Regio- and Stereoselective Stevens Rearrangement of Benzyltetrahydroprotoberberinium Salts

Maria Valpuesta,*[a] Amelia Diaz,[a] Rafael Suau,[a] and Gregorio Torres[a]

Dedicated to the memory of Dr. Fidel Jorge López Herrera

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8-(Arylmethyl)berbines are conveniently obtained through a Stevens rearrangement of the corresponding *N*-arylmethylberbinium salts with sodium methylsulfinylmethylide in DMSO. This procedure has provided two new nonnatural 8-benzylcanadines stereoselectively, without competition from the Hofmann elimination.

Introduction

Tetrahydroprotoberberine alkaloids substituted in ring position 8 constitute an uncommon group of isoquinoline alkaloids that have been isolated from several sources. The substitution pattern at the A or D rings is diverse and all of the 8-substituted tetrahydroprotoberberines possess one or more phenolic group at the D ring. However, only the methyl, hydroxymethyl, and benzyl substituents at the C-8 position have been characterised from natural sources (Figure 1). 8-Methylberbines such as (−)-corytenchirine and (−)-lienkonine were isolated from *Corydalis spp.* a long time ago,[1] and more recently, four new 8-methyl derivatives have been isolated from *Aniba canelilla*[2] and *Croton Hemiargyreus*.[3] (−)-Malacitanine is the first tetrahydroprotoberberine alkaloid described that contains a hydroxymethyl substituent at the C-8 position;[4] (±)-solidaline also possesses this group, but the oxygen atom is bridged to the C-14[5] in this case. Theoneberine constitutes a unique example of a brominated 8-benzyltetrahydroprotoberberine isolated from a marine organism, exhibiting antimicrobial and cytotoxic activities.[6] Several 8-benzyltetrahydroprotoberberines have been isolated from plant sources such as *Aristolochia sp.*[7] or *Gnetum parvifolium*.[8] Javaberine A, recently isolated from *Talinum paniculatum*, presents a 3,4-dioxysubstituted benzyl moiety at C-8 and exhibits a strong inhibitory activity on the lipopolysaccharide-induced tumour necrosis factor.[9]

Figure 2 shows the different strategies for the synthesis of 8-substituted berbines. The intramolecular Mannich reaction of 1-benzyltetrahydroisoquinoline with aldehydes under acidic conditions (*disconnection a*) constitutes a classical route for systems with an activated C ring, but this reaction lacks regio- and stereoselectivity.[4,10] This disconnection has also been exploited by the *N*-acylation of 1-benzylisoquinolines and subsequent acid catalysis[11] or by photochemical cyclisation.[12] An alternative pathway (*disconnection b*), based on the classical Bischler−Napieralski[13] or Pictet−Spengler[14] cyclisations, has been employed for 1-substituted *N*-(phenylethyl)tetrahydroisoquinoline to yield 8-alkyl- and 8-arylberbines. The imminium annelation of C2′-functionalized 3-arylisoquinolines (*disconnection c*) has proved to be efficient for the synthesis of 8-substituted tetrahydroprotoberberine based on a double cyclization approach.[15] Finally, *disconnection d*,

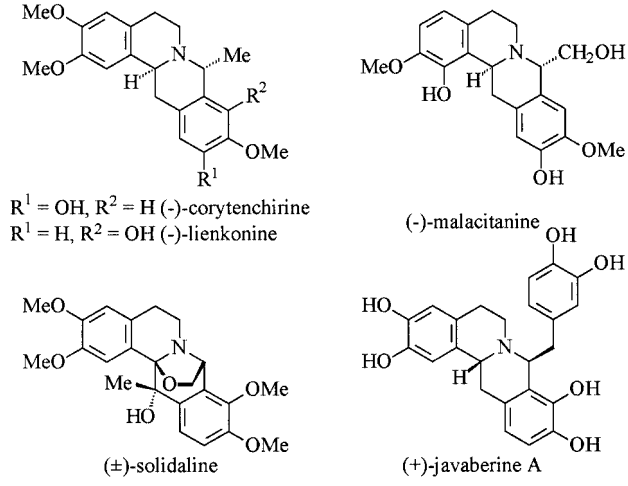


Figure 1. Structure of relevant 8-substituted tetrahydroprotoberberine alkaloids

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga,
Campus de Teatinos s/n Málaga, Spain
Fax (internat.): +34-952-13-19-41
E-mail: mvalpuesta@uma.es

based on the introduction of the C-8 substituent, has also been applied once the isoquinoline skeleton is formed. In this last case, protoberberinium salts[16] or 8-oxoprotoberberine alkaloids,[17] easily available through classical methods, are treated with organometallic reagents to yield the corresponding 8-substituted berbines. The introduction of substituents at C-8 can also be performed by photochemical hydroxymethylation[18] or through the Polonovski−Potier reaction of berbine *N*-oxides.[19] A parallel strategy for the insertion of a substituent at C-8 is based on Stevens rearrangement. This reaction has been used by Kametani et al. for the synthesis of (±)-8β-methylcanadine and (±)-xilopinine starting from the corresponding *N*-methyltetrahydroprotoberberinium salts.[20] However, in this case, two pathways compete to yield spirobenzylisoquinoline as the major product besides the 8-substituted berbine. In contrast, Takemoto et al.[21] reported that base treatment of the *N*-methylcanadinium salt exclusively yields ochotensane-type alkaloids and Hofmann elimination products.

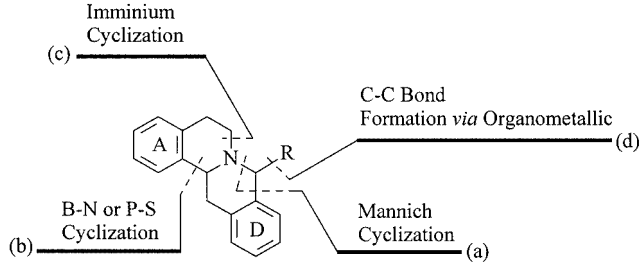


Figure 2. Strategies for the synthesis of 8-substituted berbines

As part of our studies on the synthesis of 8-substituted berbines, we describe herein the use of the Stevens rearrangement to synthesise 8-benzylberbines.

Results and Discussion

The syntheses of *N*-benzyl- and *N*-(*p*-methoxybenzyl)-canadinium bromide (**1**, **2**; Figure 4) was achieved following standard methods; both products were obtained as a mixture of *cis* and *trans* diastereomers (***cis*-1**/***trans*-1**, 8:1; ***cis*-2**/***trans*-2**, 4:1). Typically, iodomethylation of tetrahydroprotoberberines yields the *trans* diastereomer as the major product, but in the benzylation reaction, the *cis* diastereoisomer is the major product, probably due to steric and/or electronic factors. Both diastereomers were separated by fractional crystallisation. Although analogous benzyl derivatives have recently been described as sodium, potassium and calcium ion channel inhibitors,[22] no spectroscopic data for the pure diastereomers have been reported. We characterised these structures by standard spectroscopic methods. The H,H-NOESY experiment concludes that the *trans* salts possess a unique configuration, while the *cis* salts are in equilibrium between two conformations of the *B*/*C* quinolizidine moiety, namely *cis*-1 and *cis*-2. The most significant ^{13}C NMR chemical shift of both configurations is shown in Figure 3. Similarly to those for the *N*-methyl salts previously reported,[23] the signals for C-13 and *N*-CH_2Ar are shifted downfield for the *cis* configuration relative to those for the *trans* salt, while the C-6 signal exhibits an upfield shift. The reason for this behaviour is the influence of the γ-gauche effect on the ^{13}C NMR chemical shift.[24] These shifts can be used to assign the *cis* or *trans* configuration to a berbinium salt, independent of the alkyl substituent introduced at the quaternary nitrogen atom.

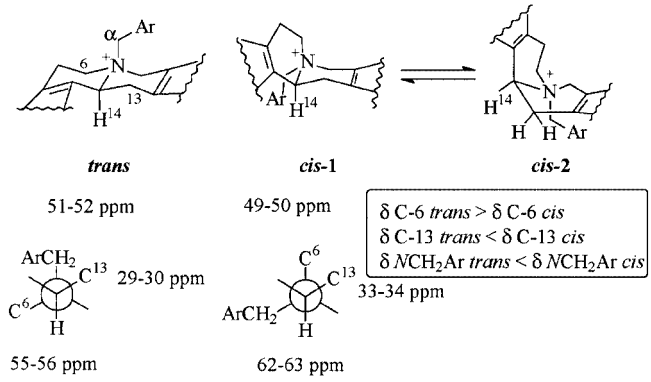


Figure 3. Relevant ^{13}C NMR spectroscopic data of the *N*-arylmethylcanadinium salts

When treated with a base, these salts may react through two competitive pathways: Hofmann elimination and/or Stevens rearrangement. The Hofmann elimination occurs by hydrogen removal at C-5 and C-13 to provide 3-arylisoquinolines **7**, **8** and dibenzoazecines **5**, **6** in a ratio that strongly depends on the base and solvent employed. Otherwise, the Stevens rearrangement exclusively yields 8-arylmethylberbines **3** and **4** (Figure 4) derived from a nitrogen ylide formed at C-8.

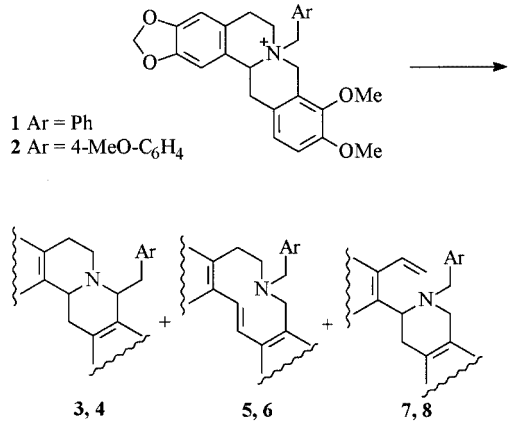


Figure 4. Reaction of benzylcanadinium salts under basic medium

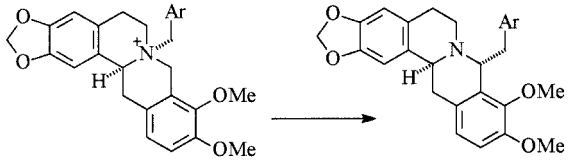
In Table 1 the yields obtained by treating *N*-benzylcanadinium bromide (**1**) with different bases and solvents are shown. As can be seen, the elimination products **5** + **7** are strongly favoured in hydroxylic solvents with medium bases, while strong bases and highly polar nonprotic solvents favour the Stevens rearrangement pathway. The behaviour of *N*-(*p*-methoxybenzyl)canadinium bromide (**2**) was also evaluated following the same pattern. The most advan-

tageous conditions for the generation of the 8-benzyl- or 8-(*p*-methoxybenzyl)canadine (**3** or **4**) make use of dimsylsodium in DMSO; under these circumstances, no elimination product was detected.

Table 1. Yields of **3** and **5** + **7** under different conditions (estimation based on the ^{1}H NMR spectrum)

Base	Solvent	Percentage [%]	
		3	**5** + **7**
	*t*BuOH	–	> 90
MeONa	THF	≈ 50	≈ 50
	DMSO	≈ 60	≈ 40
	*t*BuOH	–	> 90
*t*BuOK	THF	≈ 50	≈ 50
	DMSO	≈ 60	≈ 40
	Hexane	10	90
HNa	Benzene	15	85
	THF	55	45
	DMSO	70	30
$NaCH_2SOCH_3$	DMSO	100	–

When the optimized conditions for the Stevens rearrangement were used, the diastereomeric salts **1** or **2** yielded a mixture of diastereomers **3** or **4**, respectively, that can easily be separated by column chromatography. As is expected, the diastereomers were isolated in a ratio similar to the *cis*/*trans* ratio of the starting material as predicted by stereochemical control of the rearrangement. In order to confirm the stereochemical behaviour, we evaluated the reaction with the diastereomerically pure derivatives. Thus, treatment of the *cis*-(8-arylmethyl)canadinium salts (***cis*-1** or ***cis*-2**) with dimsylsodium in DMSO stereoselectively yielded the 8-arylmethylcanadine (***cis*-3** or ***cis*-4**) derivatives with a *cis* configuration between H-14 and the substituent at C-8 (Figure 5).

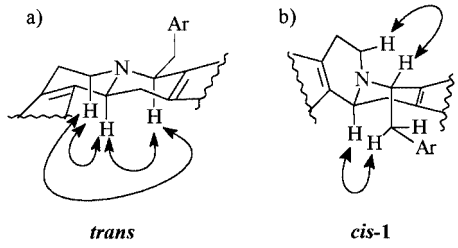


1 ***cis*** Ar = Ph
2 ***cis*** Ar = 4-MeO-C_6H_4

3 ***cis*** Ar = Ph
4 ***cis*** Ar = 4-MeO-C_6H_4

Figure 5. Stevens rearrangement of **1***cis* and **2***cis*

The H,H-NOESY experiment proves the relative configuration between H-14 and H-8 by the presence of two intense NOE effects between H-8 and H-6a and between H-14 and one hydrogen atom of the benzyl group (Figure 6, a). The quinolizidine moiety of berbine alkaloids can be present in three different conformations, which are in equilibrium in solution. As a rule of thumb, in tetrahydroprotoberberines a high-field chemical shift for carbon atoms C-14, C-6 and C-13, as well as a deshielding of H-14 suggest a major contribution of the *cis*-1 conformation to the equilibrium.[23] In our case, the spectrum for 8-benzylcanadine (***cis*-1**) exhibits a signal for H-14 at δ = 4.41 ppm (J = 10.3, 6.1 Hz), and signals for C-6 and C-13 at δ = 46.8 ppm and δ = 31.9 ppm, respectively, thus validating the major contribution of the *cis*-B/C quinolizidine conformation.



trans ***cis*-1**

Figure 6. a) Observed NOE effect for ***trans*-3** and ***trans*-4**; b) Observed NOE effect for ***cis*-3** and ***cis*-4**

Under identical conditions, the *trans*-*N*-benzylcanadinium salt (***trans*-1**) yields only one product (***trans*-1**) with a *trans*-B/C quinolizidine junction, according to its nuclear magnetic resonance and infrared (Bohlmann's bands[25]) spectra (see Table 2). This compound exhibits three intense NOE effects between H-14, H-6 and H-8, proving a *trans* relative configuration between the substituent at C-8 and H-14 (Figure 6, b). The stereoselectivity of this rearrangement is confirmed using ***trans*-2** as a substrate.

Table 2. Relevant spectroscopic data for the rearranged products

	***trans*-3**	***trans*-4**	***cis*-3**	***cis*-4**
δ (H-14) [ppm]	3.47	3.46	4.41	4.38
δ (C-14) [ppm]	58.9	58.9	50.5	50.1
δ (C-6) [ppm]	50.2	50.1	46.8	47.0
δ (C-13) [ppm]	36.8	36.9	31.9	31.9
IR Bohlmann bands [cm^{-1}]	2800, 2771	2802, 2768	absent	absent

The great efficiency of these results reveals a high reactivity of the C-8 carbanion α to the quaternary nitrogen atom relative to other potential ylides that can be produced at C-14 or C-α. Once the nitrogen ylide is generated at C-8, the subsequent step in the Stevens rearrangement implies the generation of an imminium ion or an imminium radical inside a solvent cage.[26] Any of these pathways generate 7,8-dehydrocanadine as the most stable imminium ion or radical, yielding the corresponding 8-substituted berbines. In addition, no spirobenzylisoquinoline or benzazepine structures are detected, demonstrating that the C-8 ylide is the only reactive species present in the reaction mixture. This result differs from that previously reported,[20] which accounts for a C-14 ylide formation leading to spirobenzylisoquinoline as the major compound. The difference in reactivity could be ascribed to the presence of the benzyl group, that probably assists C-8 hydrogen abstraction.

Furthermore, the observed diastereoselectivity indicates that the rearrangement takes place to yield the product that requires minimum movement, retaining the initial configuration of the salt. Remarkably, when the reaction mixture was quenched with deuterium oxide no deuterated com-

pound was isolated, suggesting that the C-8 ylide is present at a very low concentration due to its high reactivity.

Conclusion

In conclusion, we have developed an efficient and short approximation to the synthesis of 8-arylmethylberbines by using a Stevens rearrangement in a diastereoselective approach through treatment of the corresponding *N*-(arylmethyl)berberinium salts with dimsylsodium in DMSO. This method avoids the competition of alternative reactions such as Hofmann elimination, to yield products that are derived from a nitrogen ylide at C-8. Ongoing work in our laboratory involves the use of this reaction in the synthesis of natural products containing this substitution pattern and will be reported in due course.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp instrument and are given uncorrected. UV spectra were recorded with a Hewlett−Packard 8452A spectrophotometer and IR spectra with a Perkin−Elmer 883 spectrophotometer. EI MS were recorded with a HP-MS 5988A spectrometer operating at 70 eV. HRMS were recorded with a VG Autospec spectrometer. EI HRMS were recorded with *m*-nitrobenzyl alcohol as the matrix. NMR spectra were obtained with a Bruker WP-200 SY instrument at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C. ^{1}H chemical shifts are given relative to residual $CHCl_3$ (δ = 7.24 ppm) in deuteriochloroform. ^{13}C chemical shifts are given relative to $CDCl_3$ (δ = 77.0 ppm) in deuteriochloroform.

Preparation of 1 and 2: The corresponding benzyl bromide (8.3 mmol) was added to a solution of (±)-canadine (2 g, 5.90 mmol) in dried acetone (200 mL) under argon . After stirring at room temperature for 12 h, a mixture of *cis*/*trans* isomers was obtained. The solution was filtered, and the solid was recrystallized twice in chloroform to yield the pure *trans* diastereoisomer. The organic phases were concentrated under vacuum to yield the *cis* diastereoisomer.

(±)-*trans*-*N*-Benzylcanadinium Bromide (*trans*-1): White solid (241 mg, 8%). M.p. 188−189°C ($CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1610, 1500, 1460, 1280 cm^{-1}. UV (MeOH): $\lambda_{max.}$ (log ε) = 208 (4.04), 228 (3.55), 290 nm (3.18). ^{1}H NMR (400 MHz, $CDCl_3$+TFA): δ = 7.50 (t, ^3J = 8.0 Hz, 1 H, H-4′), 7.44 (t, ^3J = 8.0 Hz, 2 H, H-3′, H-5′), 7.14 (d, ^3J = 8.0 Hz, 2 H, H-2′, H-6′), 7.12 (d, ^3J = 8.6 Hz, 1 H, H-12), 7.03 (d, ^3J = 8.6 Hz, 1 H, H-11), 6.84, 6.76 (two s, 1 H each, H-1, H-4), 6.01, 5.98 (two s, 1 H each, OCH_2O), 5.68 (dd, ^3J = 11.7, 5.3 Hz, 1 H, H-14), 4.99 (d, ^3J = 16.0 Hz, 1 H, H-8), 4.69 (d, ^3J = 16.0 Hz, 1 H, H-8′), 4.31 (m, 1 H, H-6), 4.09, 4.05 (two d each, ^3J = 13.7 Hz, 1 H, H-α, H-α′), 3.97 (dd, ^3J = 17.7, 5.3 Hz, 1 H, H-13), 3.91, 3.83 (two s, 3 H each, 2 × OCH_3), 3.55−3.44 (m, 2 H, H-5, H-6′), 3.30 (m, 1 H, H-5′), 3.22 (dd, ^3J = 17.7, 11.7 Hz, 1 H, H-13′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$+TFA): δ = 151.6, 148.6, 148.0, 145.1 (C-2, C-3, C-9, C-10), 132.1 (C-2′, C-6′), 131.2 (C-4′), 129.8 (C-3′, C-5′), 125.4, 123.2, 122.2, 121.6, 120.2 (C-1′, C-4a, C-8a, C-12a, C-14a), 124.7 (C-12), 113.6 (C-11), 108.6, 105.7 (C-1, C-4), 101.8 (OCH_2O), 67.3 (C-14), 61.6, 56.0 (2 × OMe), 57.4, (C-8), 56.2 (C-6), 52.0 (CH_2Ph), 29.2 (C-13), 24.5 (C-5) ppm. EI MS: *m*/*z* = 339 (16) [M − 91], 338 (12), 174 (12), 164 (38), 149 (41), 91 (100). FAB HRMS: $C_{27}H_{28}NO_4$ calcd. 430.2018; found 430.2007.

(±)-*cis*-*N*-Benzylcanadinium Bromide (*cis*-1): White solid (2.5 g, 84%). M.p. 199−201°C (CH_3COCH_3). IR (KBr): $\tilde{\nu}$ = 1600, 1496, 1483, 1456, 1278 cm^{-1}. UV (MeOH): $\lambda_{max.}$ (log ε) = 206 (4.04), 236 (3.30), 290 (3.02) nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.6−7.5 (m, 2 H, H-2′, H-6′), 7.5−7.4 (m, 3 H, H-3′, H-4′, H-5′), 6.85 (d, ^3J = 8.5 Hz, 1 H, H-11), 6.80 (d, ^3J = 8.5 Hz, 1 H, H-12), 6.73 (s, 2 H, H-1, H-4), 6.00, 5.99 (two s, 2 H, OCH_2O), 5.46, 5.05 (two d, ^3J = 12.9 Hz, 1 H each, H-α, H-α′), 5.27 (dd, ^3J = 8.9, 6.0 Hz, 1 H, H-14), 4.98, 4.81 (two d, ^3J = 15.6 Hz, 1 H each, H-8, H-8′), 4.6−4.4 (m, 1 H, H-6), 3.89, 3.80 (two s, 3 H each, 2 × OMe), 3.6−3.5 (m, 2 H, H-5, H-6′), 3.44 (dd, ^3J = 18.3, 6.0 Hz, 1 H, H-13), 3.15 (m, 1 H, H-5′), 3.11 (dd, ^3J = 18.3, 8.9 Hz, 1 H, H-13′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 151.3, 148.6, 147.4, 145.9 (C-2, C-3, C-9, C-10), 133.3 (C-2′, 6′), 130.7 (C-4′), 129.2 (C-3′, 5′), 126.7, 124.7, 121.9, 120.3, 119.8 (C-1′, C-4a, C-8a, C-12a, C-14a), 123.3 (C-12), 113.2 (C-11), 109.1, 106.7 (C-1, C-4), 101.6 (OCH_2O), 62.7 (C-14), 62.4 (CH_2Ph), 61.3, 55.9 (2 × OMe), 53.6 (C-8), 49.5 (C-6), 33.2 (C-13), 23.7 (C-5) ppm. EI MS: *m*/*z* = 339 (22) [M − 91], 338 (15), 174 (16), 164 (47), 149 (49), 91 (100). FAB HRMS: $C_{27}H_{28}NO_4$ calcd. 430.2018; found 430.2001.

(±)-*trans*-*N*-(*p*-Methoxybenzyl)canadinium Bromide (*trans*-2): White solid (472 mg, 15%). M.p. 194−195°C. IR (KBr): $\tilde{\nu}$ = 1610, 1514, 1500, 1460, 1280 cm^{-1}. UV (MeOH): $\lambda_{max.}$ (log ε) = 208 (4.04), 224 (3.45), 290 (3.18) nm. ^{1}H NMR (400 MHz, $CDCl_3$+TFA): δ = 7.12 (d, ^3J = 8.5 Hz, 1 H, H-12), 7.06 (d, ^3J = 8.8 Hz, 2 H, H-2′, H-6′), 7.03 (d, ^3J = 8.5 Hz, 1 H, H-11), 6.93 (d, ^3J = 8.8 Hz, 2 H, H-3′, H-5′), 6.83, 6.75 (two s, 1 H each, H-1, H-4), 6.01, 5.99 (two s, 2 H, OCH_2O), 5.59 (dd, ^3J = 12.5, 5.8 Hz, 1 H, H-14), 4.88, 4.68 (two d, ^3J = 15.9 Hz, 1 H each, H-8, H-8′), 4.2−4.1 (m, 1 H, H-6), 4.03 (s, 2 H, H-α, H-α′), 4.0−3.9 (dd, ^3J = 17.4, 5.8 Hz, 1 H, H-13), 3.92, 3.84, 3.83 (three s, 3 H each, 3 × OCH_3), 3.55 (m, 1 H, H-6′), 3.45 (m, 1 H, H-5), 3.30 (m, 1 H, H-5′), 3.24 (dd, ^3J = 17.4, 12.5 Hz, 1 H, H-13′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$+TFA): δ = 161.6 (C-4′), 151.6, 148.6, 148.1, 145.0 (C-2, C-3, C-9, C-10), 133.3 (C-2′, 6′), 124.7 (C-12), 123.1, 122.1, 121.6, 120.1, 116.7 (C-1′, C-4a, C-8a, C-12a, C-14a), 115.1 (C-3′, 5′), 113.6 (C-11), 108.5, 105.5 (C-1, C-4), 101.8 (OCH_2O), 66.8 (C-14), 61.3, 55.8, 55.5 (3 × OMe), 56.7 (C-8), 55.9 (C-6), 51.5 (CH_2Ph), 29.0 (C-13), 24.3 (C-5) ppm. EI MS: *m*/*z* = 339 (16) [M − 91], 338 (12), 174 (12), 164 (38), 149 (41), 91 (100). FAB HRMS: $C_{28}H_{30}NO_5$ calcd. 460.2124; found 460.2102.

(±)-*cis*-*N*-(*p*-Methoxybenzyl)canadinium Bromide (*cis*-2): White solid (2.2 g, 70%). M.p. 177−178°C. IR (KBr): $\tilde{\nu}$ = 1610, 1500, 1460, 1285 cm^{-1}. UV (MeOH): $\lambda_{max.}$ (log ε)= 206 (4.02), 230 (3.35), 290 (3.06) nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, ^3J = 8.7 Hz, 2 H, H-2′, H-6′), 6.90 (d, ^3J = 8.7 Hz, 2 H, H-3′, H-5′), 6.83, 6.77 (two d, ^3J = 8.5 Hz, 1 H each, H-11, H-12), 6.71 (s, 2 H, H-1, H-4), 6.0−5.9 (m, 2 H, OCH_2O), 5.33, 4.94 (two d, ^3J = 13.1 Hz, 1 H each, H-α, H-α′), 5.12 (dd, ^3J = 9.3, 6.0 Hz, 1 H, H-14), 4.91, 4.79 (two d, ^3J = 15.9 Hz, 1 H each, H-8, H-8′), 4.38 (m, 1 H, H-6), 3.88, 3.79, 3.77 (three s, 3 H each, 3 × OMe), 3.55−3.45 (m, 2 H, H-5, H-6′), 3.41 (dd, ^3J = 18.4, 6.0 Hz, 1 H, H-13), 3.15 (m, 1 H, H-5′), 3.08 (dd, ^3J = 18.4, 9.3 Hz, 1 H, H-13′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.2 (C-4′), 151.3, 148.5, 147.3, 145.7 (C-2, C-3, C-9, C-10), 134.7 (C-2′, 6′), 124.7, 122.0, 120.4, 119.9, 118.3 (C-1′, C-4a, C-8a, C-12a, C-14a), 123.2 (C-12), 114.5 (C-3′, 5′), 113.2 (C-11), 109.1, 106.6 (C-1, C-4), 101.6 (OCH_2O), 62.4 (C-14, CH_2Ph), 61.2, 55.8, 55.3 (3 × OMe), 53.4 (C-8), 49.6 (C-6), 33.3 (C-13), 23.7 (C-5) ppm. EI MS: *m*/*z* = 339

(24) [M − 121], 174 (16), 164 (47), 149 (46), 121 (100). FAB HRMS: $C_{28}H_{30}NO_5$ calcd. 460.2124; found 460.2117.

General Method for the Stevens Rearrangement: A solution of HNa (3.71 mmol) in DMSO (5 mL, 65 mmol) was stirred for 90 minutes at 80°C. Once the dimsylsodium was formed, the corresponding canadinium salt (0.49 mmol) was added, and the mixture stirred for 5 h. The reaction was monitored by ^{1}H NMR spectroscopy and TLC. The reaction mixture was poured onto ice, the white precipitate was filtered off, and the corresponding 8-substituted canadine purified by column chromatography ($CHCl_3$). The yields of isolated product decreased to a great extent due to the lability of these derivatives, although the crude ^{1}H NMR spectrum exhibited a pure product resulting from the Stevens rearrangement.

(8*R,14*S**)-8-Benzylcanadine (*cis*-3):** White solid (45% after purification). M.p. 120−121°C. IR ($CHCl_3$): $\tilde{\nu}$ = 3027, 3007, 2960, 2908, 1603, 1502, 1485, 1277, 1232 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, ^3J = 7.5 Hz, 2 H, H-2′, H-6′), 7.24 (dd, ^3J = 7.5, 7.0 Hz, 2 H, H-3′, H-5′), 7.16 (t, ^3J = 7.0 Hz, 1 H, H-4′), 6.78 (s, 2 H, H-11, H-12), 6.65 (s, 1 H, H-1), 6.54 (s, 1 H, H-4), 5.90 (s, 2 H, OCH_2O), 4.41 (dd, ^3J = 10.3, 6.1 Hz, 1 H, H-14), 4.19 (dd, ^3J = 9.4, 1.8 Hz, 1 H, H-8), 3.90, 3.86 (two s, 3 H each, 2 × OMe), 3.03 (dd, ^3J = 14.1, 9.4 Hz, 1 H, H-α), 2.92 (dd, ^3J = 14.1, 1.8 Hz, 1 H, H-α′), 2.90−2.70 (m, 4 H, H-6, H-13, H-13′, H-5), 2.57−2.51 (m, 2 H, H-5′, H-6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.4 (C-10), 145.9 (C-9), 145.7, 145.6 (C-2, C-3), 142.0 (C-1′), 132.6, 132.3 (C-4a, C-8a), 129.4 (C-2′, C-6′), 127.9 (C-3′, C-5′), 127.6, 127.0 (C-12a, C-14a), 125.8 (C-4′), 123.8 (C-12), 111.7 (C-11), 108.9 (C-4), 106.0 (C-1), 100.6 (OCH_2O), 62.9 (C-8), 60.5, 56.0 (2 × OMe), 50.5 (C-14), 46.8 (C-6), 40.4 (C-α), 31.9 (C-13), 30.0 (C-5) ppm. EI MS: *m*/*z* = 429 (0.1) [M$^+$], 428 (0.1), 339 (22), 338 (100), 91 (20). EI HRMS: $C_{27}H_{27}NO_4$ calcd. 429.1940, found 429.1922.

(8*S,14*S**)-8-Benzylcanadine (*trans*-3):** Yellowish solid (52% after purification). M.p. 122−123°C. IR ($CHCl_3$): $\tilde{\nu}$ = 3028, 3009, 2960, 2942, 2904, 2800, 2771, 1601, 1503, 1484, 1275, 1230 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.1−6.9 (m, 5 H, Ph), 6.72 (d, ^3J = 8.2 Hz, 1 H, H-11), 6.71 (d, ^3J = 8.2 Hz, 1 H, H-12), 6.67 (s, 1 H, H-1), 6.54 (s, 1 H, H-4), 5.86 (s, 2 H, OCH_2O), 4.20 (m, 1 H, H-8), 3.95, 3.89 (two s, 3 H each, 2 × OMe), 3.47 (d, ^3J = 10.9 Hz, 1 H, H-14), 3.14 (m, 1 H, H-α), 3.1−2.9 (m, 1 H, H-5), 2.96 (m, 1 H, H-6), 2.95 (m, 1 H, H-α′), 2.82 (d, ^3J = 14.1 Hz, 1 H, H-13), 2.54 (dt, 1 H, H-6′), 2.46 (m, 1 H, H-5′), 2.19 (dd, ^3J = 14.1, 10.9 Hz, 1 H, H-13′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.7 (C-10), 145.8, 145.7, (C-2, C-3), 145.3 (C-9), 139.5 (C-1′), 131.8 (C-4a, C-8a), 130.7 (C-12a), 128.6 (C-14a), 130.4 (C-2′, C-6′), 127.2 (C-3′, C-5′), 125.5 (C-4′), 122.7 (C-12), 110.3 (C-11), 108.4 (C-4), 105.5 (C-1), 100.6 (OCH_2O), 62.0 (C-8), 60.4 (OMe), 58.9 (C-14), 55.8 (OMe), 50.2 (C-6), 42.5 (C-α), 36.8 (C-13), 30.3 (C-5) ppm.

(8*R,14*S**)-8-(*p*-Methoxybenzyl)canadine (*cis*-4):** White solid (62% after purification). M.p. 134−135°C. IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 2957, 2939, 2904, 1606, 1513, 1488, 1277, 1238 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, ^3J = 8.5 Hz, 2 H, H-2′, H-6′), 6.78 (s, 2 H, H-11, H-12), 6.77 (d, ^3J = 8.5 Hz, 2 H, H-3′, H-5′), 6.64 (s, 1 H, H-1), 6.54 (s, 1 H, H-4), 5.86 (s, 2 H, OCH_2O), 4.38 (dd, ^3J = 9.9, 7.3 Hz, 1 H, H-14), 4.15 (dd, ^3J = 9.2, 3.1 Hz, 1 H, H-8), 3.91, 3.85, 3.76 (three s, 3 H each, 3 × OMe), 2.99 (m, 1 H, H-α), 2.83 (m, 1 H, H-α′), 2.88 (m, 1 H, H-6), 2.86 (m, 1 H, H-13), 2.84 (m, 1 H, H-13′), 2.77 (m, 1 H, H-5), 2.54 (m, 1 H, H-5′), 2.53 (m, 1 H, H-6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.6 (C-4′), 150.4 (C-10), 145.9, 145.7, 145.5 (C-2, C-3, C-9), 134.1 (C-1′), 132.6 (C-8a), 132.3 (C-4a), 127.6 (C-14a), 127.0 (C-12a), 130.3 (C-2′, C-6′), 123.7 (C-12), 113.2 (C-3′, C-5′), 111.2 (C-11), 108.9 (C-4), 106.6 (C-1), 100.6 (OCH_2O), 63.1 (C-8), 60.3, 55.8, 55.1 (3 × OMe), 50.1 (C-14), 47.0 (C-6), 39.6 (C-α), 31.9 (C-13), 29.9 (C-5) ppm. EI MS: *m*/*z* = 459 (0.3) [M$^+$], 458 (0.3), 339 (23), 338 (100), 121 (23). EI-HRMS: $C_{28}H_{29}NO_5$ calcd. 459.2046; found 459.2047.

(8*S,14*S**)-8-(*p*-Methoxybenzyl)canadine (*trans*-4):** Yellowish solid (43% after purification). M.p. 137−138°C. IR ($CHCl_3$): $\tilde{\nu}$ = 3027, 3011, 2957, 2936, 2909, 2802, 2768, 1606, 1509, 1484, 1245, 1235 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, ^3J = 8.2 Hz, 2 H, H-2′, H-6′), 6.73, 6.69 (two d, ^3J = 8.5 Hz, 1 H each, H-11, H-12), 6.60 (d, ^3J = 8.2 Hz, 2 H, H-3′, H-5′), 6.67 (s, 1 H, H-1), 6.56 (s, 1 H, H-4), 5.87 (s, 2 H, OCH_2O), 4.16 (bs, 1 H, H-8), 3.94, 3.87, 3.70 (three s, 3 H each, 3 × OMe), 3.46 (d, ^3J = 11.3 Hz, 1 H, H-14), 3.05 (dd, ^3J = 13.4, 3.0 Hz, 1 H, H-α), 2.91 (dd, ^3J = 13.4, 5.4 Hz, 1 H, H- α′), 3.1−2.9 (m, 2 H, H-5, H-6), 2.82 (d, ^3J = 14.0 Hz, 1 H, H-13), 2.56 (m, 1 H, H-6′), 2.46 (m, 1 H, H-5′), 2.18 (dd, ^3J = 14.0, 11.3 Hz, 1 H, H-13′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.6 (C-4′), 150.7 (C-10), 145.8, 145.7, 145.3 (C-2, C-3, C-9), 131.8, 131.6 (C-1′, C-4a, C-8a), 130.8 (C-12a), 127.6 (C-14a), 131.2 (C-2′, C-6′), 122.8 (C-12), 112.6 (C-3′, C-5′), 110.4 (C-11), 108.4 (C-4), 105.5 (C-1), 100.6 (OCH_2O), 62.0 (C-8), 60.4 (OMe), 58.9(C-14), 55.9, 55.1 (2 × OMe), 50.1 (C-6), 41.4 (C-α), 36.9 (C-13), 30.7 (C-5) ppm. EI MS: *m*/*z* = 459 (0.1) [M$^+$], 458 (0.3), 339 (22), 338 (100), 121 (21).

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