyl ether was added until a precipitate was observed. The solid was filtered and dried to yield isoquinolinium salt **4** (1.05 g, 99%) as a pale-yellow solid; m.p. 176–178 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.40–7.22 (m, 7 H, Ph-H, 2′-H, 6′-H), 7.15 (s, 1 H, 8-H), 6.88 (d, *J* = 8.8 Hz, 2 H, 3′-H, 5′-H), 6.70 (s, 1 H, 5-H), 4.99 (s, 2 H, CH_2Ph), 4.41 (br. s, 2 H, α-H), 3.92, 3.76 (2 × s, 3 H each, 2 × OMe), 3.92 (t, *J* = 7.3 Hz, 2 H, 3-H), 2.90 (t, *J* = 7.3 Hz, 2 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.5 (C-1), 158.2, 155.9, 148.3 (C-4′, C-6, C-7), 136.5 (Ph-C_q), 134.0 (C-1′), 130.0 (C-2′, C-6′), 128.5, 127.9, 127.3 (Ph-CH), 125.7, 117.0 (C-4a, C-8a), 115.5 (C-3′, C-5′), 112.2, 110.9 (C-5, C-8), 69.8 (*C*H_2Ph), 56.4, 56.2 (2 × OMe), 41.0 (C-3), 37.8 (C-α), 25.1 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3032, 2958, 2661, 1644, 1603, 1583, 1508, 1454 cm^{-1}. EI-MS: *m*/*z* (%) = 388 (8) $[M]^+$, 387 (31), 386 (48), 356 (20), 296 (34), 91 (100).

1-(4-Benzyloxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxaldehyde (5): A mixture of salt **4** (1 g, 2.36 mmol) and diethoxymethyl acetate (5 mL, 30 mmol) in $CHCl_3$ (45 mL) was stirred at room temperature for 14 h under argon. After this time, water was added and the mixture was stirred for 3 h at room

temperature. The organic phase was washed with 10% aqueous K_2CO_3 until basic pH, dried with $MgSO_4$ and the solvent removed under vacuum. The residue was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 9.6:0.4) to yield compound **5** as a yellowish solid (600 mg, 61%); m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H, CHO), 7.41–7.35 (m, 5 H, Ph-H), 7.31 (d, J = 8.6 Hz, 2 H, 2′-H, 6′-H), 7.17 (s, 1 H, α-H), 6.92 (d, J = 8.6 Hz, 2 H, 3′-H, 5′-H), 6.75, 6.58 (2 × s, 1 H each, 5-H, 8-H), 5.03 (s, 2 H, CH_2Ph), 3.96 (t, J = 5.9 Hz, 2 H, 3-H), 3.93, 3.86 (2 × s, 3 H each, 2 × OMe), 2.86 (t, J = 5.9 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (CHO), 157.7 (C-4′), 149.5, 147.9 (C-6, C-7), 136.7 (Ph-C_q), 132.4 (C-1′), 130.0 (C-2′, C-6′), 128.5, 127.9, 127.4 (Ph-CH), 127.7, 127.3 (C-4a, C-8a), 123.5 (C-1), 115.2 (C-3′, C-5′), 113.3, 111.5 (C-5, C-8), 105.4 (C-α), 69.9 (*C*H_2Ph), 56.0, 55.8 (2 × OMe), 38.4 (C-3), 28.7 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3063, 2954, 2723, 1670, 1601, 1577, 1541, 1461, 1453, 1259 cm^{-1}. EI-MS: *m*/*z* (%) = 416 (20) [M + H]$^+$, 415 (54) [M]$^+$, 414 (12), 386 (22), 325 (35), 324 (100), 296 (62), 280 (20), 91 (38). HRMS: calcd. for $C_{26}H_{25}NO_4$ 415.1784; found 415.1788.

10-Benzyloxy-2,3-dimethoxyberberinium Iodide (6): A solution of enamide **5** (739 mg, 1.78 mmol) in a mixture of dioxane/*tert*-butyl alcohol (2:1, 400 mL) and HI (1.5 mL, 57%), was stirred at room temperature under helium and irradiated with a mercury lamp (125 W). After 48 h irradiation, a yellow precipitate was formed, which was filtered and washed with several portions of diethyl ether to obtain compound **6** (718 mg, 77%); m.p. 275–277 °C. ^{1}H NMR (200 MHz, DMSO): δ = 9.74 (s, 1 H, 8-H), 9.03 (s, 1 H, 13-H), 8.20 (d, J = 9.0 Hz, 1 H, 12-H), 7.92 (dd, J = 9.0, 1.9 Hz, 1 H, 11-H), 7.83 (d, J = 1.9 Hz, 1 H, 9-H), 7.71 (s, 1 H, 1-H), 7.55 (d, J = 6.8 Hz, 2 H, Ph-H), 7.48–7.38 (m, 3 H, Ph-H), 7.11 (s, 1 H, 4-H), 5.38 (s, 2 H, CH_2Ph), 4.86 (t, J = 5.9 Hz, 2 H, 6-H), 3.94, 3.87 (2 × s, 3 H each, 2 × OMe), 3.23 (t, J = 5.9 Hz, 2 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.7 (C-10), 151.4, 148.5 (C-2, C-3), 147.7 (Ph-C_q), 138.2 (C-8), 135.7 (C-14), 134.3, 130.0, 128.9, 128.4 (C-12a, C-14a, C-8a, C-1a), 128.5, 128.2, 127.8 (Ph-CH), 127.0 (C-13), 120.0, 118.7 (C-12, C-9), 111.1, 108.6, 107.5 (C-11, C-1, C-4), 70.0 (*C*H_2Ph), 56.1, 55.8 (2 × OMe), 55.4 (C-6), 25.9 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3053, 2969, 1603, 1570, 1512, 1455, 1267 cm^{-1}. EI-MS: *m*/*z* (%) = 398 (61) [M]$^+$, 396 (42), 322 (42), 308 (100), 307 (42), 306 (88), 91 (99). HRMS: calcd. for $C_{26}H_{24}NO_3$ 398.1756; found 398.1758.

10-Benzyloxy-2,3-dimethoxyberbine (7): To a solution of salt **6** (137 mg, 0.26 mmol) in MeOH, $NaBH_4$ (60 mg, 1.6 mmol) was added over a period of 15 min and the mixture was stirred for 4 h. The solvent was evaporated under vacuum and the obtained residue was dissolved in $CHCl_3$ (30 mL) and washed with water. The organic layer was dried with anhydrous $MgSO_4$ and the solvent was concentrated under vacuum to yield berbine **7** (96 mg, 91%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 7.4 Hz, 2 H, Ph-H), 7.39 (t, J = 7.4 Hz, 2 H, Ph-H), 7.33 (t, J = 7.4 Hz, 1 H, Ph-H), 7.09 (d, J = 8.3 Hz, 1 H, 12-H), 6.83 (d, J = 8.3 Hz, 1 H, 11-H), 6.75 (s, 1 H, 1-H), 6.71 (s, 1 H, 9-H), 6.63 (s, 1 H, 4-H), 5.05 (s, 2 H, CH_2Ph), 3.98 (d, J = 15.0 Hz, 1 H, 8-H), 3.90, 3.88 (2 × s, 3 H each, 2 × OMe), 3.75 (d, J = 15.0 Hz, 1 H, 8′-H), 3.59 (dd, J = 10.9, 3.1 Hz, 1 H, 14-H), 3.28 (dd, J = 15.5, 3.1 Hz, 1 H, 13-H), 3.18–3.11 (m, 2 H, 5-H, 6-H), 2.84 (dd, J = 15.5, 10.9 Hz, 1 H, 13′-H), 2.68–2.57 (m, 2 H, 5′-H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7 (C-10), 147.2 (C-2, C-3), 137.0 (Ph-C_q), 135.3 (C-12a), 129.6 (C-4a), 129.5 (C-12), 128.3, 127.7, 127.2 (Ph-CH), 126.7 (C-14a), 126.5 (C-8a), 113.3 (C-11), 111.7 (C-9), 111.1 (C-4), 108.3 (C-1), 69.8 (*C*H_2Ph), 59.5 (C-14), 58.6 (C-8), 55.8, 55.6 (2 × OMe), 51.2 (C-6), 35.9 (C-13), 28.9 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3030, 2928, 1644, 1609, 1506, 1462, 1446, 1257 cm^{-1}. EI-MS: *m*/*z* (%) = 402 (28) [M + H]$^+$, 401 (69) [M]$^+$, 400 (62) [M – H]$^+$, 311 (38), 310 (100), 210 (13), 190 (34), 176 (19), 91 (72). HRMS: calcd. for $C_{26}H_{27}NO_3$ 401.1991; found 401.1988.

Preparation of Berbinium Salts 8-*cis* and 8-*trans*: A solution of 1-(bromomethyl)-4-(trityloxy)benzene (prepared from *p*-trityloxytoluene[17] and NBS) (624 mg, 1.45 mmol) in dry CH_2Cl_2 (10 mL), was added to a mixture of berbine **7** (530 mg, 1.32 mmol) and K_2CO_3 (200 mg, 1.45 mmol) in dry CH_2Cl_2 (15 mL) under argon. The reaction mixture was stirred at room temperature for 20 h, then the K_2CO_3 was filtered off and the solvent was concentrated under vacuum. The crude ^{1}H NMR spectrum indicated a mixture of stereoisomers **8** in a *cis*/*trans* ratio of 1.5:1, which was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 9.6:0.4) to obtain the pure diastereoisomers **8-*cis*** (603 mg, 55%) and **8-*trans*** (329 mg, 30%).

(±)-*cis*-10-Benzyloxy-2,3-dimethoxy-*N*-[(*p*-trityloxy)benzyl]berbinium Bromide (8-*cis*): Yellow solid; m.p. 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 7.0 Hz, 6 H, C(Ph-H)$_3$), 7.24–7.16 (m, 16 H, 2′′-H, 6′′-H, C(Ph-H)$_3$, Ph-H), 6.93 (d, J = 8.0 Hz, 1 H, 12-H), 6.84 (dd, J = 8.0, 1.6 Hz, 1 H, 11-H), 6.78 (d, J = 1.6 Hz, 1 H, 9-H), 6.70 (d, J = 8.6 Hz, 2 H, 3′′-H, 5′′-H), 6.71, 6.58 (2 × s, 1 H each, 1-H, 4-H), 5.22 (d, J = 12.9 Hz, 1 H, α-H), 5.07 (d, J = 15.6 Hz, 1 H, 8-H), 4.99 (d, J = 5.4 Hz, 2 H, CH_2Ph), 4.89 (d, J = 15.6 Hz, 1 H, 8′-H), 4.75 (d, J = 12.9 Hz, 1 H, α′-H), 4.74 (dd, J = 10.2, 6.7 Hz, 1 H, 14-H), 4.24 (dd, J = 11.3, 9.7 Hz, 1 H, 6-H), 3.85 (s, 6 H, 2 × OMe), 3.56 (ddd, J = 11.3, 9.7, 4.8 Hz, 1 H, 6′-H), 3.44–3.26 (m, 2 H, 5-H, 5′-H), 3.14 (dd, J = 18.3, 6.7 Hz, 1 H, 13-H), 2.96 (dd, J = 18.3, 10.2 Hz, 1 H, 13′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 158.1 (C-10, C-4′′), 149.7, 148.7 (C-2, C-3), 143.4 (3 × C_q C*Ph*$_3$), 136.2 (C_q CH_2*Ph*), 133.6 (C-2′′, C-6′′), 128.9 (C-12), 128.6, 128.5, 128.0, 127.7, 127.4, 127.3 (CH C*Ph*$_3$, CH_2*Ph*), 128.4, 126.9, 124.0, 119.9, 118.9 (C-1′′, C-4a, C-8a, C-12a, C-14a), 121.4 (C-3′′, C-5′′), 116.8 (C-11), 112.2 (C-9), 111.7, 109.1 (C-1, C-4), 91.1 (*C*Ph$_3$), 70.0 (*C*H_2Ph), 61.7 (C-14), 61.6 (C-α), 58.3 (C-8), 56.3, 56.0 (2 × OMe), 48.8 (C-6), 34.6 (C-13), 23.1 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3028, 2934, 1612, 1509, 1446, 1266 cm^{-1}. FAB-MS: *m*/*z* (%) = 751 (1) [M + H]$^+$, 750 (2) [M]$^+$, 508 (100), 403 (20), 402 (71), 401 (15), 400 (37), 310 (18), 243 (42), 192 (18). HRMS: calcd. for $C_{52}H_{48}NO_4$ 750.3583; found 750.3585.

(±)-*trans*-10-Benzyloxy-2,3-dimethoxy-*N*-[(*p*-trityloxy)benzyl]berbinium Bromide (8-*trans*): Yellow solid; m.p. 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.5 Hz, 6 H, C(Ph-H)$_3$), 7.37–7.20 (m, 16 H, 2′′-H, 6′′-H, C(Ph-H)$_3$, Ph-H), 7.14 (d, J = 8.6 Hz, 1 H, 12-H), 6.98 (dd, J = 8.6, 2.1 Hz, 1 H, 11-H), 6.70–6.66 (m, 4 H, 1-H, 4-H, 3′′-H, 5′′-H), 6.49 (d, J = 2.1 Hz, 1 H, 9-H), 6.06 (dd, J = 11.8, 5.6 Hz, 1 H, 14-H), 5.71 (d, J = 15.3 Hz, 1 H, 8-H), 5.07 (d, J = 11.8 Hz, 1 H, α-H), 5.02 (s, 2 H, CH_2Ph), 4.93–4.84 (m, 1 H, 6-H), 3.96–3.93 (m, 1 H, 13-H), 3.89, 3.87 (2 × s, 3 H each, 2 × OMe), 3.80 (d, J = 15.3 Hz, 1 H, 8′-H), 3.36–3.19 (m, 4 H, α′-H, 6′-H, 5-H, 5′-H), 3.14 (dd, J = 16.9, 11.8 Hz, 1 H, 13′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 158.3 (C-10, C-4′′), 149.6, 148.8 (C-2, C-3), 143.3 (3 × C_q C*Ph*$_3$), 136.3 (C_q CH_2*Ph*), 132.1 (C-2′′, C-6′′), 130.4 (C-12), 128.7, 128.5, 127.9, 127.5, 127.3, 127.2 (CH C*Ph*$_3$, CH_2*Ph*), 129.5, 128.1, 127.7, 117.7, 116.7 (C-1′′, C-4a, C-8a, C-12a, C-14a), 121.6 (C-3′′, C-5′′), 115.3 (C-11), 112.3 (C-9), 111.1, 108.4 (C-1, C-4), 91.4 (*C*Ph$_3$), 70.2 (*C*H_2Ph), 66.2 (C-14), 60.5 (C-8), 56.3, 56.0 (2 × OMe), 54.8 (C-6), 50.8 (C-α), 29.0 (C-13), 23.7 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3058, 2919, 2850, 1647, 1607, 1508, 1448, 1263 cm^{-1}. FAB-MS: *m*/*z* (%) = 751 (2) [M + H]$^+$, 750 (3) [M]$^+$, 402 (13), 401 (10), 400 (16), 310 (10), 243 (100), 192 (10), 191 (10). HRMS: calcd. for $C_{52}H_{48}NO_4$ 750.3583; found 750.3571.

General Method for the Stevens Rearrangement:[13] A solution of NaH (150 mg, 3.71 mmol) in DMSO (5 mL, 65 mmol) was stirred for 90 min at 80 °C under argon. Once the dimsyl sodium was formed, the corresponding berbinium salt (250 mg, 0.3 mmol) was added and the mixture was stirred for 5 h at room temperature. The reaction was monitored by ^{1}H NMR spectroscopy and TLC. The reaction mixture was poured onto ice, the precipitate was filtered off, and the corresponding 8-substituted berbine was purified by column chromatography (Al_2O_3, cyclohexane/EtOAc, 9:1).

(8*R,14*S**)-10-Benzyloxy-2,3-dimethoxy-8-[(*p*-trityloxy)benzyl]berbine (9-*cis*):** According to the above procedure, the 8-arylmethyl derivative **9-*cis*** (133 mg, 59%) was obtained from **8-*cis*** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.15 (m, 20 H, C(Ph-H)$_3$, Ph-H), 6.96 (d, J = 8.1 Hz, 1 H, 12-H), 6.75 (d, J = 8.1 Hz, 1 H, 11-H), 6.74 (d, J = 8.6 Hz, 2 H, 2′′-H, 6′′-H), 6.63, 6.58 (2 × s, 1 H each, 1-H, 4-H), 6.57 (d, J = 8.6 Hz, 2 H, 3′′-H, 5′′-H), 6.16 (s, 1 H, 9-H), 4.83 (s, 2 H, CH_2Ph), 4.30 (dd, J = 10.2, 5.9 Hz, 1 H, 14-H), 3.87, 3.85 (2 × s, 3 H each, 2 × OMe), 3.84–3.82 (m, 1 H, 8-H), 3.07 (dd, J = 12.9, 6.7 Hz, 1 H, α-H), 2.96–2.87 (m, 2 H, 6-H, 13-H), 2.81–2.71 (m, 5 H, 6′-H, 5-H, 5′-H, 13′-H, α′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 154.6 (C-10, C-4′′), 147.5, 147.2 (C-2, C-3), 144.2 (3 × C_q CPh_3), 137.1 (C_q CH_2Ph), 133.2 (C-1′′), 129.6 (C-2′′, C-6′′), 129.0, 128.5, 127.9, 127.6, 127.0 (CH CPh_3, CH_2Ph), 127.2 (C-12), 131.1, 131.0, 126.2, 125.6 (C-4a, C-8a, C-12a, C-14a), 121.1 (C-3′′, C-5′′), 113.9, 113.4 (C-11, C-9), 111.5, 109.3 (C-1, C-4), 90.4 (*C*Ph$_3$), 69.7 (*C*H$_2$Ph), 67.1 (C-8), 56.0, 55.8 (2 × OMe), 50.9 (C-14), 46.9 (C-6), 39.9 (C-α), 33.2 (C-13), 29.6 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3023, 2921, 2832, 1607, 1504, 1462, 1445, 1255, 1223 cm^{-1}. FAB-MS: m/z (%) = 750 (25) [M + H]$^+$, 748 (7) [M – H]$^+$, 746 (7), 400 (80), 310 (11), 243 (100), 192 (20), 165 (31). HRMS: [MH]$^+$ calcd. for $C_{52}H_{48}NO_4$ 750.3583; found 750.3563.

(8*S,14*S**)-10-Benzyloxy-2,3-dimethoxy-8-[(*p*-trityloxy)benzyl]berbine (9-*trans*):** According to the above procedure, the 8-arylmethyl derivative **9-*trans*** (145 mg, 64%) was obtained from **8-*trans*** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.14 (m, 20 H, C(Ph-H)$_3$, Ph-H), 6.92 (d, J = 8.1 Hz, 1 H, 12-H), 6.72 (d, J = 8.1 Hz, 1 H, 11-H), 6.69, 6.58 (2 × s, 1 H each, 1-H, 4-H), 6.56 (s, 1 H, 9-H), 6.55 (d, J = 8.6 Hz, 2 H, 2′′-H, 6′′-H), 6.41 (d, J = 8.6 Hz, 2 H, 3′′-H, 5′′-H), 4.94 (s, 2 H, CH_2Ph), 3.87, 3.86 (2 × s, 3 H each, 2 × OMe), 3.88–3.85 (m, 1 H, 8-H), 3.53 (d, J = 10.8 Hz, 1 H, 14-H), 3.13 (dd, J = 11.3, 2.0 Hz, 1 H, α-H), 2.94 (d, J = 14.5 Hz, 1 H, 13-H), 2.96–2.87 (m, 2 H, 6-H, 5-H), 2.80 (dd, J = 11.3, 4.0 Hz, 1 H, α′-H), 2.54–2.48 (m, 2 H, 6′-H, 5′-H), 2.25 (dd, J = 14.5, 10.8 Hz, 1 H, 13′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 154.4 (C-4′′, C-10), 147.3, 147.1 (C-2, C-3), 144.2 (3 × C_q CPh_3), 139.0 (C_q CH_2Ph), 137.1 (C-1′′), 131.8 (C-12), 129.9 (C-2′′, C-6′′), 129.0, 128.0, 127.5, 127.2, 127.0 (CH CPh_3, CH_2Ph), 130.6, 129.4, 126.8, 126.3 (C-4a, C-8a, C-12a, C-14a), 120.5 (C-3′′, C-5′′), 112.8, 112.7 (C-11, C-9), 111.3, 108.8 (C-1, C-4), 90.3 (*C*Ph$_3$), 69.9 (*C*H$_2$Ph), 65.7 (C-8), 58.5 (C-14), 56.1, 55.8 (2 × OMe), 48.7 (C-6), 42.6 (C-α), 36.2 (C-13), 29.9 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3065, 2931, 1598, 1505, 1490, 1445, 1375, 1270 cm^{-1}. FAB-MS: m/z (%) = 750 (14) [M + H]$^+$, 749 (4) [M]$^+$, 748 (7) [M – H]$^+$, 746 (12), 400 (14), 243 (100), 192 (11), 165 (21). HRMS: [MH]$^+$ calcd. for $C_{52}H_{48}NO_4$ 750.3583; found 750.3588.

(8*R,14*S**)-10-Benzyloxy-2,3-dimethoxy-8-[(*p*-hydroxy)benzyl]berbine (10-*cis*):** To a solution of berbine **9-*cis*** (31.2 mg, 0.04 mmol) in ethanol (2 mL), were added 10% Pd/C (18.8 mg) and ammonium formate (11.4 mg, 0.18 mmol). The reaction mixture was refluxed for 2 h and filtered through Celite-512. The solvent was removed under vacuum and the residue was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 9.6:0.4) to yield berbine **10-*cis*** as a yellow oil (7 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.34 (m, 5 H, Ph-H), 6.99 (d, J = 8.1 Hz, 2 H, 2′′-H, 6′′-H), 6.99 (d, J = 8.1 Hz, 1 H, 12-H), 6.77 (dd, J = 8.1, 2.1 Hz, 1 H, 11-H), 6.72 (d, J = 8.1 Hz, 2 H, 3′′-H, 5′′-H), 6.66, 6.58 (2 × s, 1 H each, 1-H, 4-H), 6.18 (d, J = 2.1 Hz, 1 H, 9-H), 4.79 (d, J = 5.4 Hz, 2 H, CH_2Ph), 4.39 (dd, J = 11.3, 5.2 Hz, 1 H, 14-H), 3.92 (m, 1 H, 8-H), 3.88, 3.84 (2 × s, 3 H each, 2 × OMe), 3.22 (dd, J = 13.2, 5.2 Hz, 1 H, 13-H), 3.06–3.02 (m, 1 H, 6-H), 2.98 (dd, J = 17.2, 5.1 Hz, 1 H, α-H), 2.90–2.74 (m, 5 H, 6′-H, 5-H, 5′-H, α′-H, 13′-H) ppm. IR (neat): $\tilde{\nu}$ = 3442, 3015, 2954, 2919, 2851, 1608, 1513, 1504, 1455, 1257, 1225 cm^{-1}. FAB-MS: m/z (%) = 508 (42) [M + H]$^+$, 507 (13) [M]$^+$, 506 (25) [M – H]$^+$, 401 (32), 400 (100), 310 (17), 192 (36), 165 (13). HRMS: [M + H]$^+$ calcd. for $C_{33}H_{34}NO_4$ 508.2488; found 508.2491.

(8*R,14*S**)-2,3-Dimethoxy-8-(4′-hydroxybenzyl)berbin-10-ol (1-*cis*):** To a solution of **9-*cis*** (37.5 mg, 0.05 mmol) in EtOH (40 mL), was added PtO_2 (4 mg) and the mixture was stirred under hydrogen (40 psi, ≈ 3 atm) at room temperature for 48 h. The platinum oxide was filtered, the solvent concentrated under vacuum, and the residue was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 9.6:0.4) to yield **1-*cis*** as a pale-yellow solid (16 mg, 67%); m.p. 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, J = 7.9 Hz, 2 H, 2′′-H, 6′′-H), 6.84 (d, J = 8.1 Hz, 1 H, 12-H), 6.64 (d, J = 7.9 Hz, 2 H, 3′′-H, 5′′-H), 6.59–6.52 (m, 3 H, 11-H, 1-H, 4-H), 5.86 (d, J = 2.1 Hz, 1 H, 9-H), 4.29 (dd, J = 11.0, 5.0 Hz, 1 H, 14-H), 3.82 (dd, J = 7.5, 4.5 Hz, 1 H, 8-H), 3.79, 3.76 (2 × s, 3 H each, 2 × OMe), 3.15 (dd, J = 13.0, 4.5 Hz, 1 H, α-H), 3.00–2.90 (m, 1 H, 6-H), 2.97 (dd, J = 16.7, 5.0 Hz, 1 H, 13-H), 2.80–2.60 (m, 3 H, 6′-H, 5-H, 5′-H), 2.69 (dd, J = 16.7, 11.0 Hz, 1 H, 13′-H), 2.68 (dd, J = 13.0, 7.5 Hz, 1 H, α′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 153.6 (C-4′′, C-10), 147.3, 147.1 (C-2, C-3), 137.6 (C-1′′), 130.8, 129.5, 125.8, 123.8 (C-8a, C-14a, C-4a, C-12a), 130.6 (C-2′′, C-6′′), 128.6 (C-12), 114.8 (C-3′′, C-5′′), 113.9, 113.8 (C-11, C-9), 111.5, 109.2 (C-4, C-1), 67.0 (C-8), 55.8, 55.6 (2 × OMe), 51.0 (C-14), 46.8 (C-6), 39.1 (C-α), 33.3 (C-13), 28.8 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3500–3000, 3025, 2919, 2850, 1610, 1542, 1511, 1450, 1248, 1225 cm^{-1}. FAB-MS: m/z (%) = 418 (62) [M + H]$^+$, 417 (12) [M]$^+$, 416 (33) [M – H]$^+$, 414 (44), 310 (100), 192 (38). HRMS: [M + H]$^+$ calcd. for $C_{26}H_{28}NO_4$ 418.2018; found 418.2024.

(8*S,14*S**)-2,3-Dimethoxy-8-(4′-hydroxybenzyl)berbin-10-ol (1-*trans*):**[7] According to the above procedure, the 8-arylmethyl derivative **1-*trans*** (6 mg, 30%) was obtained from **9-*trans*** as a pale-yellow solid; m.p. 158–163 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.95 (d, J = 8.1 Hz, 1 H, 12-H), 6.92 (d, J = 8.6 Hz, 2 H, 2′′-H, 6′′-H), 6.81, 6.70 (2 × s, 1 H each, 1-H, 4-H), 6.69 (d, J = 8.6 Hz, 2 H, 3′′-H, 5′′-H), 6.60 (dd, J = 8.1, 2.1 Hz, 1 H, 11-H), 6.02 (d, J = 2.1 Hz, 1 H, 9-H), 4.42 (dd, J = 11.2, 5.4 Hz, 1 H, 14-H), 3.99–3.94 (m, 1 H, 8-H), 3.83, 3.80 (2 × s, 3 H each, 2 × OMe), 3.66–3.56 (m, 1 H, α-H), 3.30–3.03 (m, 3 H, α′-H, 6-H, 6′-H), 2.95–2.66 (m, 4 H, 5-H, 5′-H, 13-H, 13′-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 156.9, 155.7 (C-4′′, C-10), 149.3, 149.0 (C-2, C-3), 132.7, 132.0, 130.9, 127.3, 125.1 (C-1′′, C-8a, C-14a, C-4a, C-12a), 131.9 (C-2′′, C-6′′), 123.5 (C-12), 116.1 (C-3′′, C-5′′), 113.3 (C-11), 111.2 (C-4, C-1), 108.9 (C-9), 68.5 (C-8), 56.7, 56.5 (2 × OMe), 52.6 (C-14), 48.0 (C-6), 40.5 (C-α), 34.5 (C-13), 29.7 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3500–3000, 3050, 2929, 2854, 1604, 1539, 1508, 1448, 1255, 1225 cm^{-1}. FAB-MS: m/z (%) = 418 (40) [M + H]$^+$, 417 (22) [M]$^+$, 416 (35) [M – H]$^+$, 414 (53), 310 (100), 192 (33). HRMS: [M + H]$^+$ calcd. for $C_{26}H_{28}NO_4$ 418.2018; found 418.2026.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra for new compounds.

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