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From Berbines to Protopines: Regiocontrolled Hofmann Elimination/ Hydroboration/Oxidation of *N*-Substituted Berbinium Salts

María Valpuesta,*[a] Amelia Díaz,[a] Rafael Suau,[a] and Gregorio Torres[a]

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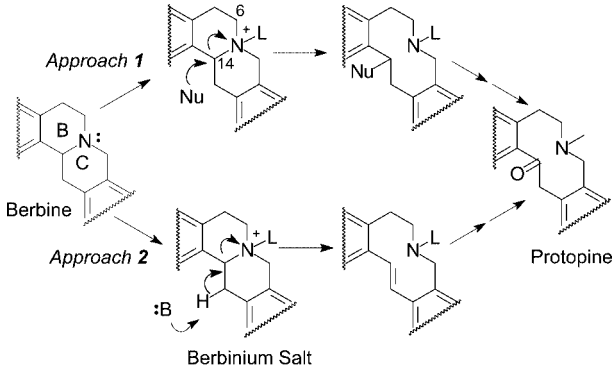
An improved synthetic approach to protopines based on the sequential Hofmann elimination, hydroboration and oxidation of *N*-(arylmethyl)berbinium salts has been designed. By using berberine chloride as the starting material, this sequence of reactions has provided two new nonnatural protopines, *N*-benzyl-*N*-nordihydroallocriptopine and *N*-(*p*-methoxybenzyl)-*N*-nordihydroallocriptopine and the natural allocriptopine.

Introduction

The protopine alkaloids are characterized by the presence of a ten-membered ring (hexahydrodibenzo[*c*,*g*]azecine) with a methylated tertiary nitrogen atom and a keto group fused to two aryl moieties. Protopines[1] are few in number but are widely distributed, being found in a broad range of plant species albeit in small amounts. In general, protopines have two oxygenated substituents on the A and D rings, although protopines with tri-[2] and monosubstituted[3] A rings have been isolated. In some instances additional substituents may be present at the C-13 atom (hydroxy, methoxy, oxo or methyl), but this is unusual.[1] Generally, protopines and some of their derivatives exhibit a number of activities such as: antihistaminic, anticholinergic and antiinflammatory effects. Their action on the cardiovascular system, including antiarrythmic, antihypertensive and inhibition of platelet aggregation, has also been reported.[4]

In contrast, the protoberberine alkaloids are extremely abundant and play a crucial role as precursors in the biosynthesis of a variety of related isoquinoline alkaloids (protopine, phthalideisoquinoline, spirobenzylisoquinoline, benzo[*c*]phenanthridine and others).[5] Protoberberine alkaloids are easily accessible either by several standardized synthetic methods or by direct isolation from natural sources.

Owing to the ready availability of protoberberines and their structural relationship with protopines, a few procedures for the semi-synthesis of protopine alkaloids from protoberberines have been devised.[6] All of these are based on a biomimetic approach that involves B/C ring-opening of the protoberberine moiety (Scheme 1). This transformation is achieved through the formation of a new covalent bond between the nitrogen atom and a suitable electrophile, providing an initial berbinium salt, and subsequent C-14 regioselective functionalization.



Scheme 1. Approaches to the synthesis of protopine alkaloids.

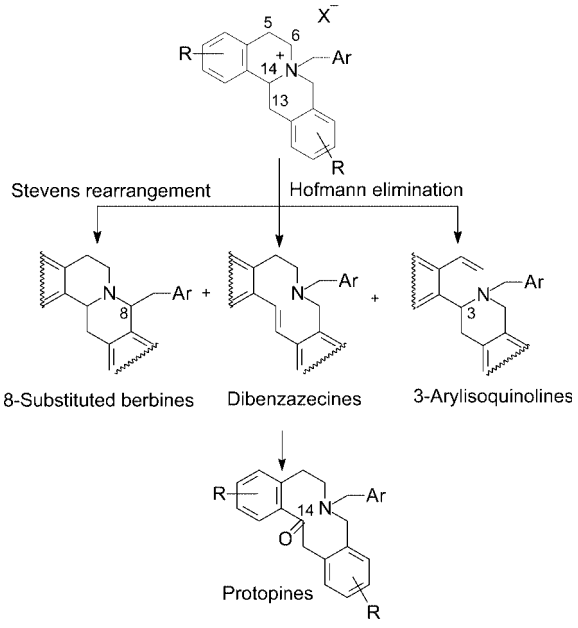
The reactivity of the initial salt depends on the nature of the electrophile (L), and two approaches have been used (Scheme 1). The first involves the use of cyanogen bromide (L = CN) as a counterattack reagent which generates, in situ, an *N*-cyanoberbinium salt that undergoes subsequent ring-opening by nucleophilic attack of the counteranion (Nu = Br). This methodology has low regioselectivity with both the C-6 and C-14 atoms acting as the electrophilic centre.[6]

The second approach allows the synthesis of protopines through the Hofmann elimination of *N*-substituted berbinium salts. This procedure has been reported only for *N*-methylated salts (L = CH_3) although, in this case, spirobenzylisoquinolines are obtained as secondary products through the competing Stevens rearrangement.[7] Note that in both procedures the dibenzazecines obtained are unstable as a result of the interaction between the nitrogen atom and the functional group at C-14, which can lead to

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga,
Campus de Teatinos s/n, 29071 Málaga, Spain
Fax: +34-952-131941
E-mail: mvalpuesta@uma.es

the regeneration of the berbinium salt. In protopines the transannular amine–ketone (N···C=O) interaction is well established and has recently been described by quantum mechanics and molecular modeling calculations.[8]

In connection with the second approach, in previous work we examined the behaviour of (±)-*N*-benzylberbinium salts in the presence of bases (Scheme 2). We reported that the prevalence of the two competitive pathways, Hofmann elimination and Stevens rearrangement, are strongly dependent on the base and the solvent employed. Remarkably, by using dimsylsodium and DMSO the Stevens rearrangement became the dominant pathway yielding the 8-substituted berbines with no competition from alternative reactions.[9] This process occurred through regioselective hydrogen abstraction to generate exclusively a C-8 ylide which rearranged in a stereoselective manner to generate 8-(arylmethyl)berbines.



Scheme 2. Reactivity of (±)-berbinium salts under basic conditions.

The Hofmann elimination process occurs by hydrogen removal from the C-5 and C-13 atoms to provide 3-arylisoquinolines and dibenzazecines, respectively, the latter being a direct precursor of the protopine alkaloids.

The lack of studies on the regiocontrol of the Hofmann elimination of (±)-*N*-substituted berbinium salts has prompted us to investigate the influence of bases and solvents on this reaction. We describe herein an efficient route to natural and nonnatural protopines through a simple procedure based on the Hofmann elimination/hydroboration/oxidation sequence.

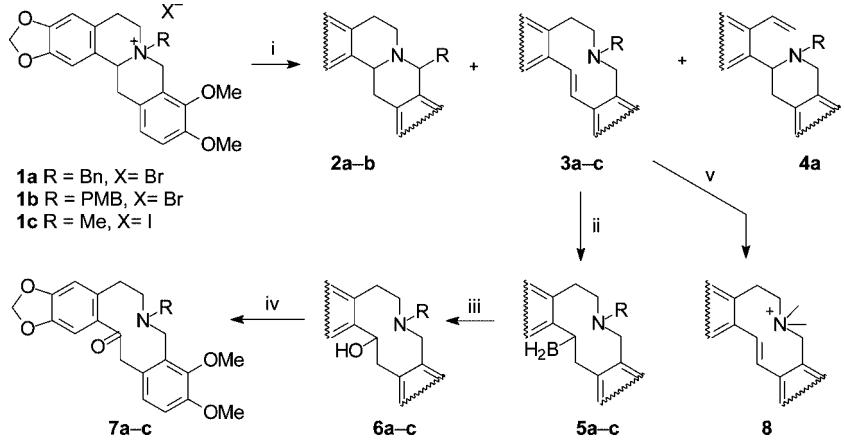
Results and Discussion

Regiocontrol of the Hofmann Elimination Reaction

The corresponding starting salts were synthesized as a *cis*/*trans* mixture of diastereoisomers according to the standard procedure described previously.[9,10] Treatment of the (±)-*N*-benzylberbinium salts with base produced a complex mixture as a result of the competition between the two processes indicated in Scheme 2.

As we established previously,[9] the use of medium-strength bases with hydroxylic solvents (e.g., MeONa/MeOH) preferentially yields the Hofmann elimination products. On the other hand, strong bases in highly polar nonprotic solvents (e.g., HNa/DMSO) favour the Stevens rearrangement, while the use of these bases in the presence of apolar solvents (e.g., HNa/benzene) leads to an increase in the yield of elimination products. This chemoselectivity occurs because effective ion-coordinating solvents stabilize the intermediate ylide precursor of the Stevens rearrangement, whereas apolar solvents increase the yields of Hofmann elimination products by dispersion of the electrical charges in the transition state.

Our initial synthetic efforts focused on maximizing the yield of the dibenzazecines formed through C-13 hydrogen removal. In order to perform this objective, we initially chose (±)-*N*-benzylcanadinium bromide[9] (**1a**) as the model compound (Scheme 3). To raise the yield of the Hofmann



Scheme 3. Synthesis of protopines: i) HNa/benzene/DMSO, room temp.; ii) BH_3·THF, room temp.; iii) H_2O_2/phosphate buffer (pH = 8)/THF, reflux; iv) PCC/CH_2Cl_2/NaAcO, room temp.; v) MeI/$CHCl_3$, room temp.

Table 1. Reaction of **1a**–**c** with base.

Entry[a]	Compound (*cis*/*trans* ratio)	Base/solvent	Time [h]/temp.	Yield [%][b]		
				2	**3**	**4**
1	**1a** (8:1)	MeONa/MeOH	12/room temp.	10	10	80
2		HNa/*n*-hexane[c]	35/reflux	10	45	45
3		HNa/benzene[c]	14/reflux	15	75	10
4		HNa/benzene[d]	4/room temp.	10	80	10
5	**1b** (4:1)	HNa/benzene[d]	3/room temp.	10	83	7
6	**1c** (1:4)	HNa/benzene[d]	5/room temp.	–	>95	<5[e]

[a] Reaction conditions: substrate (0.5 mmol), base (4.5 mmol), solvent (2 mL). [b] Percentage determined by ^{1}H NMR spectroscopy; we estimated that the detection limit for products in the NMR spectra of the crude product was 5%. [c] Solvent (60 mL). [d] DMSO as co-solvent (0.2 mL). [e] The yield is quoted as <5% but no compound **4** was observed by NMR spectroscopy.

elimination reaction, we used two different combinations of base and solvent: medium bases with hydroxylic solvents and strong bases with nonpolar solvents. The yields of the Stevens product **2** and the two Hofmann elimination products **3** and **4** in a series of reactions are shown in Table 1.

As expected, the treatment of **1a** with MeONa in MeOH (Entry 1) yielded almost exclusively the elimination products; however, the undesired product **4a** (vinylic proton signals at δ = 7.20, 5.49 and 5.19 ppm) was the major one obtained. The use of HNa with *n*-hexane or benzene (Entries 2 and 3) strongly favours the Hofmann elimination reaction but the regioselectivity is poor in the first case. Because of the low solubility of the berbinium salts in benzene, a few drops of DMSO were added which considerably reduced the reaction time and temperature and provided good regioselectivity (Entry 4). These conditions were chosen for C-13 hydrogen removal yielding **3a** (two olefinic protons as two doublets at δ = 7.12 and 6.52 ppm with J = 16.4 Hz) and were also used in the reactions of (±)-canadinium salts **1b** and **1c**. Similar results were obtained for the **1b** derivative, whereas the reaction of **1c** under identical conditions yielded exclusively the Hofmann elimination products with no products from the Stevens rearrangement being observed.

Influence of the Configuration of the Initial Salts on Regioselectivity

In order to verify whether the configuration of the initial salts has any effect on the regioselectivity of the Hofmann elimination reaction, the reaction was performed with diastereomerically pure berbinium salts. The diastereoisomers were separated by fractional crystallization and characterized by standard spectroscopic techniques. We had previously established a method, based on configurational and conformational differences, to assign unequivocally the *cis* or *trans* configuration to the berbinium salts using ^{13}C NMR spectroscopic data.[9,10]

The treatment of each of the diastereoisomers of **1a**–**c** with the optimized conditions for the Hofmann elimination reaction gave different yields of the isomers **3** and **4**. As can be seen in Table 2, all the *trans* stereoisomers yielded almost exclusively dibenzazecine derivative **3** while the *cis* stereoisomers exhibited a lower regioselectivity.

Table 2. Results of the Hofmann elimination reaction with diastereomerically pure salts **1a**–**c**.

Entry[a]	Compound	Hofmann elimination yield [%][b]	
		3	**4**
1	*cis*-**1a**	88	12
2	*trans*-**1a**	>95	<5[c]
3	*cis*/*trans*-**1a** (8:1)	89	11
4	*cis*-**1b**	90	10
5	*trans*-**1b**	>95	<5[c]
6	*cis*/*trans*-**1b** (4:1)	92	8
7	*cis*-**1c**	80	20
8	*trans*-**1c**	>95	<5[c]
9	*cis*/*trans*-**1c** (1:4)	>95	<5[c]

[a] Reaction conditions: substrate (0.5 mmol), base (HNa, 4.5 mmol), solvent (benzene/DMSO: 2 mL/0.2 mL). [b] Yield determined by ^{1}H NMR spectroscopy; we estimated that the detection limit for products in the crude NMR spectra was 5%. [c] The yield is quoted as <5% but no compound **4** was observed by NMR spectroscopy.

A possible explanation for the observed regioselectivity could be obtained with the aid of molecular modelling[11] and quantum chemical[12] calculations. For this theoretical study we used an *N*-methylated berbinium salt with no substitution on the aromatic rings as a simplified model.[13]

As shown in Figure 1 both diastereoisomers can be in conformational equilibrium in solution (**Ia**, **Ib** and **IIa**, **IIb**). The two lowest energy conformations of the *trans* stereoisomer possess a rigid half-chair in the C ring (conformations **Ia** and **Ib**), while the B ring can adopt two different conformations, boat (**Ia**) and half-chair (**Ib**), and therefore is less

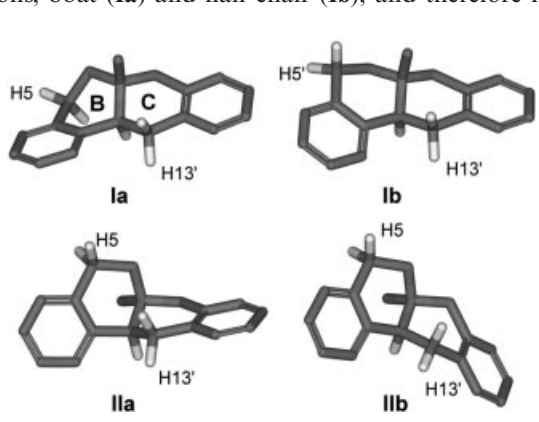


Figure 1. 3D structures of the more stable conformations of the *trans* and *cis* diastereoisomers.

rigid. For this reason, 13′-H elimination is preferred in the Hofmann elimination process yielding almost exclusively the dibenzazecine derivative **3**. In the *cis* stereoisomer the two lowest energy conformations, **IIa** and **IIb**, have a less rigid C ring, so 5,6-H elimination (product **4**) competes with the 13′-H elimination that provides **3**. From these data, we conclude that the initial configuration of the salts only has a small influence on the elimination process. The dibenzazecine derivative **3** is the major compound formed under the optimized conditions.

Synthesis of Protopines

After studying the regiocontrol of the Hofmann elimination reaction, we directed our attention towards the completion of the synthesis of protopines, as shown in Scheme 3.

The treatment of **1a** (as a *cis*/*trans* mixture, 8:1) with HNa in dry benzene and DMSO as co-solvent gave a mixture of **2a**, **3a** and **4a** in a 1:8:1 ratio, as indicated by ^{1}H NMR spectroscopic analysis of the crude reaction product (Entry 4, Table 1). However, when the mixture was separated chromatographically, only a small amount of **3a** could be isolated owing to its instability under acidic and neutral conditions. The low stability of this key intermediate prompted us to perform direct hydroboration with BH_3·THF under thermodynamic conditions. The ^{1}H NMR spectrum of this crude product exhibited the almost exclusive presence of a single boranyl derivative. After purification by column chromatography, compound **5a** was isolated and the position of boron substituent at C-14 was determined by 2D-NMR experiments. Comparable results were obtained with the **1b** derivative, with **5b** obtained as the major compound.

The regioselectivity of this hydroboration reaction could be attributed to the initial presence of a dative N–B complex which subsequently undergoes intramolecular hydroboration. Two possible intermediate bicycles could be obtained: 1-aza-11-borabicyclo[4.4.1]undecane (**V**), with two fused seven-membered rings, or 1-aza-11-borabicyclo[5.3.1]-undecane (**VI**), the former being thermodynamically more stable and obtained through a dehydroboration/rehydroboration process (Figure 2).[14]

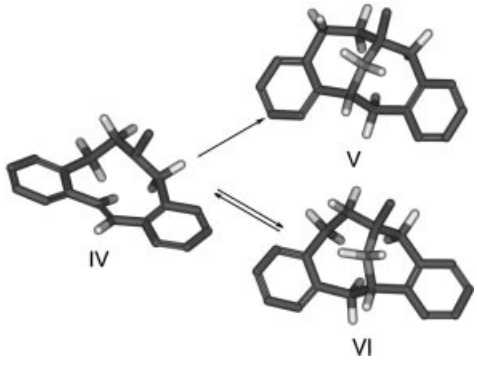


Figure 2. Assumed 3D structures in the hydroboration reaction.

After oxidation of the boranyl derivatives **5a**,**b** with hydrogen peroxide under a stream of oxygen, the corresponding dihydroprotopines **6a**,**b** were isolated in good yields. Interestingly, these two new compounds exhibited, unlike the related dibenzazecines or protopines, well-resolved ^{1}H NMR spectra in their aliphatic regions, probably due to a favoured conformation in solution resulting from intramolecular hydrogen bonding. The assignment by HMQC and HMBC of the hydroxy group at the C-14 position confirms the high regioselectivity of the hydroboration process.

The final oxidation step, under either Swern or pyridinium chlorochromate (PCC)/CH_2Cl_2 conditions, failed as a result of the ease of intramolecular cyclization of the dihydroprotopines[10] under weak acidic conditions. In order to avoid this competitive process a minor modification of the standard PCC oxidation procedure, using sodium acetate and molecular sieves,[15] allowed us to obtain the corresponding protopine derivatives **7a**,**b** in good yields.

Finally, this methodology has also been applied to the synthesis of natural allocriptopine (**7c**). Application of our Hofmann elimination procedure to (±)-*N*-methylcanadinium iodide (**1c**, *cis*/*trans* = 1:4) yielded a crude mixture which was shown by ^{1}H NMR spectroscopy to contain a single product **3c** (two olefinic protons as two doublets at δ = 7.09 and 6.43 ppm with J = 16.5 Hz) after 4 h. Despite prolonged efforts, we were unable to isolate this derivative as it readily underwent cyclization, although direct treatment of the reaction mixture with methyl iodide allowed the corresponding *N*-methyl salt **8** to be isolated. In contrast to **5a**,**b**, the boranyl derivative **5c** was unstable; therefore we performed the reaction sequence without a separation step. The complete sequence Hofmann elimination/hydroboration/oxidation was performed in a one-pot procedure to yield the corresponding allocryptopine (**7c**) in 45% overall yield starting from berberine chloride.

Conclusions

These results demonstrate that the Hofmann elimination/hydroboration/oxidation of benzyl-, PMB- and methylberbinium salts is an efficient and short approach to the synthesis of new protopine derivatives with different substituents on the nitrogen atom. This protocol is based on two different highly regioselective processes, Hofmann elimination and hydroboration, which allows the selective C-14 functionalization of berbines.

A study of the application of this methodology to the synthesis of novel protopines and protopine analogues, and the evaluation of their bioactivity is currently under way.

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 spectrometer. EI-MS data were recorded with an HP-MS 5988A spectrometer operating at 70 eV. HR-MS data were recorded with a VG Autospec spectrometer. EI-HR-MS data were recorded using *m*-nitrobenzyl alcohol as the matrix. NMR spectra were obtained with a Bruker ARX 400 instru-

ment at 400 MHz for ^1H and 100.6 MHz for ^{13}C. Chemical shifts are given relative to residual $CHCl_3$ (δ_H = 7.24 ppm) and $CDCl_3$ (δ_C = 77.0 ppm) in deuteriochloroform. All glassware, syringes and needles were dried in an oven heated to 250 °C for at least 12 h and cooled under argon prior to use. All solvents were dried and distilled prior to use. Reaction mixtures were magnetically stirred and monitored by TLC. Products were purified by column chromatography using 0.063–0.200 mm silica gel (Merck 7734). Sodium hydride, borane (1 M THF solution) and pyridinium chlorochromate were purchased from Aldrich Chemical Co. and used without further purification. Berberine chloride, used as starting material for the synthesis of (±)-canadine, was purchased from Lancaster Co.

Preparation of (±)-Canadinium Salts 1a and 1b: The (±)-canadinium salts **1a** and **1b** were prepared according to the standard procedure.[9] The *cis*/*trans* diastereomer ratio was 8:1 for **1a** and 4:1 for **1b**.

Reaction of 1a with HNa in Refluxing Benzene: A suspension of **1a** (*cis*/*trans* = 8:1) (250 mg, 0.49 mmol) and HNa (60% mineral oil, 500 mg, 12.4 mmol) in dried benzene (60 mL) was refluxed under argon. The reaction was monitored by ^1H NMR spectroscopy; after 14 h, a mixture of products **2a**, **3a** and **4a** was observed (Entry 3, Table 1). The solvent was removed under vacuum and the crude reaction product was washed with *n*-hexane and purified by chromatography on a silica column (*n*-hexane/$CHCl_3$, 2:1) to obtain **2a**[9] (20 mg, 10%), **3a** (10 mg, 5%) and **4a** (20 mg, 10%).

6-Benzyl-3,4-dimethoxy-5,6,7,8-tetrahydro-11*H*-benzo[*c*][1,3]benzodioxolo[5,6-*g*]azecine (3a): Unstable product. ^1H NMR ($CDCl_3$/[D_6]DMSO, 10:1): δ = 7.26 (m, 2 H, H_{arom}), 7.12, 6.52 (2 d, ^3J = 16.4 Hz, 1 H each, $H_{olefinic}$), 7.1–6.9 (m, 5 H, H_{arom}), 6.80 (d, ^3J = 8.0 Hz, 1 H, H_{arom}), 6.50 (s, 1 H, H_{arom}), 5.94 (s, 2 H, OCH_2O), 3.95 (br. s, 2 H, CH_2-Ph), 3.85, 3.78 (2 s, 3 H each, 2×OMe), 3.50 (br. s, 2 H), 2.70 (br. s, 4 H) ppm.

(±)-2-Benzyl-7,8-dimethoxy-3-(2-vinyl-4,5-methylenedioxyphenyl)-3,4-dihydro-1*H*-isoquinoline (4a): Yellow solid. M.p. 114–115 °C. IR (KBr): $\tilde{\nu}$ = 1607, 1500, 1495, 1478, 1425, 1275, 1235, 1215 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.35–7.25 (m, 5 H, *Ph*-CH_2), 7.20 (dd, ^3J = 17.0, 12.1 Hz, 1 H, -C*H*=CH_2), 7.05, 6.98 2 s, 1 H each, 3′-H, 6′-H), 6.79, 6.72 (2 d, ^3J = 8.5 Hz, 1 H each, 5-H, 6-H), 5.9 (m, 2 H, OCH_2O), 5.49 (d, ^3J = 17.0 Hz, 1 H, -CH=CH_2), 5.19 (d, ^3J = 12.1 Hz, 1 H, -CH=CH_2), 4.09 (d, J = 16.5 Hz, 1 H, 1-H), 3.95 (dd, J = 9.7, 4.1 Hz, 1 H, 3-H), 3.92 (d, J = 13.2 Hz, 1 H, Ph-CH_2), 3.80, 3.64 (2 s, 3 H each, 2×OMe), 3.34 (d, J = 16.5 Hz, 1 H, 1′-H), 3.10 (d, J = 13.2 Hz, 1 H, Ph-CH_2), 3.05 (dd, J = 16.5, 9.7 Hz, 1 H, 4-H), 2.85 (dd, J = 16.5, 4.1 Hz, 1 H, 4′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 150.4, 147.7, 146.8, 145.3 (O-C_{arom}), 139.2, 134.7, 130.9, 128.8, 127.8 (C-C_{arom}), 134.4 (*C*H=CH_2), 128.6, 128.1, 126.4 (H-C_{arom}, *Ph*-CH_2), 123.1 (H-C_{arom}), 114.4 (CH=*C*H_2), 110.9, 107.4, 105.9 (H-C_{arom}), 101.0 (OCH_2O), 60.1 (3-C), 60.0 (OMe on C-8), 58.8 (Ph-CH_2), 55.3 (OMe), 50.0 (1-C), 35.9 (4-C) ppm. EI-MS: *m*/*z* (%) = 429 (2) $[M]^+$, 338 (7) $[M - 91]^+$, 164 (10), 149 (20), 91 (100). EI-HR-MS: calcd. for $C_{27}H_{27}NO_4$ 429.1940; found 429.1941.

Synthesis of (±)-*N*-Benzyl-14-boranyl-14-deoxy-*N*-nordihydroallocryptopine (5a): A suspension of HNa (60% in mineral oil, 200 mg, 4.8 mmol), DMSO (0.2 mL), benzene (2 mL) and **1a** (*cis*/*trans* = 8:1) (300 mg, 0.59 mmol) was stirred at room temperature under argon. After 4 h, the crude product was concentrated under vacuum at 40 °C. The ^1H NMR spectrum exhibited the Hofmann elimination products **3a** as the major one as well as **2a** and **4a** (Entry 4, Table 1). The dry residue was dissolved in dry THF (20 mL) and a solution of BH_3 (1 M THF solution, 3 mL) was added dropwise under argon. After stirring for 30 min, the solvent was removed under vacuum and the ^1H NMR spectrum of the crude product exhibited a single hydroboration product. The crude product was purified by column chromatography (*n*-hexane/$CHCl_3$, 2:1) to obtain **5a** as a white solid in 42% (110 mg) yield. M.p. 211–212 °C. IR (KBr): $\tilde{\nu}$ = 2345 (H–B), 2275 (H–B), 1582, 1485, 1447, 1270, 1250, 1205, 1072 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 206 (3.74), 292 (2.95), 340 (2.56) nm. ^1H NMR ($CDCl_3$): δ = 7.60 (m, 2 H, *Ph*-CH_2), 7.40 (m, 3 H, *Ph*-CH_2), 6.89 (d, ^3J = 8.2 Hz, 1 H, 12-H), 6.84 (d, ^3J = 8.2 Hz, 1 H, 11-H), 6.68, 6.52 (2 s, 1 H each, 1-H, 4-H), 5.85 (s, 2 H, OCH_2O), 4.37, 4.35 (2 d, ^3J = 13.6 Hz, 1 H each, Ph-CH_2), 4.10, 3.99 (2 d, ^3J = 13.7 Hz, 1 H each, 8-H, 8′-H), 3.89, 3.86 (2 s, 3 H each, 2×OMe), 3.69 (dd, ^3J = 17.0, 12.0 Hz, 1 H, 5-H), 3.17 (t, ^3J = 12.0 Hz, 1 H, 6-H), 3.03 (m, 2 H, 13-H, 13′-H), 2.81 (dd, ^3J = 12.0, 4.7 Hz, 1 H, 6′-H), 2.66 (dd, ^3J = 17.0, 4.7 Hz, 1 H, 5′-H), 2.12 (t, ^3J = 8.2 Hz, 1 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 150.6, 147.7, 146.5, 145.9 (O-C_{arom}), 143.8, 137.7, 131.2, 129.6, 125.4 (C-C_{arom}), 133.2, 128.9, 123.3 (H-C_{arom}, *Ph*-CH_2), 123.6, 111.9, 111.1, 110.2 (H-C_{arom}), 100.4 (OCH_2O), 67.6 (C-8), 60.9 (OMe on C-9), 58.8 (C-6), 55.7 (OMe), 47.9 (Ph-*C*H_2), 38.7 (C-13), 38.3 (C-14), 32.3 (C-5) ppm. EI-MS: *m*/*z* (%) = 443 (2) $[M]^+$, 442 (1), 352 (19) $[M - 91]^+$, 351 (12), 350 (13), 188 (13), 187 (5), 186 (4), 164 (40), 149 (33), 91 (100). EI-HR-MS: calcd. for $C_{27}H_{30}BNO_4$ 443.2268; found 443.2261.

(±)-14-Boranyl-*N*-(*p*-methoxybenzyl)-14-deoxy-*N*-nordihydroallocryptopine (5b): The corresponding boranyl derivative **5b** (111 mg, 42%) was obtained as a white solid in a similar manner from **1b** (*cis*/*trans* = 4:1) (300 mg, 0.55 mmol). M.p. 190–191 °C. IR (KBr): $\tilde{\nu}$ = 2324 (H–B), 2267 (H–B), 1580, 1485, 1445, 1250, 1205, 1043 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 206 (3.74), 290 (2.92), 338 (2.60) nm. ^1H NMR ($CDCl_3$): δ = 7.52, 6.91 (2 d, ^3J = 8.8 Hz, 2 H each, *Ar*-CH_2), 6.87, 6.82 (2 d, ^3J = 8.5 Hz, 1 H each, 11-H, 12-H), 6.66, 6.50 (2 s, 1 H each, 1-H, 4-H), 5.84 (s, 2 H, OCH_2O), 4.34, 4.26 (2 d, ^3J = 14.0 Hz, 1 H each, Ar-CH_2), 4.03, 3.92 (2 d, ^3J = 13.4 Hz, 1 H each, 8-H, 8′-H), 3.87, 3.85, 3.82 (3 s, 3 H each, 3×OMe), 3.6–3.5 (m, 1 H, 5H), 3.11 (t, ^3J = 12.1 Hz, 1 H, 6-H), 3.1–2.9 (m, 2 H, 13-H, 13′-H), 2.81 (dd, ^3J = 12.1, 4.3 Hz, 1 H, 6′-H), 2.65 (dd, ^3J = 16.5, 4.3 Hz, 1 H, 5′-H), 2.11 (t, ^3J = 8.5 Hz, 1 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 160.1, 150.6, 147.6, 146.6, 146.0, (O-C_{arom}), 143.9, 137.8, 129.6, 125.4, 123.2 (C-C_{arom}), 134.4, 113.6 (H-C_{arom}, *Ar*-CH_2), 123.6, 111.9, 111.1, 110.2 (H-C_{arom}), 100.5 (OCH_2O), 67.1 (C-8), 61.0 (OMe on C-9), 58.6 (C-6), 55.7, 55.3 (2×OMe), 47.7 (Ar-*C*H_2), 38.7 (C-13), 38.1 (C-14), 32.3 (C-5) ppm. EI-MS: *m*/*z* (%) = 473 (2) $[M]^+$, 352 (14) $[M - 121]^+$, 188 (13), 164 (6), 149 (12), 121 (100). EI-HR-MS: calcd. for $C_{28}H_{32}BNO_5$ 473.2374; found 473.2372.

(±)-*N*-Benzyl-*N*-nordihydroallocryptopine (6a): A solution of the boranyl derivative **5a** (60 mg, 0.135 mmol) in THF (10 mL) was added dropwise to a solution of phosphate-buffered hydrogen peroxide (10%, 1.5 mL, pH = 8).[16] The mixture was refluxed for 3 h under a stream of oxygen. The crude reaction product was concentrated under vacuum and the residue was dissolved in $CHCl_3$ (40 mL) and washed with HCl (2%, 2×15 mL) and H_2O (2×15 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 7:3) to yield the dihydro derivative **6a** (43 mg, 74%) as a white solid. Decomposition at 93–94 °C. IR (KBr): $\tilde{\nu}$ = 3420, 1590, 1485, 1470, 1280 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.2–7.0 (m, 2 H, *Ph*-CH_2), 7.11 (s, 1 H, 1-H), 6.92 (d, ^3J = 8.2 Hz, 1 H, 12-H), 6.9–6.7 (m, 3 H, *Ph*-CH_2), 6.73 (d, ^3J = 8.2 Hz, 1 H, 11-H), 6.50 (s, 1 H, 4-H), 5.93 (s, 2 H, OCH_2O), 5.41 (d, ^3J = 7.0 Hz, 1 H, 14-H), 4.13, 3.89 (2 d, ^3J = 15.1 Hz, 1 H each, 8-H, 8′-H), 3.83, 3.76 (2 s, 3 H each, 2×OMe), 3.81 (d, ^3J = 14.0 Hz, 1 H, 13-H), 3.63, 3.29 (2 d, ^3J =

14.0 Hz, 1 H each, Ph-CH_2), 3.09 (m, 1 H, 5-H), 2.72 (dd, ^3J = 14.0, 7.0 Hz, 1 H, 13′-H), 2.70 (m, 1 H, 6-H), 2.60 (m, 1 H, 6′-H), 2.39 (m, 1 H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 151.4, 148.0, 146.3, 146.2 (O-C_{arom}), 139.1, 137.7, 132.1, 131.4, 130.5 (C-C_{arom}), 128.8, 127.9, 126.5 (H-C_{arom}, *Ph*-CH_2), 126.7, 110.2, 110.1, 105.4 (H-C_{arom}), 100.7 (OCH_2O), 70.3 (C-14), 60.7 (OMe on C-9), 58.3 (Ph-*C*H_2) 55.9 (C-6), 55.8 (OMe), 49.6 (C-8), 46.9 (C-13), 33.2 (C-5) ppm. EI-MS: *m*/*z* (%) = 447 (2) $[M]^+$, 356 (7) $[M - 91]^+$, 339 (9), 338 (7), 174 (7), 164 (67), 149 (43), 91 (100). EI-HR-MS: calcd. for $C_{27}H_{29}NO_5$ 447.2046; found 447.2038.

(±)-*N*-(*p*-Methoxybenzyl)-*N*-nordihydroallocryptopine (6b): According to the procedure used to synthesize **6a**, the dihydro derivative **6b** (42 mg, 70%) was obtained from **5b** (60 mg, 0.127 mmol) as a white solid. Decomposition at 90–92 °C. IR (KBr): $\tilde{\nu}$ = 3400, 1590, 1500, 1480, 1270, 1250, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.11 (s, 1 H, 1-H), 6.92 (d, ^3J = 8.5 Hz, 1 H, 12-H), 6.79 (d, ^3J = 8.5 Hz, 2 H, *Ar*-CH_2), 6.72 (d, ^3J = 8.5 Hz, 1 H, 11-H), 6.65 (d, ^3J = 8.5 Hz, 2 H, *Ar*-CH_2), 6.50 (s, 1 H, 4-H), 5.92 (s, 2 H, OCH_2O), 5.41 (d, ^3J = 6.7 Hz, 1 H, 14-H), 4.09 (d, ^3J = 15.3 Hz, 1 H, 8-H), 3.90–3.80 (m, 2 H, 8′-H, 13-H), 3.83, 3.76, 3.73 (3 s, 3 H each, 3×OMe), 3.55, 3.24 (2 d, ^3J = 14.0 Hz, 1 H each, Ar-CH_2), 3.06 (ddd, ^3J = 15.3, 10.4, 3.8 Hz, 1 H, 5-H), 2.8–2.6 (m, 3 H, 13′-H, 6-H, 6′-H), 2.39 (dt, ^3J = 14.6, 3.4 Hz, 1 H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.2, 151.4, 147.9, 146.3, 146.2 (O-C_{arom}), 139.1, 132.1, 131.6, 130.7, 129.5 (C-C_{arom}), 130.1, 113.3 (H-C_{arom}, *Ar*-CH_2), 126.7, 110.2, 110.0, 105.4 (H-C_{arom}), 100.7 (OCH_2O), 70.4 (C-14), 60.7 (OMe on C-9), 57.5 (Ar-*C*H_2), 55.6, 55.1 (2×OMe), 55.5 (C-6), 49.4 (C-8), 46.9 (C-13), 32.3 (C-5) ppm. EI-MS: *m*/*z* (%) = 477 (25) $[M]^+$, 356 (54) $[M - 121]^+$, 339 (14), 338 (25), 192 (17), 164 (49), 149 (28), 121 (100). EI-HR-MS: calcd. for $C_{28}H_{31}NO_6$ 477.2151; found 477.2154.

***N*-Benzyl-*N*-norallocryptopine (7a):** Pyridinium chlorochromate (PCC; 20 mg, 0.093 mmol), sodium acetate (16 mg, 0.19 mmol) and molecular sieves (3 Å; 50 mg) were added to a stirred solution of the dihydro derivative **6a** (20 mg, 0.045 mmol) in dried CH_2Cl_2 (20 mL) under argon. The mixture was stirred at room temperature for 2 h. The solution was filtered and washed with H_2O (3×5 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography ($CHCl_3$/MeOH, 8:0.1) to yield the protopine **7a** (12 mg, 60%) as a white solid. M.p. 154–155 °C. IR (KBr): $\tilde{\nu}$ = 1660, 1580, 1500, 1250, 1230, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.2–7.0 (m, 5 H, *Ph*-CH_2), 7.00 (s, 1 H, 1-H), 6.92, 6.81 (2 d, ^3J = 8.2 Hz, 1 H each, 11-H, 12-H), 6.60 (s, 1 H, 4-H), 5.95 (s, 2 H, OCH_2O), 3.90 (br. s, 4 H), 3.86, 3.75 (2 s, 3 H each, 2×OMe), 3.3–2.7 (m, 4 H), 2.5–2.3 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 195.6 (O=C), 151.7, 148.3, 147.8, 146.1 (O-C_{arom}), 136.3, 136.1, 133.2, 133.1, 128.4 (C-C_{arom}), 130.1, 128.0 (H-C_{arom}, *Ph*-CH_2), 126.9, 110.7, 110.6, 108.4 (H-C_{arom}), 101.2 (OCH_2O), 61,1 (OMe on C-9), 61.0, 56.1 (C-6, Ph-*C*H_2), 55.7 (OMe), 53.8 (C-8), 46.7 (C-13), 31.5 (C-5) ppm. EI-MS: *m*/*z* (%) = 445 (2) $[M]^+$, 354 (21) $[M - 91]^+$, 164 (47), 149 (25), 91 (100). EI-HR-MS: calcd. for $C_{27}H_{27}NO_5$ 445.1889; found 445.1911.

***N*-(*p*-Methoxybenzyl)-*N*-norallocryptopine (7b):** According to the above procedure the protopine derivative **7b** (16 mg, 65%) was obtained from **6b** (25 mg, 0.052 mmol) as a white solid. M.p. 145–146 °C. IR (KBr): $\tilde{\nu}$ = 1680, 1600, 1590, 1510, 1490, 1280, 1260, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.05 (d, ^3J = 8.6 Hz, 2 H, *Ar*-CH_2), 7.01 (s, 1 H, 1-H), 6.94, 6.83 (2 d, ^3J = 8.2 Hz, 1 H each, 11-H, 12-H), 6.76 (d, ^3J = 8.6 Hz, 2 H, *Ar*-CH_2), 6.61 (s, 1 H, 4-H), 5.95 (s, 2 H, OCH_2O), 4.00 (br. s, 4 H), 3.86 (s, 3 H, OMe), 3.75 (s, 6 H, 2×OMe), 3.3–2.7 (m, 4 H), 2.7–2.4 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 199.0 (O=C), 158.3, 154.0, 146.4, 146.2, 145.7 (O-C_{arom}), 134.3, 133.4, 131.1, 128.0, 127.8 (C-C_{arom}), 130.5, 113.1 (H-C_{arom}, *Ar*-CH_2), 124.4, 112.6, 110.4, 109.6 (H-C_{arom}), 100.7 (OCH_2O), 60.8 (OMe on C-9), 57.0, 56.5 (C-6, Ar-*C*H_2), 55.8, 55.1 (2×OMe), 47.7 (C-8), 45.3 (C-13), 30.8 (C-5) ppm. EI-MS: *m*/*z* (%) = 475 (7) $[M]^+$, 354 (69) $[M - 121]^+$, 164 (54), 121 (100). EI-HR-MS: calcd. for $C_{28}H_{29}NO_6$ 475.1995; found 475.2004.

Preparation of (±)-Canadinium Salt 1c: Methyl iodide was added to a solution of (±)-canadine (2 g, 5.90 mmol) in acetone (200 mL). After stirring at room temperature, a mixture of *cis*/*trans* (1:4) diastereoisomers **1c** was obtained. The crude reaction product was filtered and the solid was recrystallized in acetone to yield the *trans* diastereoisomer. The filtrate was concentrated under vacuum and the residue was purified by column chromatography ($CHCl_3$/MeOH, 10:1) to yield the pure *cis* diastereoisomer.

(±)-*trans*-*N*-Methylcanadinium Iodide (*trans*-1c): White solid. M.p. 237–238 °C (ref.[17] 252–253 °C). IR (KBr): $\tilde{\nu}$ = 1612, 1497, 1480, 1287 cm^{-1}. UV (MeOH): λ_{max} (logε) = 208 (4.30), 220 (3.94), 288 (3.44) nm. ^{1}H NMR ($CDCl_3$ + TFA): δ = 7.02, 6.98 (2 d, ^3J = 8.3 Hz, 1 H each, 11-H, 12-H), 6.75, 6.70 (2 s, 1 H each, 1-H, 4-H), 6.00 (s, 2 H, OCH_2O), 4.81 (dd, ^3J = 12.3, 4.7 Hz, 1 H, 14-H), 4.88, 4.56 (2 d, ^3J = 15.9 Hz, 1 H each, 8-H, 8′-H), 4.2–4.0 (m, 1 H, 6-H), 3.88, 3.87 (2 s, 3 H each, 2×OMe), 3.76 (dd, ^3J = 17.6, 4.7 Hz, 1 H, 13-H), 3.8–3.7(m, 1 H, 6′-H), 3.4–3.3 (m, 5-H), 3.14 (m, 1 H, 5′-H), 3.00 (dd, ^3J = 17.6, 12.3 Hz, 1 H, H-13′), 2.93 (s, 3 H, NMe) ppm. ^{13}C NMR ($CDCl_3$ + TFA): δ = 151.3, 148.4, 147.9, 145.3 (O-C_{arom}), 123.2, 121.8, 121.1, 119.7 (C-C_{arom}), 124.4, 113.5, 108.5, 105.4 (H-C_{arom}), 101.7 (OCH_2O), 66.2 (C-14), 61.9 (C-8), 61.7 (C-6), 61.3 (OMe on C-9), 55.9 (OMe), 39.5 (NMe), 28.8 (C-13), 23.9 (C-5) ppm. EI-MS: *m*/*z* (%) = 354 (1) $[M]^+$, 339 (1), 164 (100). $C_{21}H_{24}INO_4 \cdot H_2O$ (499.35): calcd. C 50.51, H 5.25, N 2.81; found C 50.70, H 5.10, N 2.94.

(±)-*cis*-*N*-Methylcanadinium Iodide (*cis*-1c): Yellow solid. M.p. 241–243 °C (ref.[18] 249–251 °C). IR (KBr): $\tilde{\nu}$ = 1600, 1500, 1485, 1280, 1230 cm^{-1}. UV (CH_3CN): λ_{max} (logε) = 204 (4.20), 230 (3.84), 292 (3.40) nm. ^{1}H NMR ($CDCl_3$): δ = 6.89, 6.83 (2 d, ^3J = 8.5 Hz, 1 H each, 11-H, 12-H), 6.74, 6.67 (2 s, 1 H each, 1-H, 4-H), 5.96 (s, 2 H, OCH_2O), 5.33 (dd, ^3J = 9.4, 6.3 Hz, 1 H, 14-H), 5.20 (d, ^3J = 16.0 Hz, 1 H, 8-H), 4.99 (d, ^3J = 16.0 Hz, 1 H, 8′-H), 4.1–3.9 (m, 1 H, 6-H), 3.92, 3.83 (2 s, 3 H each, 2×OMe), 3.8–3.6 (m, 1 H, 5-H), 3.64 (s, 3 H, NMe), 3.45 (dd, ^3J = 18.6, 6.3 Hz, 1 H, 13-H), 3.39 (ddd, ^3J = 12.5, 12.5, 8.8 Hz, 1 H, 6′-H), 3.15 (dd, ^3J = 18.0, 5.0 Hz, 1 H, 5′-H), 3.04 (dd, ^3J = 18.6, 9.4 Hz, 1 H, 13′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 151.4, 148.7, 147.4, 145.7 (O-C_{arom}), 124.4, 121.1, 120.7, 119.6 (C-C_{arom}), 123.5, 113.5, 108.9, 107.0 (H-C_{arom}), 101.7 (OCH_2O), 65.2 (C-14), 61.6 (OMe on C-9), 59.6 (C-8), 56.0 (OMe), 52.7 (C-6), 50.5 (NMe), 33.4 (C-13), 23.8 (C-5) ppm.

Reaction of 1c with HNa: A suspension of HNa (60% in mineral oil, 180 mg, 4.5 mmol), DMSO (0.2 mL), benzene (2 mL) and **1c** (*cis*/*trans* = 8:1) (250 mg, 0.52 mmol) was stirred at room temperature under argon. After 5 h, the crude product was concentrated under vacuum and the ^{1}H NMR spectrum clearly indicated the exclusive presence of the Hofmann elimination product **3c**. Attempts to crystallize this product from an MeOH solution yielded a small amount of the corresponding dibenzazecine **3c** as well as a methanolic solution of the starting material.

3,4-Dimethoxy-6-methyl-5,6,7,8-tetrahydro-11*H*-benzo[*c*][1,3]benzodioxolo[5,6-*g*]azecine (3c): White solid. M.p. 126–128 °C (MeOH). ^{1}H NMR ($CDCl_3$): δ = 7.09, 6.43 (2 d, ^3J = 16.5 Hz, 1 H each, $H_{olefinic}$), 6.95, 6.80 (2 d, ^3J = 8.4 Hz, 1 H each, H_{arom}), 6.91, 6.64 (2 s, 1 H each, H_{arom}), 5.92 (s, 2 H, OCH_2O), 3.86, 3.79 (2 s, 3 H

each, 2×OMe), 3.66 (s, 2 H), 2.73 (br. s, 4 H), 2.21 (s, 3 H, NMe) ppm.

3,4-Dimethoxy-6,6-dimethyl-5,6,7,8-tetrahydro-11*H*-benzo[*c*][1,3]-benzodioxolo[5,6-*g*]azecin-6-ium Iodide (8): The dry crude product containing the elimination product **3c**, resulting from treatment of **1c** (*cis*/*trans* = 1:4) (250 mg, 0.52 mmol) with HNa/DMSO/benzene as described above, was dissolved in dry $CHCl_3$ and an excess of methyl iodide was added dropwise. The mixture was stirred under argon for 12 h and concentrated to dryness. The residue was washed with *n*-hexane and purified by column chromatography ($CHCl_3$/MeOH) to yield **8** (148 mg, 57%) as a yellow solid. M.p. 114–115 °C. IR (KBr): $\tilde{\nu}$ = 1600, 1480, 1450, 1415, 1265, 1220, 1210 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon$) = 208 (4.41), 302 (3.91) nm. ^1H NMR ($CDCl_3$): δ = 7.19, 7.08 (2 d, ^3J = 8.2 Hz, 1 H each, $H_{aromatic}$), 7.15, 6.39 (2 d, ^3J = 16.9 Hz, 1 H each, $H_{olefinic}$), 6.82, 6.66 (2 s, 1 H each, $H_{aromatic}$), 5.88 (m, 2 H, OCH_2O), 5.10, 4.44 (2 d, ^3J = 14.0 Hz, 1 H each), 4.09 (m, 1 H), 3.94, 3.84 (2 s, 3 H each, 2×OMe), 4.0–3.5 (m, 2 H), 3.63 (br. s, 3 H, NMe), 3.22 (m, 1 H), 3.04 (s, 3 H, NMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 151.4, 149.5, 147.3, 147.1 (O-C_{arom}), 134.4, 130.5, 127.1, 120.1 (C-C_{arom}), 135.5, 133.2 (H-$C_{olefinic}$), 121.3, 115.8, 113.1, 109.1 (H-C_{arom}), 101.4 (OCH_2O), 61.7 (OMe on C-9), 56.0 (OMe), 53.3, 52.5 (2×NMe), 61.6, 57.7, 30.2 (3×CH_2) ppm. EI-MS: *m*/*z* (%) = 368 (10) $[M]^+$, 338 (7), 164 (19), 149 (21), 142 (100), 127 (50).

(±)-Dihydroallocryptopine (6c): According to the procedure described for the synthesis of **3c**, the dry crude product was redissolved in THF (20 mL) and BH_3 (1 M THF solution, 3 mL) was added dropwise under argon. The ^1H NMR spectrum of the hydroboration product exhibited the exclusive presence of **5c**. This mixture was treated with a basic solution of hydrogen peroxide (10% H_2O_2, 3 N NaOH, 1.5 mL) and refluxed. On completion of the reaction (2 h) the mixture was washed with H_2O and the aqueous phase extracted with diethyl ether. The organic phase was dried with $MgSO_4$, concentrated under vacuum and purified by column chromatography ($CHCl_3$/MeOH, 8:0.3) to yield **6c** (137 mg, 72%) as a white solid. M.p. 160–161 °C (ref.[6c] 169 °C). IR (KBr): $\tilde{\nu}$ = 3450, 1600, 1480, 1450 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) = 202 (3.83), 232 (3.24), 290 (2.92) nm. ^1H NMR ($CDCl_3$): δ = 7.10, 6.58 (2 s, 1 H each, 1-H, 4-H), 6.95, 6.73 (2 d, ^3J = 7.9 Hz, 1 H each, 11-H, 12-H), 5.91 (s, 2 H, OCH_2O), 5.31 (d, ^3J = 7.3 Hz, 1 H, 14-H), 4.01 (d, ^3J = 14.6 Hz, 1 H, 8-H), 3.83, 3.75 (2 s, 3 H each, 2×OMe), 3.60 (d, ^3J = 14.6 Hz, 1 H, 8′-H), 3.41 (d, ^3J = 14.1 Hz, 1 H, 13-H), 3.0–2.9 (m, 1 H, 5-H), 2.82 (ddd, ^3J = 12.2, 3.7, 2.4 Hz, 1 H, 6-H), 2.65 (dd, ^3J = 14.1, 7.3 Hz, 1 H, 13′-H), 2.6–2.4 (m, 2 H, 5′-H, 6′-H), 2.08 (s, 3 H, NMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 151.3, 147.7, 146.2, 146.1 (O-C_{arom}), 139.4, 137.0, 132.4, 131.7 (C-C_{arom}), 126.4, 110.1, 110.0, 105.5 (H-C_{arom}), 100.7 (OCH_2O), 71.0 (C-14), 60.6 (OMe on C-9), 55.6 (OMe), 59.8 (C-6), 52.2 (C-8), 46.9 (C-13), 42.1 (NMe), 33.4 (C-5) ppm. EI-MS: *m*/*z* (%) = 371 (2) $[M]^+$, 353 (12) $[M - 18]^+$, 204 (17), 188 (60), 164 (49), 149 (100). EI-HR-MS: calcd. for $C_{21}H_{25}NO_5$ 371.1733; found 371.1731.

Allocryptopine (7c): PCC (75 mg, 0.35 mmol), AcONa (59 mg, 0.70 mmol) and molecular sieves (3 Å; 14 mg) were added to a solution of (±)-dihydroallocriptopine (**6c**) (90 mg, 0.24 mmol) in dry CH_2Cl_2 (25 mL) under argon. After 2 h, the chromium salts were filtered off and the organic layer was washed with water (3×15 mL), dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography ($CHCl_3$/MeOH, 8:0.3) to give **7c** (56 mg, 63%) as a white solid. M.p. 166–167 °C (ref.[1c] 160–161 °C). IR (KBr): $\tilde{\nu}$ = 1660, 1590, 1500, 1460, 1240, 1050 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.04, 6.81 (2 d, ^3J = 8.4 Hz, 1 H each, 11-H, 12-H), 6.81, 6.61 (2 s, 1 H each, 1-H, 4-H), 5.91 (s, 2 H, OCH_2O), 4.2–3.9 (m, 4 H), 3.86, 3.79 (2 s, 3 H each, 2×OMe), 3.2–2.5 (m, 4 H), 1.80 (s, 3 H, NMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.9 (O=C), 153.7, 146.4, 146.3, 145.9 (O-C_{arom}), 134.5, 133.5, 131.4, 128.0 (C-C_{arom}), 123.5, 112.6, 110.5, 109.7 (H-C_{arom}), 100.8 (OCH_2O), 60.6 (OMe on C-9), 60.5 (C-6), 55.8 (OMe), 51.1 (C-8), 46.3 (C-13), 42.9 (NMe), 31.3 (C-5) ppm. EI-MS: *m*/*z* (%) = 369 (2) $[M]^+$, 164 (100), 149 (40).

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