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First total synthesis, stereochemical revision and biological evaluation of transalpinecine and analogues thereof

Cécile DEHOUX,*[a] Tessa CASTELLAN, [a] Morgane ENEL,[a] Christiane ANDRÉ-BARRÈS,[a] Sandra MIRVAL,[b] Frédéric BECQ,[b] Stéphanie BALLEREAU*[a] and Yves GÉNISSON*[a]

Abstract: The first total synthesis of transalpinecine, a pyrrolizidine alkaloid extracted from *Heliotropium transalpinum* is reported. The concise synthetic route developed towards these unusual iminosugar-like natural compounds relies on an intramolecular Morita-Baylis-Hillman reaction. The four diastereoisomers of transalpinecine as well as the two diastereoisomers of the parent epoxide subulacine were prepared. ^{1}H NMR-based stereochemical assignment of these different diastereoisomers was substantiated by quantum calculations of NMR shifts and coupling constants, allowing revision of the initially reported transalpinecine structure. One of these synthetic compounds significantly potentiates the activity of the F508del-CFTR corrector VX-809.

Introduction

Pyrrolizidine alkaloids (PAs) are of particular interest for synthetic chemists because of the panel of biological activities associated to their relatively simple structure.[1] In 2009, Vidotti's group[2] reported the isolation and characterization of transalpinecine (1β,2β-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine), a new saturated PA extracted from *Heliotropium transalpinum* var. *transalpinum Vell.* (Boraginaceae), in addition to the parent epoxide subulacine (1β,2β-epoxy-1α-hydroxymethyl-8α-pyrrolizidine)[3] and its α-diastereoisomer **1** (Figure 1). Whereas subulacine is a common alkaloid extracted from several plants,[3a, 4] isolation of its α-isomer hadn't been reported earlier. The relative configuration of the transalpinecine stereochemical triad was established on the basis of NOE 1D experiments. Theoretical calculations were included to support the NMR shift values assigned for subulacine and its α-isomer.

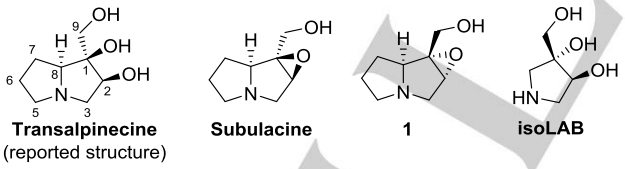
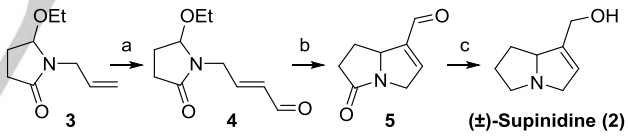


Figure 1. Transalpinecine proposed structure, subulacine, its α-isomer **1** and isoLAB.

While antineoplastic and antiviral activities of subulacine were evaluated,[4a] the other compounds described by Vidotti[2] were never submitted to any biological evaluation.[5] However, these pyrrolizidines alkaloids can be seen as analogs of carbon-branched pyrrolidine iminosugars described by Best *et al.*,[6] especially isoLAB (Figure 1) which proved to partially rescues the defective function of F508del-cystic fibrosis transmembrane conductance regulator (F508delCFTR) responsible for cystic fibrosis.[7] In order to assess the biological potential of these iminosugars-like natural compounds embedding an uncommon stereogenic quaternary center, we developed a concise stereodivergent synthetic route.

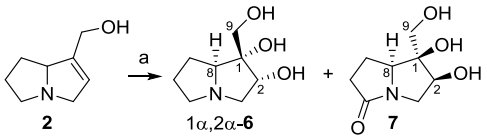
Results and Discussion

We envisioned that transalpinecine could be readily obtained by the dihydroxylation of supinidine (**2**). Since its first preparation in 1971,[8] supinidine has prompted many syntheses, either formal,[9] in racemic[10] or optically active series.[11]. Inspired by the Aggarwal's synthesis of heliotridine,[12] we implemented a rapid, atom economic and efficient access to (±)-supinidine (Scheme 1). Olefin cross-metathesis of the *N*-allyl pyrrolidine **3**[13] with acrolein delivered the enal intermediate **4**. The key intramolecular Morita-Baylis-Hillman reaction of **4** was mediated by a Brønsted acid.[14] It furnished the bicyclic aldehyde **5** that was reduced by LAH to give (±)-supinidine (**2**).



Scheme 1. Synthesis of (±)-supinidine. *Reagents and conditions:* a) Hoveyda-Grubbs II (5% mol), acrolein, CH_2Cl_2, rt, 72%; b) TfOH, Me_2S, CH_3CN, -15 °C to rt; c) LAH, THF, 70°C, 94% over two steps.

En route to transalpinecine, we then studied the dihydroxylation of (±)-supinidine (**2**). The OsO_4-catalysed dihydroxylation with *N*-methylmorpholine-*N*-oxide as co-oxidant gave a mixture of *cis* -diols with low yield. Careful purification afforded the α,α-diol 1α,2α-**6**, diastereoisomeric to the reported transalpinecine (isolated as an inseparable 90:10 mixture with its β,β-diastereoisomer), and the diastereoisomerically pure β,β-diol as the over-oxidized lactam **7** (Scheme 2).



Scheme 2. Dihydroxylation of (±)-supinidine. *Reagents and conditions:* a) OsO_4 (cat.), NMO, Acetone/H_2O, rt, 25% for 1α,2α-**6** (de=80%), 10% for **7**.

[a] SPCMIB, UMR5068 CNRS-Université Paul Sabatier-Toulouse III, 118 route de Narbonne, Toulouse, F-31062, France
Phone: (+033) 5-61-55-62-99; Fax: (+033) 5-61-55-60-11
E-mail: ballereau@chimie.ups-tlse.fr (SB), baudoin@chimie.ups-tlse.fr (CD), genisson@chimie.ups-tlse.fr (YG)
[b] Laboratoire Signalisation et Transports Ioniques Membranaires, Université de Poitiers, Bâtiment B36, Pôle Biologie Santé, 1 rue Georges Bonnet, TSA 51106, 86073 Poitiers, France.

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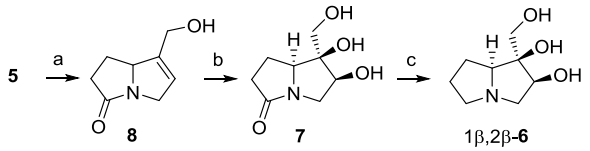
The stereochemistry of these two *cis*-diols was determined by NOESY NMR experiments. For diol 1α,2α-**6** a NOE correlation between H-2 and H-9 hydrogens but neither between H8 and H9 nor between H2 and H8 proved the 1α,2α configuration. The 1β,2β was assigned to **7** on the basis of NOE correlations observed between H-2, H-9 and H-8.

Such stereochemical outcome accompanied by the selective over-oxidation of a single diastereoisomer was already described for the *cis*-dihydroxylation of unsaturated pyrrolizidines[15] and could be circumvent in reacting, instead of supinidine, the corresponding lactam.[16] The lactam **8** (Scheme 3), obtained by partial reduction of aldehyde **5**, was submitted to OsO_4-catalysed dihydroxylation. This dihydroxylation proved totally diastereoselective and gave the β,β-diol **7** with a 45% yield. The lactam was then reduced by LAH to give 1β,2β-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine (1β,2β-**6**), described as transalpinecine.[2]



Scheme 3. Synthesis of 1β-2β-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine (1β,2β-**6**) (transalpinecine proposed structure). *Reagents and conditions:* a) $NaBH_4$, EtOH, -10 °C, 98%; b) OsO_4 (cat.), NMO, Acetone/H_2O, rt, 45%; c) LAH, THF, 70°C, 24%.

A thorough analysis of the ^1H and ^{13}C NMR spectra of these two *cis*-diols led us to propose that the transalpinecine described[2] was not the claimed 1β-2β-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine. Beyond the difference in chemical shifts, likely due to the protonation variations,[17] the most significant differences in ^1H-NMR are observed on coupling constants for H-2 and H-3 (Table 1). The reported NMR spectra (^1H and ^{13}C) of transalpinecine did not match either the other *cis*-diol, 1α,2α-**6**.

As the reported transalpinecine was not the claimed *cis*-structure, we decided to use NMR calculations to determine which one of the four diastereoisomers of 1,2-dihydroxy-1-hydroxymethyl-pyrrolizidine (Figure 2) displays the NMR computed values closest to the ones reported for transalpinecine.

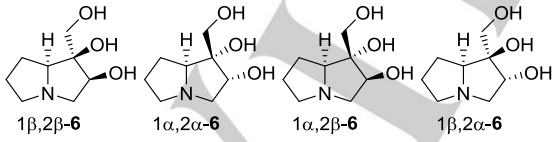


Figure 2. Diastereoisomers of 1,2-dihydroxy-1-hydroxymethyl-pyrrolizidine.

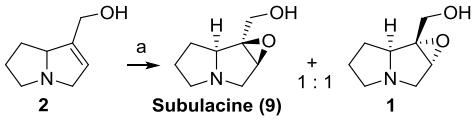
For each compound, the conformers were modeled by DFT, using Gaussian 09 at the B3LYP/6-31+G(d,p) level.[18] Frequencies calculations were performed on the optimized geometries at 298K, showing all positive frequencies and allowing evaluation of the Gibbs free energy of the minima.

^{13}C NMR and ^1H chemical shift calculations were then performed using the GIAO NMR method with B3LYP/6-31+(d,p) and using the methanol polarizable continuum model (PCM) on optimized geometries at the B3LYP/6-31+G(d,p) level. For each conformer, isotropic shielding constants (σ) for the ^{13}C nucleus and ^1H were transformed in chemical shifts (δ) using linear regression procedure proposed by Tantillo and coll.[19] The contribution of each conformer in the constitution of the overall spectrum was based on previous Boltzmann conformational analysis in the methanol continuum. Calculated values are consigned in ESI.

NMR spectra were calculated for the four diastereoisomers of **6**. Computed spectra of *cis*-diols 1α,2α-**6** and 1β,2β-**6** were in accordance with experimental data. Calculations thus confirmed that transalpinecine was not the claimed structure. It also showed that among computed NMR values the closest to the spectral data reported for transalpinecine were that of the diastereoisomer 1β,2α-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine (1β,2α-**6**).

Warned by this first erroneous assignment, we also reconsidered the structure of the unprecedented α-isomer of subulacine. We thus used calculations to predict the ^1H and ^{13}C NMR spectra of subulacine and its α-isomer **1**. Whereas the calculated NMR data for subulacine were concordant with literature,[3b] it ruled out the assignment of the α-isomer of subulacine for the compound described by Vidotti.

In order to confirm experimentally the NMR calculation obtained for the two *trans*-diastereoisomers of 1,2-dihydroxy-1-hydroxymethyl-pyrrolizidine and the α-isomer **1** of subulacine we envisioned the synthesis of these compounds. As described,[20] epoxidation of (±)-supinidine with peracetic acids (*m*CPBA or TFAA/H_2O_2) proceeded in our hands with very low yield because of undesired nitrogen atom oxidation. We thus relied on the base-catalyzed intramolecular cyclisation of a bromohydrine[21] to obtain the two easily separable epoxides **9** and **1** with a 60% combined yield (Scheme 4).



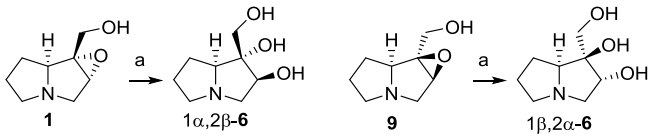
Scheme 4. Synthesis of subulacine and its α-isomer. *Reagents and conditions:* a) i) TFA, NBS, H_2O, rt; ii) NaOH 15%, 60%.

The relative configuration of each epoxide was determined by NOESY NMR experiments. In addition, the experimental NMR spectra of subulacine were in accordance with the spectra both issued from calculations and literature.[2, 3b, 20]

For its α-isomer **1**, the experimental NMR spectra confirmed the calculated spectra but were not in agreement with the data described by Vidotti[2] invalidating the claimed isolation of 1α,2α-epoxy-1β-hydroxymethyl-8α-pyrrolizidine. Indeed, whereas Vidotti reported ^{13}C NMR chemical shifts for C-1, C-3 and C-8 very different from those of subulacine (Δδ between 4.3 and 13.6 ppm, justified by intense theoretical calculation), we observed for these carbons Δδ values inferior to 3 ppm between the two diastereoisomeric epoxides.

Both epoxides **1** and **9** were separately engaged in ring opening reaction under acidic conditions to generate the corresponding *trans*-diols 1α,2β-**6** and 1β,2α-**6** through selective nucleophilic attack at C-2 (Scheme 5). For these two *trans*-diols, the

experimental and calculated NMR data were in accordance (see ESI).



Scheme 5. Ring opening of epoxides **1** and **9**. *Reagents and conditions:* a) TFA, H_2O, THF, 70 °C, 55%.

Comparative analysis of the ^{1}H and ^{13}C NMR spectra of the four stereoisomers of **6** evidenced two clear-cut stereochemical signatures (Figure 3). First, for *cis*-diols, (1β,2β-**6**, 1α,2α-**6**) H-2 presents coupling constants above 6 Hz with both H-3 and H-3' while for *trans*-diols (1α,2β-**6**, 1β,2α-**6**) H-2 is coupled with only one proton at C-3 with a small coupling constant (around 3 Hz). Secondly, for 1α-hydroxy isomers (1α,2α-**6**, 1α,2β-**6**), Δδ between C-6 and C-7 is around -0.5 ppm while for 1β-hydroxy isomers (1β,2β-**6**, 1β,2α-**6**), Δδ between C-6 and C-7 is above to 2 ppm (Table 1).

Taking these observations into account, the NMR data described for transalpinecine were reconsidered. H-2 was described as a doublet with a single coupling constant of 3.3 Hz, revealing a *trans* relative configuration of the 1,2-diol and Δδ between C-6 and C-7 was 3.4 ppm denoting a 1β-hydroxy group. These analysis confirmed the results already obtained by calculation: the transalpinecine isolated by Vidotti[2] was not the claimed 1β,2β-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine but rather the diastereoisomeric 1β,2α-dihydroxy-1α-hydroxymethyl-8α-pyrrolizidine.

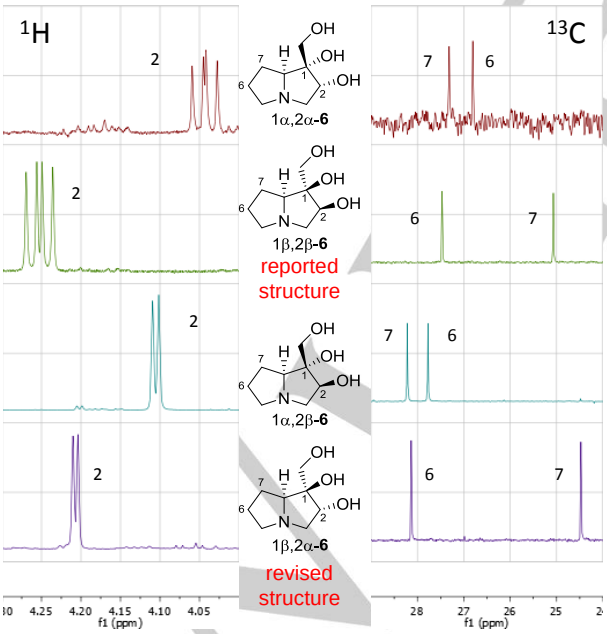


Figure 3. Discriminant NMR signals (H-2 for ^{1}H NMR, C-6, C-7 for ^{13}C NMR in MeOD) for compounds **6.**

The *trans*-diol 1β,2α-**6** could biosynthetically derive from subulacine or, alternatively be formed upon chemical hydrolysis under the extraction/purification process used by Vidotti group. Transalpinecine would thus, in this event, be an isolation artefact.

Relying on the structural analogy with isoLAB (Figure 1), we then recorded the short-circuit currents (Isc) in F508delCFTR-expressing human airway epithelial cells CFBE. To correct the abnormal trafficking of F508del, we incubated cells for 4h with either the diastereoisomers of transalpinecine and subulacine or 24h with VX-809[22] (Figure 4A). The F508del-Isc was stimulated using forskolin and genistein. Compared to the respective vehicle (DMSO or water), incubation of CFBE cells in presence of VX-809 (Figure 4B) but not the compound **1** (Figure 4C), allow stimulation of F508del-Isc. None of the 6 compounds studied here were efficient in correcting the abnormal F508delCFTR Isc. We next co-treated CFBE cells with a combination of VX-809 and synthetized compounds to determine whether the correction of F508delCFTR function by VX-809 could be further improved. Interestingly, the stimulation of F508del-Isc was significantly increased (n = 12, $P<0.01$) in cells co-treated with VX-809 plus compound **1** (Figure 4D) with a potentiation of 24% compared to the level of F508del-Isc after VX-809 alone (n = 12, Figure 4E). None of the other combinations tested, i.e. VX-809 plus 1β,2α-**6**, 1α,2β-**6,** 1α,2α-**6,** 1β,2β-**6** or VX-809 plus isoLAB were significantly better than VX-809 alone (Figure 4E). The selective CFTR inhibitor CFTRinh172[23] was used at the end of each experiment. It fully inhibited the F508del-Isc recovered by either VX-809 or VX-809 plus compound **1** (Figure 4A-D).

These results show that compound **1**, the α-isomer of subulacine, uniquely improved the correction of F508delCFTR function by VX-809.

Conclusion

In summary, this communication reports the first total synthesis of the four stereoisomers of transalpinecine as well as the synthesis of two diastereoisomers of the parent epoxide subulacine. This synthetic work, substantiated by NMR quantum calculations, allowed the stereochemical revision of the initially reported transalpinecine structure. Tested for its capacity to rescue the defective function of cystic fibrosis transmembrane conductance regulator (CFTR) responsible for cystic fibrosis, the compound **1**, α-isomer of subulacine, proved to significantly enhance the correction of F508delCFTR function by VX-809.

Table 1. Characteristic spectral data (^{1}H δ (mult., J in Hz) and ^{13}C δ in MeOD) for compounds **6** and transalpinecine

Nucleus	1α,2α-**6**	1β,2β-**6**	1α,2β-**6**	1β,2α-**6**	Transalpinecine[2]
H-2	4.04 (dd, 8.8, 7.0)	4.25 (dd, 10.1, 6.7)	4.11 (d, 3.9)	4.21 (d, 3.1)	4.81 (d, 3.3)
H-3 and H-3'	3.06 (dd, 11.4, 8.9) 2.82 (dd, 11.3, 7.0)	3.43 (dd, 9.6, 6.6) 2.75 (t, 10.0)	3.70 (dd, 12.5, 3.9) 3.02 (d, 12.6)	3.37 (d, 11.4) 3.20 (dd, 11.4, 3.2)	3.86 (d, 12.0) 3.38 (dd, 12.0, 3.3)
C-6	26.8	27.5	27.8	28.1	28.0
C-7	27.3	25.1	28.2	24.4	24.6

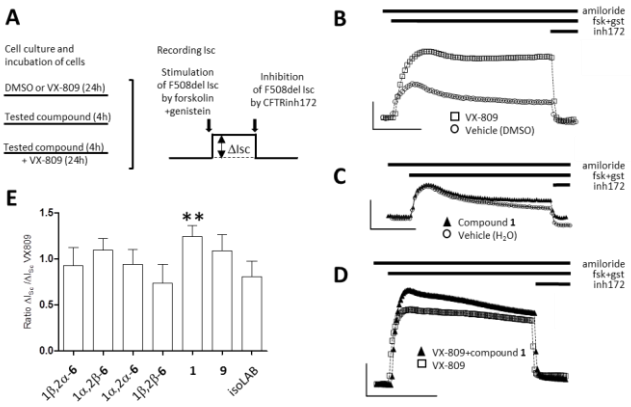


Figure 4. Transepithelial short-circuit currents (Isc) recorded in F508del-CFTR expressing CFBE cells. (**A**) Protocols used in this study and model trace indicating the ΔIsc. (**B-D**) Tracings of Isc recorded with CFBE cells incubated 24h in B with vehicle (DMSO) or VX-809 (10 μM) or incubated 4h in C with vehicle (water) or compound **1** (100 μM), and in D with VX-809 (10 μM, 24h) or VX-809+compound **1** (100 μM, 4h). F508del-CFTR was activated by application of forskolin (10 μM) and genistein (30 μM) and inhibited by CFTRinh172 (10 μM) as indicated in the scheme in A and by the bars above tracings in B to D. (**E**) Summary of the ratio ΔIsc/ ΔIsc VX-809 (mean ± SEM, *n* = 4-12; ***P*<0.01) for each compound as indicated. A ratio above 1 means a potentiation. Isc was recorded with CFBE cells incubated with the test compound combined to VX-809 as function of the Isc recorded with cells incubated only with VX-809 in the same set of experiment. Scale bars in B, C and D are 5mA/cm^2 (vertical) and 7.5 min (horizontal).

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Keywords: alkaloids • natural products • transalpinecine • subulacine • CFTR • cystic fibrosis

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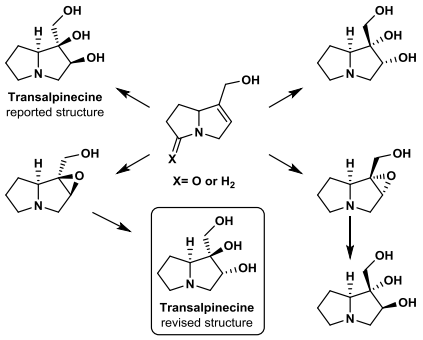
COMMUNICATION

The first total synthesis of transalpinecine, is reported. The four diastereoisomers of transalpinecine as well as the two diastereoisomers of the parent epoxide subulacine were prepared, allowing revision of the initially reported transalpinecine stereochemistry. One of these synthetic compounds significantly potentiates the activity of the F508del-CFTR corrector VX-809.



Cécile DEHOUX, Tessa CASTELLAN, Morgane ENEL, Christiane ANDRÉ-BARRÈS, Sandra, MIRVAL, Frédéric BECQ, Stéphanie BALLEREAU* and Yves GÉNISSON**

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First total synthesis, stereochemical revision and biological evaluation of transalpinecine and analogues thereof