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The Polonovski–Potier Reaction of Berbine *N*-Oxides. Synthesis of 8-Hydroxymethyl and 8-Methylberbines

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Abstract—The Polonovski–Potier reaction of *trans* and *cis* berbines *N*-oxides was studied. The 8-cyano derivative obtained from *trans* *N*-oxides were used to synthesize 8-hydroxymethyl and 8-methyl berbines. This procedure was applied to the stereocontroled synthesis of (8*R*, 14*S*)-(−)-8-methylcanadine from (14*S*)-(−)-canadine.

The protoberberines are a class of isoquinoline alkaloids characterized by the dibenzo[*a*,*g*]quinolizidine ring system, with oxygenated substituents at rings A and D. A number of this class of alkaloids with alkyl substituted in ring C are also known.[1] Various tetrahydroprotoberberine alkaloids (berbines) with a C-8 substituent have been isolated as minor components from plants, including corytenchirine (**1**, R=H) from *Corydalis ochotensis*,[2] solidaline (**2**) from *Corydalis solida*,[3] malacitanine (**3**) from *Ceratocapnos heterocarpa*[4] and the benzylberbinol **4** from *Aristolochia constricta* (Fig. 1).[5]

The total syntheses of C-8 substituted berbines has been accomplished by formation of ring C from benzylisoquinoline using a biogenetic approach.[4,6] Also, partial syntheses of racemic C-8 alkyl substituted berbines have been achieved by inserting the substituent on aromatic berberinium salts in two different ways: (i) by addition of carbon nucleophiles at the sufficiently electrophilic position 8 [in this way, (±)-8-methylcanadine, (±)-**6**, was synthesized from berberine chloride (**5**) by reaction with MeMgI, followed by reduction with $NaBH_4$];[7] (ii) and by hydroxymethylation of berberinium salts by photoinduced single electron transfer and reduction as in the recently reported synthesis of (±)-solidaline (**2**) from palmatine chloride.[8] The asymmetric synthesis of (8*R*, 14*S*)-(−)-8-methylcanadine [(−)-**6**)] was accomplished by regioselective complexation of enantiopure (−)-canadine [(−)-**7**] to $Cr(CO)_3$, separation of the diasteroisomers, silylation at position 11 (followed by a stereoselective deprotonation at C-8) and addition of MeI (Scheme 1).[7]

One alternative approach to transforming chiral, naturally occurring tetrahydroprotoberberine alkaloids to enantiopure C-8 alkyl substituted protoberberines may be the selective oxidation to the 7,8-dehydro derivative and insertion of the substituent as a nucleophile (Scheme 2).

The partial oxidation of berbines (tetrahydroprotoberberines) to the corresponding 7,8-dehydroberbines with iodine is of limited use since only berbines substituted at position 1, with a preferred *cis*-B/C-quinolizidine conformation, give the reaction.[9] Predictably, functionalization

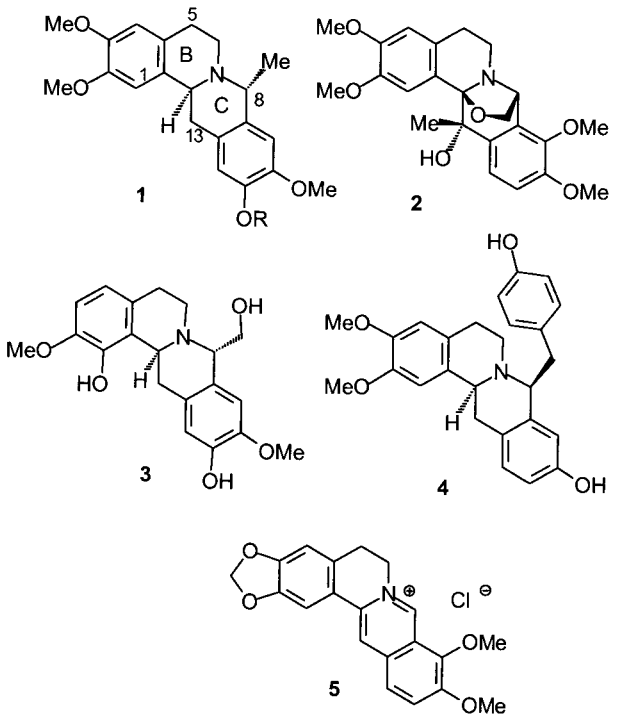

Figure 1.

Keywords: alkaloids; isoquinolines; Polonovski reaction; protoberberines.
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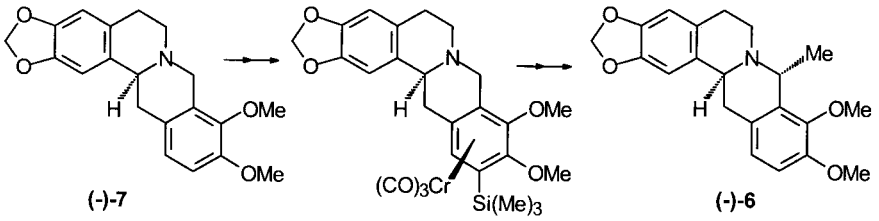
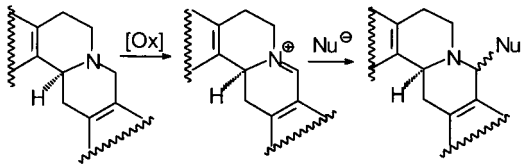


Scheme 1.



Scheme 2.

of C-8 berbines is also possible by the Polonovski–Potier reaction (viz. the modified Polonovski reaction), by which an *N*-oxide is converted into an iminium ion intermediate.[10] In this paper, we report on the differential behavior of *cis*- and *trans*-berbines *N*-oxides towards the modified Polonovsky reaction.[11] The synthetic applications of the reaction leading to 8-hydroxymethyl and 8-methyl berbines are also described.

Results and Discussion

The 9,10-substituted, readily accessible, *trans*- and *cis*-canadine *N*-oxides [(−)-**8**, (±)-**8** and (±)-**9**], the 10,11-substituted *trans*-(±)-xylopinine *N*-oxide (**11**) and *trans*-(±)-thalictricavine *N*-oxide (**10**), were selected for this study (Fig. 2).[12,13]

(±)-Canadine [(±)-**7**] was prepared by reduction of berberine chloride (**5**). Enantiomer (−)-**7** was obtained by resolution of racemic canadine by fractional crystalization with (+)-di-*O*,*O*′-*p*-toluoyl-D-tartaric acid.[14] (±)-Xylopinine (**12**) was synthesized by cyclization of *N*-norlaudanosine.[15] (±)-Thalictricavine (**13**), a 13-methyl canadine with a *trans* stereochemistry relative to H-14, was obtained by methylation of 13,14-dehydrocanadine, available from the partial reduction of **5**.[16] The corresponding *N*-oxides were prepared by reaction with *m*CPBA. Only in the case of (±)-canadine was a large enough amount of the *cis* isomer available to study its reactivity.

The Polonovski–Potier reaction of *trans*-berbine *N*-oxides

The *trans N*-oxides, with a rigid *trans*-B/C-quinolizidine junction (**I**),[12] possess three hydrogens (H-6ax, H-8ax and H-14) in an anti-periplanar arrangement with respect to the oxygen in the *N*-oxide function, so they could yield three different iminium salts in the Polonovski reaction (Fig. 3).

The reaction of *trans*-canadine *N*-oxide under Polonovski–Potier conditions (TFAA 15 equiv., in $CHCl_3$, at −30°C for 30 min and then allowing to rise to 25°C) was monitored by ^1H and ^{13}C NMR. After complete disappearance of the *N*-oxide, only two products were formed, in a 37:63 ratio, the structures of which were tentatively assigned as 7,8-dehydrocanadine (**14**) and 7,14-dehydrocanadine (**15**). ^1H NMR data for **15** matched those for the protonated 13,14-dehydrocanadine (+TFA). A low-field singlet (9.25 ppm) and a benzyl iminium carbon (163.3 ppm) suggested structure **14**. $NaBD_4$ reduction of the mixture of iminium salts **14** and **15** gave a mixture of 8-*d*-canadine and 14-*d*-canadine as inferred from the retro Diels–Alder fragmentation in the mass spectra (Scheme 3).

A similar behavior was observed in the other *trans N*-oxides. Thalictricavine *N*-oxide (**10**) underwent H-14 elimination to a much greater extent (18:82 ratio) than H-8 elimination; on the other hand xylopinine *N*-oxide (**11**) yielded the 7,8-dehydroxylopinine as the main product (64:36 ratio), probably reflecting the substantial effect of the substituent on C-9 on the course of the reaction. In all cases,

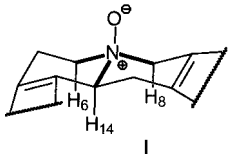


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Figure 3.

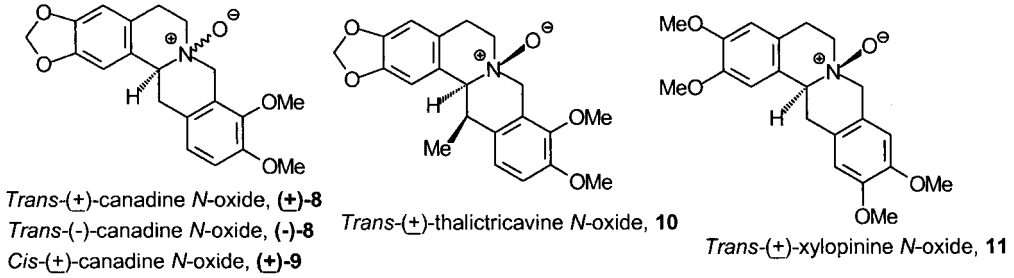
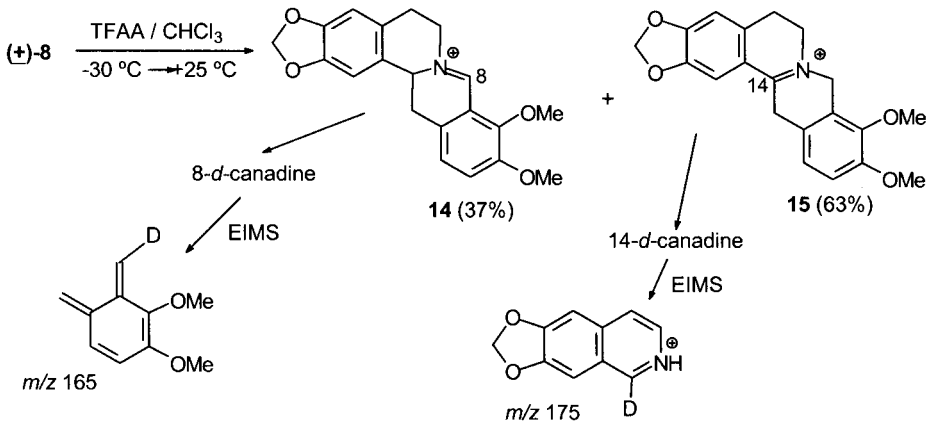


Figure 2.



Scheme 3.

Table 1. Regioselectivity of the Polonovski reaction of *trans*-berbine *N*-oxides as determined by ^{1}H NMR

Activating agent	Temperature (°C)	Reaction time (h)	(±)-**8**	(±)-**10**	(±)-**11**
			7,8-dehydro/7,14-dehydro ratio		
TFAA	−30 to +25	1	37/63	18/82	64/36
AcCl	25	2	39/61	20/80	50/50
MsCl	60	2	58/32[a]	49/51[a]	84/16[a]

[a] Characterized as the corresponding protoberberinium salt.

the absence of 6,7-dehydro derivatives was significant; it probably resulted from the weak acidity of H-6 and the lower stability of the corresponding iminium ion.

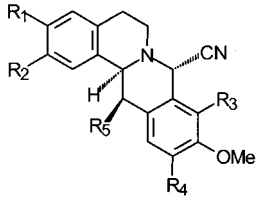
Acetyl chloride as activating agent provided quite similar results; the reaction however, was slower. Mesyl chloride required heating at 60°C for the reaction to start. The preferential formation of the 7,8-dehydro derivatives may be due to a concomitant intramolecular *syn*-elimination of H-8eq together with the normal anticoplanar H-8ax elimination (Table 1).[17]

7,8- and 7,14-Dehydroberbines proved highly prone to oxidation (particularly the latter, which aromatized easily to the protoberberinium salt); attempts at isolating them were unsuccessful. Therefore, the Polonovski–Potier reaction was conducted under the conditions described above, with the final addition of KCN in a saturated aqueous solution of NaOAc to trap the iminium ion formed. After the reaction of (±)-**8** with TFAA, addition of cyanide and preparative TLC afforded berberine (**5**) and crystalline (8*R**, 14*S**)-(±)-8-cyano-canadine [(±)-**16**, 29%]. The absence of the 14-cyano derivative can be ascribed to the reaction pH rising upon addition of the KCN/NaOAc solution, the 7,14-dehydro iminium ion (**15**) tautomerizing to the enamine (13,14-dehydrocanadine), which is readily oxidized.

Although two 8-cyanoderivatives were to be expected from the addition of KCN to 7,8-dehydrocanadine (**14**), only diastereoisomer (**16**), with a *cis* arrangement between H-14 and the cyano group, was observed. The stereochemistry of **16** was established from the observed nOe between H-8 and both hydrogens of the methylene group at C-6, and also from the absence of nOe between H-14 and H-8 (Fig. 4). A *cis*-B/C-quinolizidine conformation was inferred from the ^{13}C NMR signals at 55.1 (C-14), 48.9 (C-6) and 36.4 ppm (C-13).[18]

The high diastereoselectivity observed, with the cyano group in an axial position, reveals that the attack on the *Re* face is favored, a finding that is not unprecedented.[19] Semi-empirical calculations (PM3) for both 8-cyanocanadine diastereoisomers indicate that the *cis* isomer (**16**) is 2.3 kcal more stable than the *trans* isomer, which suggests that the reaction is thermodynamically controlled.[20]

The Polonovski–Potier reaction of *trans*-(±)-xylopinine *N*-oxide (**11**) (TFAA), with subsequent addition of KCN,



(+)-16, R_1+R_2= OCH_2O, R_3= OMe, R_4= R_5= H
(-)-16, R_1+R_2= OCH_2O, R_3= OMe, R_4= R_5= H
17, R_1= R_2= R_4= OMe, R_3= R_5= H
18, R_1+R_2= OCH_2O, R_3= OMe, R_4= H, R_5= Me

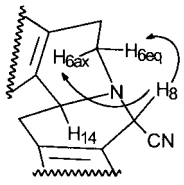


Figure 4.

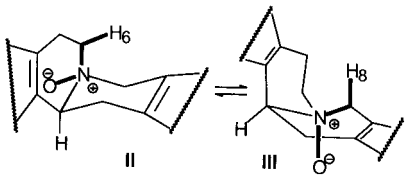
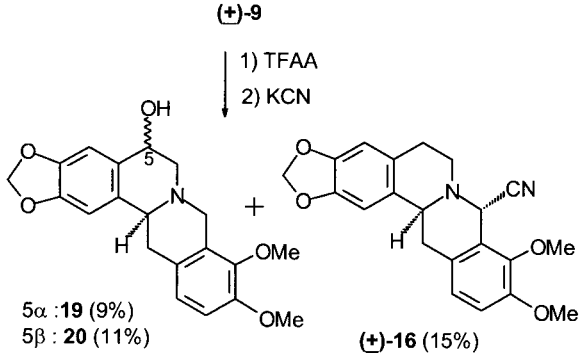


Figure 5.

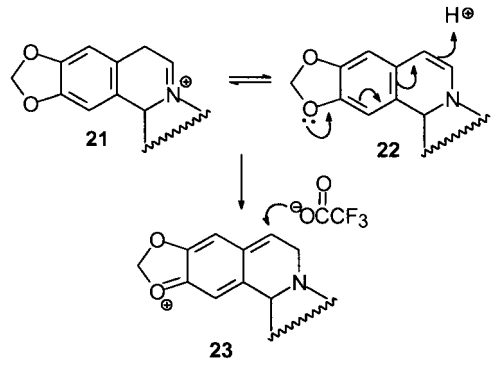


Scheme 4.

gave (8*S**, 14*S**)-(±)-8-cyanoxylopinine (**17**) in a 49% yield, together with pseudopalmatine, the quaternary form of xylopinine. Compound **17** also exhibits a *cis*-B/C-quinolizidine conformation with the cyano group *cis* to H-14. *trans*-(±)-Thalictricavine *N*-oxide (**10**) was reacted with MsCl to give the corresponding cyanide, **18**, after work up.

The Polonovski–Potier reaction of *cis*-canadine *N*-oxide

cis-(±)-Canadine *N*-oxide (**9**) occurs in a *cis*-B/C-quinolizidine conformation,[12] so the *N*-oxide bond (Fig. 5) is in a *quasi*-antiperiplanar arrangement respect to H-6 (**II**) and H-8 (**III**), while H-14 is in a *syn*-coplanar arrangement.[21]



Scheme 5.

Two elimination processes could therefore be expected to occur leading to the 6,7- and 7,8-dehydro derivatives.

The Polonovski–Potier reaction of (±)-**9** with TFAA, followed by ^{1}H NMR, suggested a much complex process than with the *trans* isomer: the 7,8-dehydrocanadine was the only product identified in the complex mixture. Neutralization of the reaction crude and chromatography allowed the isolation of two tertiary bases that were characterized as (±)-5α-hydroxycanadine (**19**), and its C-5 epimer, (±)-5β-hydroxycanadine (**20**) (in 9 and 10% yield, respectively). When the reaction was performed with final addition of KCN, **16** (15%) was isolated together with **19** (9%) and **20** (11%) (Scheme 4).

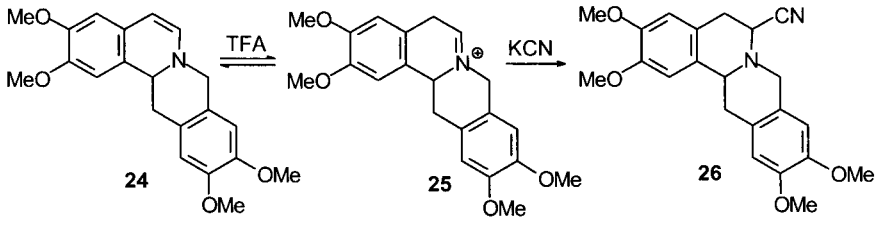
The relative stereochemistry of the hydroxy group in **19** and **20** was derived from the ^{1}H NMR signal for H-5. In the α-isomer **19**, H-5 gives a broad singlet at 4.48 ppm; in the β-isomer **20**, the H-5 signal appears downfield (4.81 ppm), as a dual doublet ($J_{5,6ax}$=7.5 Hz and $J_{5,6eq}$=4.0 Hz). These data are in agreement with those reported for other synthetic 5-hydroxy protoberberines.[22]

There is at least one precedent of an analogous incorporation of a hydroxyl group in the Polonovski–Potier reaction of a *cis*-quinolizidine *N*-oxide. Thus, the reaction of N_a,*O*-di-Boc-*Z*-geissoschizine *cis*-N_b-oxide with TFAA afforded N_a,*O*-di-Boc-6α-hydroxy-*Z*-geissoschizine in a 3% yield; no explanation for the process was proposed, however.[23]

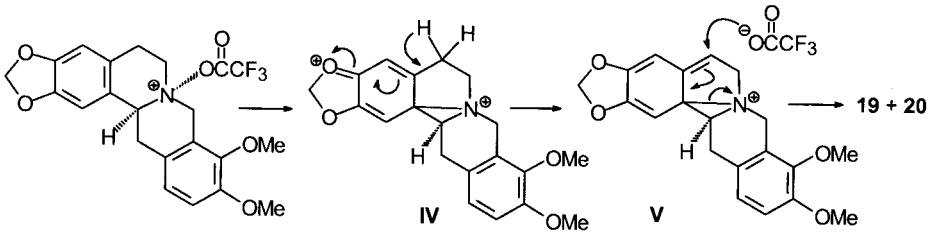
The formation of these unexpected compounds suggests that the C-5 becomes an electrophilic site. The simplest possible process would start with the expected elimination of H-6 leading to the key intermediate 6,7-dehydrocanadine (**21**) (Scheme 5). Tautomeric equilibrium with the enamine (**22**) and reprotonation at C-6 (**23**) induced by the oxygen at C-2 would allow the attack of the TFA anion on C-5.

This hypothesis was tested by examining the behavior of 5,6-dehydroberbines. The most readily accessible 5,6-dehydroxylopinine (**24**) (Scheme 6), was prepared by condensation of papaverine with DMF/$POCl_3$ to give 5,6-dehydropseudopalmatine, followed by ring-C reduction.[24] Quantitative protonation of **24** provided the 6,7-dehydroxylopinine (**25**), subjection of which to Polonovski–Potier reaction conditions resulted in no 5-hydroxy derivatives only the 6-cyanoxylopinine (**26**) was isolated.

Moreover, treating the enamine **24** with TFA-*d* resulted in no incorporation of deuterium on C-6 which was to be expected if the oxygen at C-2 were involved in the process. These findings seemingly exclude the participation of a



Scheme 6.



Scheme 7.

6,7-dehydroberbine as a common intermediate leading to both the 6-cyano and the 5-hydroxy products.

It does not seem unreasonable to postulate a mechanism involving aromatic ring A (Scheme 7). The loss of trifluoracetate from the *N*-oxide may be assisted by the oxygen at C-3 to yield the aziridinium dication **IV**, the deprotonation of which would give the aziridinium monocation **V**, from which compounds **19** and **20** can be obtained.

A similar mechanism was tentatively proposed by Danishefsky to explain the anomalous results of the Polonovski reaction of mitosane derivatives.[25] More recently, Potier also described an unusual intramolecular oxygen transfer in the Polonovski reaction of the *Amarillidaceae* alkaloid galanthamine *N*-oxide, a process that neither involves an iminium ion as intermediate.[26]

Synthetic applications

We recently found the photoaddition of methanol to protoberberinium ions to take place in a regioselective manner at position 8, with subsequent stereoselective reduction yielding (8*R**, 14*S**)-hydroxymethylberbines with a *trans* arrangement between H-14 and the substituent.[8] As stated above, the Polonovski–Potier reaction of the *trans*-berbine *N*-oxides gave the corresponding *cis*-cyanides; consequently, the reaction could be used to prepare (8*S**, 14*S**)-8-hydroxymethylberbines such as **29a** and **29b**, which are epimeric with those provided by the photochemical approach.

The reaction sequence involved in these transformation is as follows:[27] (i) rigorously controlled hydrolysis of the cyano derivatives **16** and **17** (conc HCl at 0°C) to afford the 8-carbamoylberbines (**27a** and **27b**, in 50% and 75% yields); (ii) quantitative conversion of these amides to the methyl ester derivatives **28a** and **28b** by use of the acid resin Amberlite® IR-120 in methanol; and (iii) reduction with $LiAlH_4$ to obtain (8*S**, 14*S**)-8-hydroxymethylcanadine (**29a**) and (8*S**, 14*S**)-8-hydroxymethylxylopinine (**29b**) in 70% and 91% yield, respectively (Fig. 6).

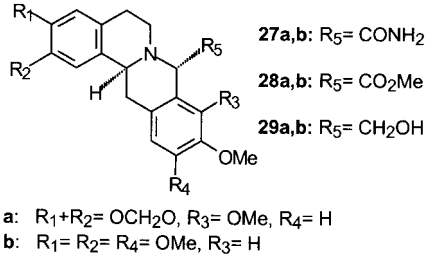


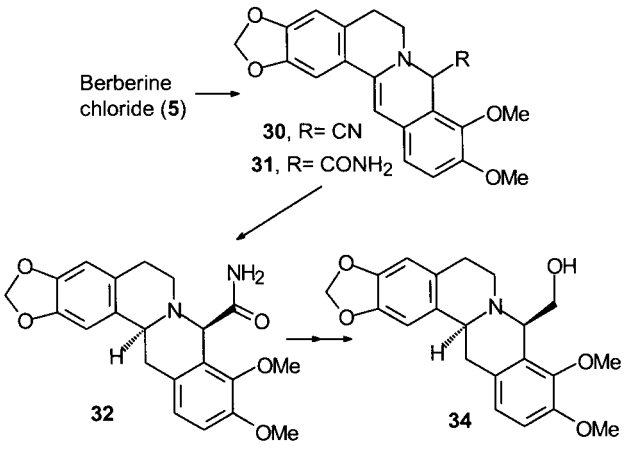
Figure 6.

The addition of MeMgBr at C-8 of berberine chloride, followed by hydride reduction, is highly diastereoselective; entry of the hydride occurs exclusively from the less hindered face away from the substituent.[7] We realized that this sequence could be used with cyanide as the nucleophile, thus opening alternative access to 8-hydroxymethylberbines in a 8*R**, 14*S**-configuration.

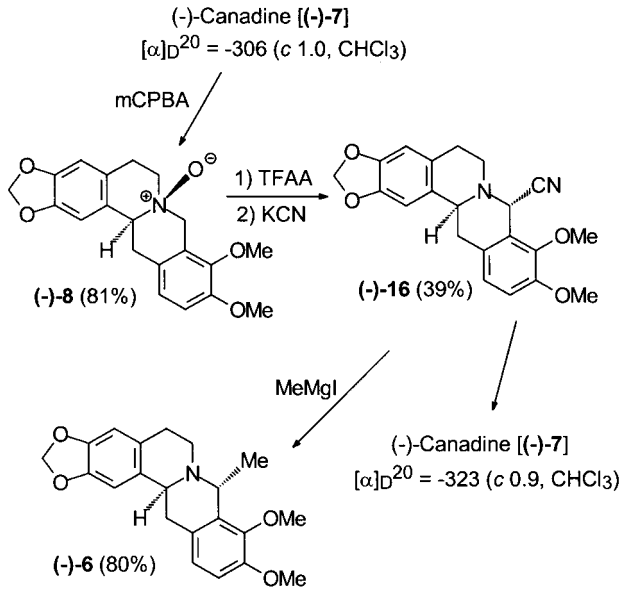
In fact, addition of KCN to a methanolic solution of berberine chloride (**5**) gave 8-cyano-13,14-dehydrocanadine (**30**) quantitatively; however, addition of $NaBH_4$ was found to remove the substituent and cause the reduction to (±)-**7**. Elimination of the substituent was avoided by a previous transformation to the amide **31**.

As expected, reduction of (±)-8-carbamoyl-13,14-dehydrocanadine (**31**) gave (8*R**, 14*S**)-(±)-8-carbamoylcanadine (**32**) with the predicted stereochemistry. The nOe observed between H-8, H-6_{ax} and H-14, and the downfield appearance of C-14 in the ^{13}C NMR spectra suggested a *trans*-B/C-quinolizidine conformation with *trans* arrangement between H-14 and the carbamoyl group, for the amide **32**. Transformation into the methyl ester **33** and reduction afforded the epimeric (8*R**, 14*S**)-(±)-8-hydroxymethylcanadine (**34**) (Scheme 8).[8]

8-Methylberbines can be synthesized by conversion of the cyano derivatives into 7,8-dehydroberbinium ions, followed by addition of methyl magnesium iodide. However, direct treatment of the cyano derivatives with the Grignard reagent gave higher yields, in a stereoselective reaction where the



Scheme 8.



Scheme 9.

methyl group retained the configuration of the cyano group.[28] In this way, *O*-methylcorytenchirine (1, R=Me) was prepared in a 80% yield.

The stereoselective nature of the reaction implies that the chirality at C-14 guides the nucleophile entry at C-8. As a result, Polonovski–Potier reaction of homochiral tetrahydroprotoberberines could be used to prepare C-8 alkylated derivatives, provided the chirality at C-14 is not affected during the reaction (Scheme 9). In order to test this possibility, the *trans*-*N*-oxide (−)-**8** was treated, under Polonovski–Potier conditions, to afford (8*S*, 14*S*)-(−)-8-cyanocanadine, (−)-**16**, in a 39% yield. Treatment of (−)-**16** with TFA gave (14*S*)-7,8-dehydrocanadine, which was reduced with $NaBH_4$ to obtain (−)-canadine ($[\alpha]_D^{20}=-323$ (*c* 0.9, $CHCl_3$)), thus showing that the chirality at C-14 is retained in the reaction. Thus, the treatment of (−)-**16** with MeMgI/Et_2O afforded (8*R*, 14*S*)-(−)-8-methylcanadine, (−)-**6**, in a 80% yield and a high purity ($[\alpha]_D^{20}=-236$ (*c* 1.0 $CHCl_3$)).[7]

In summary, *trans*-berbine *N*-oxides undergo anti-periplanar elimination as their major mechanism for the Polonovski–Potier reaction. The easy access to 8-cyanoberbines without affecting the chirality of C-14, together with the preferential nucleophilic attack on the *Re* face, make an effective asymmetric approach to the synthesis of enantiopure C-8 alkylated berbines. *cis*-Berbine *N*-oxides undergo a more complex Polonovski reaction involving a non-stereoselective hydroxylation at C-5, a process that is currently being investigated by our group.

Experimental

General methods

Mps were determined on a Gallenkamp instrument (MFB595010M) and are given uncorrected. UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer and IR spectra on a Perkin–Elmer 883 spectrophotometer. Low resolution mass spectra were recorded on a HP-MS 5988a, and high resolution MS were recorded on a Kratos MS 50 or a VG Autospec M spectrometers, operating at 70 eV. NMR spectra were obtained on Bruker WP-200 SY at 200 MHz for ^1H, and at 50.3 MHz for ^{13}C. ^1H Chemical shifts (δ_H) are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform. *J*=values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography was carried out on silica gel 60 (70–230 mesh).

(±)-Canadine, (±)-7. Was prepared by $NaBH_4$ reduction of a methanolic solution of berberine chloride obtained from roots of *Berberis vulgaris* subsp *australis*.[29] White crystals; mp 167–168°C (MeOH), [lit: 169–170°C].[1]

(−)-Canadine, (−)-7. Was obtained by fractional crystallization of an equimolecular mixture (+)-Di-*O*,*O*′-*p*-toluoyl-D-tartaric acid and (±)-canadine, dissolved in the minimum amount of MeOH. White crystals; mp 131–132°C (MeOH); $[\alpha]_D^{20}=-306$ (*c* 1.0, $CHCl_3$) [lit: 131–132°C (MeOH), $[\alpha]_D^{20}=-298$ (*c* 1.05, $CHCl_3$)].[14]

(±)-Xylopinine, 12. Was synthesized by refluxing (±)-*N*-norlaudanosine hydrochloride and 35% aqueous formaldehyde; mp 146–148°C (MeOH), [lit: 148–149°C].[1]

(±)-Thalictricavine, 13. Partial reduction of vacuum-dried berberine choride ($NaBH_4$/dry pyridine) gave 13,14-dehydrocanadine as a yellow amorphous powder of mp 148–150°C [lit: 152–158°C].[30] Alkylation of the enamine with 40% formaldehyde in AcOH/NaOAc gave 13-methylberberine iodide, yellow crystals mp 201–203°C (MeOH) [lit: 185–195°C (H_2O)dec.],[31] which was reduced ($NaBH_4$/MeOH) to give (±)-thalictricavine, white crystals, mp 203–205°C (MeOH) [lit: 204–206°C].[1]

trans-Berbine *N*-oxides

A $CHCl_3$ solution of the tertiary bases was stirred with *m*CPBA (1:1.1 mmol) at room temperature overnight. The reaction mixture was washed with 10% aqueous Na_2CO_3, dried and the solvent evaporated. The residue was purified by vacuum column chromatography (1:1 MeOH/EtOAc).

(±)-*trans*-Canadine *N*-oxide, (±)-8. Yield 81%, white crystals; mp 217°C (MeOH), [lit: 203–204°C].[12]

(−)-*trans*-Canadine *N*-oxide, (−)-8. White crystals; mp 181°C (acetone); [Found: C, 66.35; H, 6.06; N, 3.86. $C_{20}H_{21}NO_5$ 1/3H_2O requires C, 66.47; H, 6.04; N, 3.88%]; $[\alpha]_D^{20}=-166$ (*c* 1, MeOH); HRMS (EI) M^+, found 355.1431. $C_{20}H_{21}NO_5$ requires 355.1420.

(±)-*trans*-Thalictricavine *N*-oxide, 10. Yield 80%, white crystals; mp 198–200°C (acetone) [lit: 206–208°C ($CHCl_3$–EtOAc)].[13]

(±)-*trans*-Xylopinine *N*-oxide, 11. Yield 55%, white

crystals; mp 158–159°C (acetone) [lit: 167–168°C (MeOH– $CHCl_3$)].[12]

(±)-*cis*-Canadine *N*-oxide, (±)-9. (±)-7 Was dissolved in CH_2Cl_2/MeOH (3:1) and excess aqueous H_2O_2 (30% w/v) was added and allowed to stand at rt for 7 days. Pd/C was added to destroy excess H_2O_2 and the solution was filtered, washed with water, dried and the solvent evaporated. The syrup obtained was separated by vacuum column chromatography (MeOH/EtOAc 1:1). Yield 9%; white crystals; mp 145°C (acetone), [lit: 144°C (acetone)].[13]

Polonovski–Potier reaction of *trans*-(±)-berbine *N*-oxides (±)-8 and 11

A solution of (0.3 mmol) *trans*-(±)-berbine *N*-oxide in dry CH_2Cl_2 (10 mL) was cooled at −30°C under an N_2 atmosphere. TFAA (0.75 mL, 5.4 mmol) was added dropwise and the mixture stirred for 30 min, with the temperature kept at −30°C; then the temperature was allowed to rise to room temperature. KCN (26 mg, 0.4 mmol) in an aqueous saturated solution of NaOAc was added and the mixture stirred at rt for 30 min, and extracted with $CHCl_3$. Extracts were washed with a 10% Na_2CO_3 solution, dried and the solvent evaporated to obtain a residue from which the corresponding (8*S**, 14*S**)-(±)-8-cyanoberbines were separated by preparative TLC ($CHCl_3$/MeOH, 9:1).

(8*S,14*S**)-(±)-8-Cyanocanadine, (±)-16.** Yield 29%; white crystals; mp 153°C (MeOH); [Found: C, 69.06; H, 5.46; N, 7.55. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%]; ν_{max} (KBr) cm^{-1} 2842, 2224 (CN); λ_{max} nm (log ϵ) MeOH: 228 (4.04), 288 (3.81); δ_H ($CDCl_3$) 6.90 (d, 1H, *J*=8.5 Hz, H-12), 6.81 (d, 1H, *J*=8.5 Hz, H-11), 6.67 (s, 1H, H-1), 6.56 (s, 1H, H-4), 5.90 (s, 2H, OCH_2O), 5.15 (s, 1H, H-8), 4.01 (s, 3H, OMe), 3.95 (m, 1H, H-14), 3.82 (s, 3H, OMe), 3.17 (dd, 1H, *J*=16.5, 4.5 Hz, H-13eq), 3.05 (m, 2H, H-6eq, H-13ax), 2.70 (m, 3H, H-5ax, H-5eq, H-6ax); δ_C ($CDCl_3$) 150.2, 146.3, 146.1, 145.2 (C2, C3, C9, C10), 129.6, 127.3, 127.1, 123.6 (C4a, C8a, C12a, C14a), 123.9, 113.3, 108.3, 105.7 (C1, C4, C11, C12), 116.7 (CN), 100.8 (OCH_2O), 60.4 (OMe), 55.9 (OMe), 55.1 (C14), 53.3 (C8), 48.9 (C6), 36.4 (C13), 29.4 (C5); *m/z* (EI) 364 (M^+, 11), 338 (M^+−CN, 33), 337 (100), 322 (50), 307 (42), 278 (30%); *m/z* (FAB): 365 (100%, MH^+); HRMS (EI) M^+, found 364.1432. $C_{21}H_{20}N_2O_4$ requires 364.1423.

(8*S, 14*S**)-(±)-8-Cyanoxylopinine, 17.** Yield 49%; white crystals; mp 150°C (MeOH); [Found: C, 68.52; H, 6.31; N, 7.23. $C_{22}H_{24}N_2O_4$ 1/3 MeOH requires C, 68.58; H, 6.53; N, 7.16%]; ν_{max} (KBr) cm^{-1} 2839, 2224 (CN); λ_{max} nm (log ϵ) MeOH: 216 (4.26), 286 (3.83); δ_H ($CDCl_3$) 6.70 (s, 1H, H-1), 6.69 (s, 1H, H-12), 6.65 (s, 1H, H-4), 6.60 (s, 1H, H-9), 4.89 (s, 1H, H-8), 4.09 (dd, 1H, *J*=10.5, 4.0 Hz, H-14), 3.89, 3.88 (2×s, 12H, 4×OMe), 3.22 (dd, 1H, *J*=15.5, 4.0 Hz, H-13eq), 2.90–3.10 (m, 2H, H-5eq, H-6eq), 2.60-2.90 (m, 3H, H-5ax, H-6ax, H-13ax); δ_C ($CDCl_3$) 149.3, 147.7 (C1, C4, C10, C11), 126.9, 126.0, 121.1, (C4a, C8a, C12a, C14a), 116.9 (CN), 111.5, 111.3, 109.4, 108.7 (C1, C4, C9, C12), 57.5 (C8), 56.1 (2×OMe), 55.9 (2×OMe), 55.0 (C14), 49.2 (C6), 36.6 (C13), 29.0 (C5); *m/z* (EI) 380 (M^+, 8), 354 (M^+−CN, 18), 352 (50), 190 (35), 164 (100%); HRMS (EI) M^+, found 380.1738. $C_{22}H_{24}N_2O_4$ requires 380.1736.

Modified Polonovski reaction of 10

To a solution of *trans*-(±)-thalictricavine *N*-oxide (**10**, 70 mg, 0.2 mmol) in dry CH_2Cl_2 (10 mL), MsCl (0.3 mL, 3.6 mmol) was added dropwise, the solution being warmed at 60°C and stirred for 2 h. KCN (10 mg, 0.2 mmol) in a aqueous saturated solution of NaOAc was added and the mixture stirred for 30 min, followed by extraction with $CHCl_3$, washing with 10% Na_2CO_3, drying and solvent evaporation to obtain a syrup. Preparative TLC ($CHCl_3$/MeOH 25:1) of the residue afforded **(8*S**, 13*R**, 14*S**)-(±)-8-cyanothalictricavine, 18:** yield 21%; white crystals; mp 167°C (MeOH); ν_{max} (KBr) cm^{-1} 2937, 2228 (CN), λ_{max} nm (log ϵ) $CHCl_3$: 242 (3.80), 288 (3.88); δ_H ($CDCl_3$) 6.92 (d, 1H, *J*=8.5 Hz, H-12), 6.86 (d, 1H, *J*=8.5 Hz, H-11), 6.63 (s, 1H, H-1), 6.57 (s, 1H, H-4), 5.92 (m, 2H, OCH_2O), 5.13 (s, 1H, H-8), 4.09 (brd, 1H, *J*=3.2 Hz, H-14), 4.01 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.09 (dq, 1H, *J*=6.8, 3.2 Hz, H-13), 3.03 (m, 3H, H-5ax, H-6ax, H-6eq), 2.64 (m, 1H, H-5eq), 0.85 (d, 3H, *J*=6.8 Hz, C13-Me); δ_C ($CDCl_3$) 150.0, 146.5, 145.9, 145.1 (C2, C3, C9, C10), 134.5, 128.7, 128.5, 123.2 (C4a, C8a, C12a, C14a), 117.1 (CN), 124.2, 113.4, 108.2, 105.8 (C1, C4, C11, C12), 100.8 (OCH_2O), 60.4 (OMe), 58.8 (C14), 56.0 (OMe), 53.8 (C8), 48.5 (C6), 38.4 (C13), 29.6 (C5), 17.9 (C13-Me); *m/z* (EI) 378 (M^+, 54), 358 (43), 203 (100), 176 (87%); HRMS (EI): M^+ found 378.1563. $C_{22}H_{22}N_2O_4$ requires 378.1579.

Polonovski–Potier reaction of *cis*-(±)-canadine *N*-oxide, (±)-9

A solution of (±)-**9** (200 mg, 0.6 mmol) in dry CH_2Cl_2 (10 mL) under an N_2 atmosphere was cooled to −30°C. TFAA (0.5 mL, 3.6 mmol) was added dropwise and the temperature was kept at −30°C for half an hour, after which the reaction mixture was allowed to reach rt. The mixture was then washed with 10% Na_2CO_3 and dried. Solvent evaporation afforded a syrup consisting of a mixture of two 5-hydroxycanadines which were separated by preparative TLC ($CHCl_3$/MeOH 9:1).

(±)-5α-Hydroxycanadine, 19. Yield 9%; yellowish crystals; mp 170°C (MeOH); [Found: C, 66.49; H, 5.72; N, 3.92. $C_{20}H_{21}NO_5$ 1/4 H_2O requires C, 66.75; H, 6.02; N, 3.89%]; ν_{max} (KBr) cm^{-1} 3455 (OH); λ_{max} nm (log ϵ) MeOH: 212 (4.24), 228 (3.98), 286 (3.57), 336 (2.96); δ_H ($CDCl_3$) 6.88 (d, 1H, *J*=9.5 Hz, H-12), 6.82 (s, 1H, H-4), 6.79 (d, 1H, *J*=9.5 Hz, H-11), 6.73 (s, 1H, H-1), 5.94 (s, 2H, OCH_2O), 4.48 (brs, 1H, H-5), 4.19 (d, 1H, *J*=15.5 Hz, H-8eq), 3.84 (s, 6H, 2×OMe), 3.59 (d, 1H, *J*=15.5 Hz, H-8ax), 3.52 (m, 1H, H-14), 3.24 (m, 2H, H-6eq, H-13eq), 2.83 (m, 2H, H-6ax, H-13ax); δ_C ($CDCl_3$) 150.4, 147.8, 146.4, 145.0 (C2, C3, C9, C10), 131.3, 130.1, 128.3, 127.2 (C4a, C8a, C12a, C14a), 123.8, 111.2, 109.2, 105.3 (C1, C4, C11, C12), 101.1 (OCH_2O), 66.8 (C5), 60.2 (OMe), 59.5 (C14), 58.5 (C6), 55.9 (OMe), 53.4 (C8), 36.4 (C13); *m/z* (EI) 355 (M^+, 18), 338 (M^+−17, 19), 164 (100), 149 (97%); HRMS (EI) M^+, found 355.1410. $C_{20}H_{21}NO_5$ requires 355.1419.

(±)-5β-Hydroxycanadine, 20. Yield 10%; yellowish

crystals; mp 181°C (MeOH); [Found: C, 66.84; H, 5.90; N, 3.89. $C_{20}H_{21}NO_5$ 1/5 H_2O requires C, 66.91; H, 6.01; N, 3.90%]; ν_{max} (KBr) cm^{-1}: 3453 (OH); λ_{max} nm (log ϵ) MeOH: 212 (4.23), 228 (3.97), 286 (3.53), 322 (2.74); δ_H ($CDCl_3$) 7.05 (s, 1H, H-4), 6.81 (d, 1H, *J*=9.5 Hz, H-12), 6.78 (d, 1H, *J*=9.5 Hz, H-11), 6.65 (s, 1H, H-1), 5.92 (s, 2H, OCH_2O), 4.81 (dd, 1H, *J*=7.5, 4.0 Hz, H-5), 4.15 (d, 1H, *J*=16.6 Hz, H-8eq), 3.87 (s, 6H, 2×OMe), 3.75 (d, 1H, *J*=16.6 Hz, H-8ax), 3.68 (dd, 1H, *J*=12.5, 4.5 Hz, H-14), 3.35 (dd, 1H, *J*=11.5, 4.0 Hz, H-6eq), 3.07 (dd, 1H, *J*=16.0, 12.5 Hz, H-13eq), 2.71 (dd, 1H, *J*=16.0, 12.5 Hz, H-13ax), 2.52 (dd, 1H, *J*=11.5, 7.5 Hz, H-6ax); δ_C ($CDCl_3$) 150.4, 147.2, 146.6, 145.2 (C2, C3, C9, C10), 131.6, 131.2, 127.8, 127.0 (C4a, C8a, C12a, C14a), 123.8, 111.1, 106.8, 105.2 (C1, C4, C11, C12), 101.0 (OCH_2O), 66.8 (C5), 60.2 (OMe), 58.6 (C14), 57.7 (C6), 55.9 (OMe), 52.8 (C8), 34.4 (C13); *m/z* (EI) 355 (M^+, 18), 338 (M^+-17, 20), 164 (100), 149 (94%); HRMS (EI): M^+ found 355.1413. $C_{20}H_{21}NO_5$ requires 355.1419.

(±)-6-Cyanoxylopinine, 26

To a solution of 5,6-dehydroxylopinine (**24**)[24] (200 mg) in dry CH_2Cl_2 (10 mL), a mixture of TFA and TFAA was added, followed by standing at rt for 1 h. Excess KCN in an aqueous saturated solution of NaOAc was then added, the mixture being stirred at rt for 30 min, extracted with $CHCl_3$, washed with 10% Na_2CO_3 and dried, the solvent being evaporated to obtain **26**: yield 89%; white crystals; mp 156°C (MeOH); [Found: C, 68.52; H, 6.31; N, 7.23. $C_{22}H_{24}N_2O_4$ 1/4 H_2O requires C, 68.64; H, 6.42; N, 7.28%]; ν_{max} (KBr) cm^{-1} 2840, 2224 (CN); δ_H ($CDCl_3$) 6.52 (s, 1H, H-1), 6.40 (s, 1H, H-9), 6.33 (s, 1H, H-12), 6.30 (s, 1H, H-4), 3.87 (d, 1H, *J*=14.7 Hz, H-8eq), 3.78 (dd, 1H, *J*=11.2, 3.6 Hz, H-14), 3.56 (brd, 1H, *J*=5.4 Hz, H-6), 3.53, 3.52, 3.50, 3.46 (4×s, 3H, OMe), 3.42 (d, 1H, *J*=14.7 Hz, H-8ax), 3.05 (dd, 1H, *J*=15.6, 5.4 Hz, H-5), 3.00 (dd, 1H, *J*=15.5, 3.6 Hz, H-13ax), 2.77 (dd, 1H, *J*=15.5, 11.2 Hz, H-13eq), 2.50 (brd, 1H, *J*=15.6 Hz, H-5); δ_C ($CDCl_3$) 148.3, 147.9, 147.8, 147.6 (C2, C3, C10, C11), 128.1, 125.6, 125.0, 121.8 (C4a, C8a, C12a, C14a), 116.6 (CN), 111.3, 111.2, 108.8, 108.4 (C1, C4, C9, C12), 55.9, 55.8, 55.7 (4×OMe, C6, C14), 51.5 (C8), 36.9 (C13), 32.3 (C5); *m/z* (EI) 380 (M^+, 5), 353 (M^+-CN, 12), 164 (100%); HRMS (EI) M^+, found 380.1728. $C_{22}H_{24}N_2O_4$ requires 380.1736.

Synthesis of (8*S**, 14*S**)-(±)-8-hydroxymethylberbines, 29a,b

The (8*S**, 14*S**)-(±)-8-cyanoberbines (±)-**16** and **18** were dissolved in the minimum amount of concentrated HCl at 0°C and kept at 5°C for 48 h. Then, they were made alkaline with concentrated aqueous NH_3 extracted with $CHCl_3$ and dried, the solvent being finally evaporated. Preparative TLC ($CHCl_3$/MeOH 9:1) of the syrups thus obtained afforded the corresponding (±)-8-carbamoylberbines, **27a** and **27b**.

(8*S, 14*S**)-(±)-8-Carbamoylcanadine, 27a.** Yield 50%; white crystals mp 190°C (acetone); [Found: C, 66.00; H, 5.82; N, 7.49. $C_{21}H_{22}N_2O_5$ requires C, 65.96; H, 5.80; N, 7.33%] ν_{max} (KBr) cm^{-1} 3400 (NH), 3220 (NH), 1665 (CO); δ_H ($CDCl_3$+CD_3OD) 6.81 (d, 1H, *J*=8.6 Hz, H-12), 6.76 (d, 1H, *J*=8.6 Hz, H-11), 6.55 (s, 1H, H-1), 6.53 (s, 1H, H-4), 5.85 (s, 2H, OCH_2O), 4.69 (s, 1H, H-8), 4.33 (dd, 1H, *J*=11.0, 5.2 Hz, H-14), 3.85 (s, 3H, OMe), 3.79 (s, 3H, OMe), 2.93 (dd, 1H, *J*=16.7, 5.2 Hz, H-13eq), 2.98-2.69 (m, 5H, H-5ax, H-5eq, H-6ax, H-6eq, H-13ax); *m/z* (EI) 382 (M^+, 2), 338 (M^+-44, 100), 322 (15%).

(8*S, 14*S**)-(±)-8-Carbamoylxylopinine, 27b.** Yield 75%; white crystals; mp 197°C (acetone); [Found: C, 64.80; H, 6.44; N, 6.88. $C_{22}H_{26}N_2O_5$ 1/2 H_2O requires C, 64.85; H, 6.68; N, 6.88%]; ν_{max} (KBr) cm^{-1} 3409 (NH), 3216 (NH), 2841, 1663 (CO), 1515, 1256; λ_{max} nm (log ϵ) MeOH: 214 (4.28), 286 (3.83); δ_H ($CDCl_3$) 7.41 (brd, 1H, *J*=4.6 Hz, $CONH_2$), 6.99 (s, 1H, H-9), 6.63 (s, 1H, H-4), 6.57 (s, 1H, H-1), 6.52 (s, 1H, H-12), 5.50 (brd, 1H, *J*=4.6 Hz, $CONH_2$), 4.24 (s, 1H, H-8), 4.16 (dd, 1H, *J*=11.2, 5.8 Hz, H-14), 3.88 (s, 3H, OMe), 3.85 (s, 6H, 2×OMe), 3.82 (s, 3H, OMe), 3.12 (m, 4H, H-5ax, H-5eq, H-6ax, H-6eq), 3.04 (dd, 1H, *J*=16.6, 5.8 Hz, H-13eq), 2.81 (dd, 1H, *J*=16.6, 11.2 Hz, H-13ax); δ_C ($CDCl_3$) 174.2 ($CONH_2$), 148.3, 147.8, 147.2, 147.1 (C2, C3, C10, C11), 130.5, 125.3, 125.1, 122.1 (C4a, C8a, C12a, C14a), 112.8, 111.6, 110.6, 109.3 (C1, C4, C9, C12), 66.9 (C8), 56.0 (OMe), 55.9 (2×OMe), 55.8 (OMe), 52.6 (C14), 45.3 (C6), 31.1 (C13), 29.2 (C5); *m/z* (EI) 398 (M^+, 2), 354 (M^+-44, 100), 338 (14), 355 (23%); *m/z* (CI, CH_4) 399 (100%, MH^+); HRMS (EI) M^+, found 398.1838. $C_{22}H_{26}N_2O_5$ requires 398.1842.

A methanolic solution of **27a** and **27b** (0.1 mmol in 10 mL) was stirred with 0.2 g of Amberlite® IR-120 at 60°C for 12 h. The resin was washed with MeOH and suspended in 5 mL of MeOH/Et_3N (3:1) for 48 h, followed by filtering and solvent evaporation to quantitatively obtain the corresponding (8*S**, 14*S**)-(±)-8-methoxycarbonylberbines (**28a** and **28b**). Without further purification, a THF solution (5 mL) of the esters **28a** and **28b** was dropped at room temperature over a solution of $LiAlH_4$ in dry THF (0.3 mmol in 5 mL) and stirred for 2 h. The reaction was quenched by addition of a water-saturated Et_2O solution (5 mL) and stirred for 1 h before Celite® was added and the reaction mixture was filtered. Removal of the organic solvent and preparative TLC ($CHCl_3$/MeOH 25:1) of the residue afforded the corresponding (8*S**, 14*S**)-(±)-8-hydroxymethylberbines, **29a** and **29b**.

(8*S, 14*S**)-(±)-8-Methoxycarbonylcanadine, 28a.** Colorless syrup, ν_{max} (film) cm^{-1} 2854, 1734 (CO); λ_{max} nm (log ϵ) MeOH: 210 (4.27), 226h (4.01), 288 (3.64); δ_H ($CDCl_3$) 6.87 (d, 1H, *J*=8.8 Hz, H-12), 6.82 (d, 1H, *J*=8.8 Hz, H-11), 6.65 (s, 1H, H-1), 6.55 (s, 1H, H-4), 5.89 (s, 2H, OCH_2O), 4.83 (s, 1H, H-8), 4.33 (dd, 1H, *J*=11.0, 3.92 Hz, H-14), 3.82 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.70 (s, 3H, COOMe), 3.10 (dd, 1H, *J*=16.0, 3.9 Hz, H-13eq), 2.73 (dd, 1H, *J*=16.0, 11.0 Hz, H-13ax), 3.26–2.62 (m, 4H, H-5ax, H-5eq, H-6ax, H-6eq); δ_C ($CDCl_3$) 171.5 (CO), 150.0, 146.0, 145.8, 145.5 (C2, C3, C9, C10), 131.2, 128.0, 127.3, 126.5 (C4a, C8a, C12a, C14a), 124.0, 112.3, 108.4, 106.1 (C1, C4, C11, C12), 100.7 (OCH_2O), 63.2 (C8), 59.9 (OMe), 55.9 (C14), 52.5 (OMe), 51.6 (COOMe), 47.8 (C6), 36.2 (C13), 30.1 (C5); *m/z* (EI) 338 (M^+-59, 100), 322 (9%); HRMS (EI) M^+, found 397.1510. $C_{22}H_{23}NO_6$ requires 397.1525.

(8*S, 14*S**)-(±)-8-Hydroxymethylcanadine, 29a.** Yield 70%; yellowish crystals; mp 157°C (MeOH); [Found: C, 68.02; H, 6.34; N, 4.02. $C_{21}H_{23}NO_5$ requires C, 68.28; H, 6.28; N, 3.79%]; ν_{max} (film) cm^{-1} 3455 (OH); λ_{max} nm (log ϵ) MeOH: 226 (4.00), 288 (3.55); δ_H ($CDCl_3$) 6.78 (s, 2H, H-11, H-12), 6.58 (s, 1H, H-1), 6.55 (s, 1H, H-4), 5.90 (s, 2H, OCH_2O), 4.14 (m, 2H, H-8, H-14), 3.87 (dd, 1H, *J*=10.4, 5.2 Hz, CH_2OH), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.47 (t, 1H, *J*=10.4 Hz, CH_2OH), 2.91 (dd, 1H, *J*=17.1, 11.1 Hz, H-13ax), 2.75 (brd, 1H, *J*=17.1 Hz, H-13eq), 3.26-2.65 (m, 4H, H-5ax, H-5eq, H-6ax, H-6eq); δ_C ($CDCl_3$) 150.5, 146.4, 146.2, 145.8 (C2, C3, C9, C10), 126.6, 126.5 (C4a, C8a, C12a, C14a), 123.9, 111.7, 108.8, 106.6 (C1, C4, C11, C12), 100.8 (OCH_2O), 62.3 (C8), 61.4 (CH_2OH), 60.7 (OMe), 55.8 (OMe), 50.0 (C14), 45.7 (C6), 30.3 (C13), 29.7 (C5); *m/z* (EI) 338 (M^+-31, 100), 322 (10%).

(8*S, 14*S**)-(±)-8-Methoxycarbonylxylopinine, 28b.** IR, UV, ^1H NMR, ^{13}C NMR and EI-MS identical with those for an authentic sample obtained by condensation of *N*-norlaudanosine with glyoxylic acid.[4]

(8*S, 14*S**)-(±)-8-Hydroxymethylxylopinine, 29b.** IR, UV, ^1H NMR, ^{13}C NMR and EI-MS identical with those for an authentic sample.[4]

Synthesis of (8*R**, 14*S**)-(±)-8-hydroxymethylcanadine, 34

To a suspension of berberine chloride (**5**, 1 g, 2.7 mmol) in MeOH (50 mL) was added KCN (175 mg dissolved in the minimum amount of water). The yellow precipitate that immediately appeared was filtered and identified as (±)-8-cyano-13,14-dehydrocanadine (**30**). Hydrolysis of **30** with conc. HCl (5 mL) at 0°C was carried out as above to obtain (±)-8-carbamoyl-13,14-dehydrocanadine (**31**), that proved to be rather unstable and was immediately dissolved in methanol (25 mL) and reduced with excess $NaBH_4$. The reaction was followed by TLC and worked up in the usual way to afford (8*R**, 14*S**)-(±)-8-carbamoylcanadine (**32**). The reaction sequence which includes methanolysis of the amide **32** to the methyl ester **33** and reduction to the target (8*R**, 14*S**)-(±)-8-hydroxymethylcanadine (**34**), was carried out as above.

(±)-8-Cyano-13,14-dehydrocanadine, 30. Yield 95%; yellowish crystals; mp 174°C (MeOH); [Found: C,68.88; H, 4.89; N, 7.61. $C_{21}H_{18}N_2O_4$ 1/4 H_2O requires C, 68.75; H, 5.08; N, 7.64%]; ν_{max} (KBr) cm^{-1} 2837, 2224 (CN); λ_{max} nm (log ϵ) $CHCl_3$: 276 (4.07), 368 (4.29); δ_H ($CDCl_3$) 7.15 (s, 1H, H-1), 6.88 (d, 1H, *J*=8.4 Hz, H-12), 6.82 (d, 1H, *J*=8.4 Hz, H-11), 6.58 (s, 1H, H-4), 6.13 (s, 1H, H-13), 5.95 (d, 2H, *J*=2.1 Hz, OCH_2O), 5.73 (s, 1H, H-8), 3.96 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.41 (ddd, 1H, *J*=15.2, 11.9, 4.0 Hz, H-6eq), 3.25 (ddd, 1H, *J*=15.2, 4.0, 3.0 Hz, H-5ax), 2.98 (ddd, 1H, *J*=15.2, 11.9, 4.0 Hz, H-6ax), 2.81 (ddd, 1H, *J*=15.2, 3.0, 3.0 Hz, H-5eq); δ_C ($CDCl_3$) 150.6, 147.7, 146.9, 144.4 (C2, C3, C9, C10), 138.4, 128.4, 126.9, 124.1 (C4a, C8a, C12a, C14a), 119.8 (C1), 117.0 (C14), 116.5 (CN), 113.8 (C4), 107.8 (C11), 104.1 (C12), 101.2 (OCH_2O), 98.1 (C13), 60.9 (OMe), 56.1 (OMe), 49.9 (C8), 47.9 (C6), 29.6 (C5); *m/z* (EI) 362 (M^+, 68), 347 (M^+-15, 20), 336 (M^+-26, 100), 320 (41%); HRMS (EI) M^+, found 362.1256. $C_{21}H_{18}N_2O_4$ requires 362.1266.

(±)-8-Carbamoyl-13,14-dehydrocanadine, 31. Yield 67%; δ_H ($CDCl_3$) 7.09 (s, 1H, H-1), 6.75 (d, 1H, *J*=8.4 Hz, H-12), 6.69 (d, 1H, *J*=8.4 Hz, H-11), 6.55 (s, 1H, H-4), 6.25 (brs, 1H, $CONH_2$), 5.89 (s, 2H, OCH_2O), 5.76 (s, 1H, H-13), 5.58 (brs, 1H, $CONH_2$), 5.19 (s, 1H, H-8), 3.94 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.55 (ddd, 1H, *J*=10.6, 5.4 Hz, H-6eq), 3.19 (ddd, 1H, *J*=11.1, 4.3 Hz, H-5ax), 2.84 (m, 2H, H-5eq, H-6ax); δ_C ($CDCl_3$) 172.1 (CO), 149.8, 147.3, 146.5, 143.9 (C2, C3, C9, C10), 140.3, 128.9, 127.7, 125.0 (C4a, C8a, C12a, C14a), 119.5 (C14), 119.1, 112.6, 107.7, 104.3 (C1, C4, C11, C12), 100.9 (OCH_2O), 93.7 (C13), 61.4 (C8), 60.8 (OMe), 55.8 (OMe), 47.5 (C6), 30.0 (C5); *m/z* (EI) 380 (M^+, 3), 336 (M^+-44, 100), 320 (20%).

(8*R, 14*S**)-(±)-8-Carbamoylcanadine, 32.** Yield 95%; white crystals; mp 207°C (MeOH); [Found: C, 65.70; H, 5.64; N, 7.07. $C_{21}H_{22}N_2O_5$ requires C, 65.96; H, 5.80; N, 7.33%]; ν_{max} (KBr) cm^{-1} 3400 (NH), 3220 (NH), 1665 (CO); λ_{max} nm (log ϵ) MeOH: 212 (4.26), 226h (4.05), 288 (3.67); δ_H ($CDCl_3$+CD_3OD) 6.87 (d, 1H, *J*=9.2 Hz, H-12), 6.82 (d, 1H, *J*=9.2 Hz, H-11), 6.68 (s, 1H, H-1), 6.54 (s, 1H, H-4), 5.87 (s, 2H, OCH_2O), 4.26 (s, 1H, H-8), 3.83 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.56 (brd, 1H, *J*=11.0, 2.8 Hz, H-14), 3.43 (dd, 1H, *J*=11.0, 4.4 Hz, H-6eq), 3.13 (dd, 1H, *J*=15.5, 2.8 Hz, H-13eq), 2.93 (m, 1H, H-5ax), 2.81 (dd, 1H, *J*=15.5, 11.0 Hz, H-13ax), 2.60 (m, 2H, H-5eq, H-6ax); δ_C ($CDCl_3$+CD_3OD) 176.7 (CO), 150.3, 145.9, 145.8 (C2, C3, C9, C10), 129.9, 128.3, 127.5, 126.5 (C4a, C8a, C12a, C14a), 123.5, 112.2, 107.8, 105.2 (C1, C4, C11, C12), 100.5 (OCH_2O), 68.3 (C8), 59.2 (C14), 58.2 (OMe), 55.5 (OMe), 48.5 (C6), 36.6 (C13), 29.4 (C5); *m/z* (EI) 338 (M^+-44, 100), 336 (17), 322 (14%); *m/z* (CI, CH_4) 383 (100%, MH^+).

(8*R, 14*S**)-(±)-8-Methoxycarbonylcanadine, 33.** Yield 80%; white crystals; mp 206–208°C (MeOH); ν_{max} (KBr) cm^{-1} 2854, 1732 (CO), 1439, 1280; λ_{max} nm (log ϵ) MeOH: 210 (4.27), 228h (4.01), 288 (3.64); δ_H ($CDCl_3$) 6.89 (d, 1H, *J*=8.5 Hz, H-12), 6.83 (d, 1H, *J*=8.5 Hz, H-11), 6.71 (s, 1H, H-1), 6.55 (s, 1H, H-4), 5.89 (s, 2H, OCH_2O), 4.32 (s, 1H, H-8), 3.83 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.74 (s, 3H, COOMe), 3.60 (brd, 1H, *J*=11.3 Hz, H-14), 3.31 (dd, 1H, *J*=11.1, 3.8 Hz, H-6eq), 3.14 (dd, 1H, *J*=15.3, 3.6 Hz, H-13eq), 3.08 (m, 1H, H-5ax), 2.90 (dd, 1H, *J*=15.3, 11.3 Hz, H-13ax), 2.57 (m, 2H, H-5eq, H-6ax); δ_C ($CDCl_3$) 172.8 (CO), 150.4, 146.1, 146.0, 145.5 (C2, C3, C9, C10), 130.3, 128.3, 128.1, 127.1 (C4a, C8a, C12a, C14a), 123.8, 112.1, 108.2, 105.5 (C1, C4, C11, C12), 100.8 (OCH_2O), 67.3 (C8), 59.8 (OMe), 59.1 (C14), 55.9 (OMe), 52.4 (Me), 49.1 (C6), 36.6 (C13), 29.7 (C5); *m/z* (EI) 397 (M^+, 3), 338 (M^+-59, 100), 322 (9%); HRMS (EI) M^+, found 397.1518. $C_{22}H_{23}NO_6$ requires 397.1525.

(8*R, 14*S**)-(±)-8-Hydroxymethylcanadine, 34.** Yield 81%; yellowish crystals; mp 157–158°C (MeOH); [Found: C, 67.99; H, 6.28; N, 3.80. $C_{21}H_{23}NO_5$ requires C, 68.28; H, 6.28; N, 3.79%]; ν_{max} (KBr) cm^{-1} 3455 (OH), 1485, 1277, 1230, 1033; λ_{max} nm (log ϵ) MeOH: 226 (4.07), 288 (3.75); δ_H (C_6D_6) 6.70 (d, 1H, *J*=8.3 Hz, H-12), 6.64 (s, 1H, H-1),

6.53 (d, 1H, J=8.3 Hz, H-11), 6.42 (s, 1H, H-4), 5.38 (s, 2H, OCH_2O), 4.03 (s, 3H, H-8, H-16, H-16′), 3.73 (s, 3H, OMe), 3.49 (brd, 1H, J=10.9 Hz, H-14), 3.34 (s, 3H, OMe), 3.10–2.60 (m, 5H, H-5ax, H-6eq, H-13ax, H-13eq, OH), 2.40–2.10 (m, 2H, H-5eq, H-6ax); δ_C ($CDCl_3$) 150.8, 146.1, 146.0, 145.6 (C2, C3, C9, C10), 130.9, 129.9, 129.6, 128.0 (C4a, C8a, C12a, C14a), 123.2, 111.3, 108.4, 105.6 (C1, C4, C11, C12), 100.8 (OCH_2O), 63.8 (C16), 61.9 (C8), 60.3 (OMe), 58.3 (C14), 55.9 (OMe), 49.0 (C6), 37.2 (C13), 30.6 (C5); m/z (EI) 369 (M^+, 2), 368 (M^+-1, 7), 338 (M^+-31, 100), 322 (14%); m/z (FAB) 370 (100%, MH^+). HRMS (EI) M^+, found 369.1567. $C_{21}H_{23}NO_5$ requires 369.1576.

(±)-*O*-Methylcorytenchirine (1, R=Me)

A solution of (8*S**, 14*S**)-(±)-8-cyanoxylopinine (50 mg) in Et_2O (5 mL) was added over freshly prepared MeMgI in Et_2O (5:1 excess) and the mixture refluxed for 2 h. The reaction mixture was extracted with 6 M HCl, the aqueous layer being neutralized (aqueous NH_3) and extracted with $CHCl_3$. A syrup was obtained after evaporation of the solvent that was chromatographed over silica gel (2:1 hexane/Et_2O) to obtain (±)-*O*-methylcorytenchirine (**1**, R=Me).[32] Yield: 80% (yellowish syrup); ν_{max} (film) cm^{-1} 1509, 1275, 1145; δ_H ($CDCl_3$) 6.67 (s, 1H, H-12), 6.60 (s, 1H, H-1), 6.56 (s, 2H, H-4, H-9), 4.26 (dd, 1H, J=11.1, 4.8 Hz, H-14), 4.11 (q, 1H, J=6.7 Hz, H-8), 3.86 (s, 3H, OMe), 3.84 (s, 6H, 2×OMe), 3.82 (s, 3H, OMe), 3.06 (dd, 1H, J=16.4, 4.8 Hz, H-13eq), 3.07-2.85 (m, 4H, H-5ax, H-5eq, H-6ax, H-6eq), 2.79 (dd, 1H, J=16.4, 11.1 Hz, H-13ax), 1.41 (d, 3H, J=6.7 Hz, C8-Me); δ_C ($CDCl_3$) 147.6, 147.5, 147.4 (C2, C3, C10, C11), 131.3, 130.2, 126.2, 125.0 (C4a, C8a, C12a, C14a), 111.4, 111.1, 109.7, 109.0 (C1, C4, C9, C12), 59.3 (C8), 56.0, 58.8, 50.4 (4×OMe), 47.2 (C14), 35.5 (C13), 29.2 (C5), 18.2 (C8-Me); m/z (EI) 369 (M^+, 5), 354 (M^+-15, 34), 178 (100), 163 (16%); HRMS (EI) M^+, found 369.1926. $C_{22}H_{27}NO_4$ requires 369.1940.

(8*S*, 14*S*)-(−)-8-Cyanocanadine, (−)-16. Was prepared as previously described for the racemate. Yield: 39%; white crystals; mp 150°C (MeOH); [Found: C, 69.27; H, 5.78; N, 7.42. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%]; $[\alpha]_D^{20}=-238$ (c 1.00, $CHCl_3$).

(8*R*, 14*S*)-(−)-8-Methylcanadine, (−)-6. From the reaction of (−)-**16** with MeMgI as above. Yield 80%; white crystals mp 116°C (MeOH); $[\alpha]_D^{20}=-236$ (c 1.0, $CHCl_3$) [lit: foam, $[\alpha]_D^{20}=-170$ (c 1.1, $CHCl_3$)].[7]; [Found: C, 71.36; H, 6.42; N, 3.96. $C_{21}H_{23}NO_4$ requires C, 71.37; H, 6.56; N, 3.96%]; ν_{max} (KBr) cm^{-1} 1486, 1277, 1226, 1037; λ_{max} nm (log ϵ) MeOH: 222 (4.05), 288 (3.69); δ_H ($CDCl_3$) 6.81 (d, 1H, J=8.5 Hz, H-12), 6.75 (d, 1H, J=8.5 Hz, H-11), 6.66 (s, 1H, H-1), 6.56 (s, 1H, H-4), 5.89 (s, 2H, OCH_2O); 4.32 (q, 1H, J=6.6 Hz, H-8), 4.19 (dd, 1H, J=11.2, 4.9 Hz, H-14), 3.87 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.05 (dd, 1H, J=16.4, 4.9 Hz, H-13eq), 2.99–2.81 (m, 4H, H-5ax, H-5eq, H-6ax, H-6eq), 2.72 (dd, 1H, J=16.4, 11.2 Hz, H-13ax), 1.73 (d, 3H, J=6.6 Hz, C8-Me); δ_C ($CDCl_3$) 150.4, 146.0, 145.3 (C2, C3, C9, C10), 132.9, 131.4, 127.1, 125.9 (C4a, C8a, C12a, C14a), 123.9, 111.3, 108.6, 106.1 (C1, C4, C11, C12), 100.8 (OCH_2O), 60.5 (OMe), 55.8 (OMe), 50.6 (C8), 47.0 (C6), 34.9 (C13), 29.4 (C5), 16.0 (C8-Me); m/z (EI) 353 (M^+, 7), 338 (M^+-15, 100), 178 (62), 163 (53%).

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