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Flow Conditions-Controlled Divergent Oxidative Cyclization of Reticuline-Type Alkaloids to Aporphine and Morphinandienone Natural Products

Bi Bali Judicaël Tra,^[a, b] Abollé Abollé,^[b] Vincent Coeffard,^[a] and François-Xavier Felpin^{*[a]}

Described herein is a divergent continuous-flow approach for the biomimetic oxidative cyclization of reticuline-type alkaloids to aporphine and morphinandienone natural products using hypervalent iodine(III) reagents. The method was based on the detailed knowledge of the reaction mechanisms in order to develop robust reaction conditions toward the selective synthesis of either aporphine or morphinandienone natural products. In this frame, we exploited the ability of HFIP to

stabilize radical cation intermediates and to activate hypervalent iodine(III) oxidants for the flow synthesis of aporphine natural products such as glaucine, rogersine and nantenine. On the other hand, we established that PhI(OAc)(OTf), prepared by action of TMSOTf on PhI(OAc)₂, was a powerful oxidant for the synthesis of morphinandienone natural products such as sebiferine and amurine.

Introduction

Biogenetic-type intramolecular oxidative coupling of reticuline-type alkaloids^[1] is a long-standing issue that continues to stimulate intense research works^[2,3] since it leads to a number of iconic natural products such as (+)-corytuberine (1) and (–)-morphine (5) (Scheme 1B). The difficulty in achieving such transformations is related to the possibility of forming four regioisomers (Scheme 1A). Coupling at C8 furnishes two regioisomers sharing the aporphine skeleton while coupling at C4a affords two morphinandienone regioisomers. The regioselectivity of the oxidative cyclization with respect to the aporphine and morphinandienone backbone essentially depends on the experimental conditions. On the other hand the distribution of regioisomers into a family of alkaloids, i.e., aporphine versus morphinandienone, is essentially governed by geometrical and steric constraints.

The biomimetic oxidative cyclization of reticuline-type alkaloids to either the aporphine or morphinandienone backbone has been intensively studied using heavy metals. While the synthesis of aporphine alkaloids proved to be effective with Fe(OH)₅(OAc)₂, Ce(OH)₄ and RuO₂·2H₂O,^[4,5] the preparation of morphinandienones revealed to be much more tricky and the

use of VOCl₃,^[6] Ti(TFA)₃,^[7] KFeCN₆,^[8] or Mn(acac)₃^[9] gave poor selectivities and yields. However, because of their very low solubility in conventional organic solvents these heavy metal oxidants need to be used in excess and under prolonged reaction times. A significant breakthrough was reported by Opatz et al. with the synthesis of morphine alkaloids via anodic oxidative cyclization of reticuline-type alkaloids.^[10,11] The use of hypervalent iodine(III) reagents is another appealing approach due to the low toxicity and ease of handling of these organic oxidants. In this frame the remarkable work from Kita et al. who extensively studied the formation of morphinandienones has to be mentioned.^[12,13]

Despite the promising results obtained with electrochemistry and λ³-iodanes, the biomimetic oxidative cyclization of reticuline-type alkaloids remains a great challenge due to the sensitivity of the tertiary amine toward strong oxidants which often led to irreproducible results. Protection of the nitrogen atom with trifluoroacetyl or alkylcarbamate groups prevents unwanted amine oxidation but at the cost of extra steps.^[12,14–16]

Continuous flow chemistry is now recognized as an essential enabling technology that offers considerable opportunities to unlock long-standing chemical problem and access hazardous transformations or “forbidden” reactivities.^[17–23] Good mixing efficiency, high heat transfer, safety, precision and reproducibility are some of the main benefits offered by continuous flow reactors.^[24,25] In the line with our interest for natural product synthesis in flow,^[26–28] we reasoned that the complex regioselectivity issues pertaining to the oxidative cyclization of reticuline-type alkaloids usually observed in traditional batch processes might be addressed, at least in part, through the development of a continuous flow approach using hypervalent iodine(III) reagents. To our knowledge, the oxidative cyclization of reticuline-type alkaloids to either the aporphine or morphinandienone backbone has never been studied in flow, and the results described herein represent the very first contribution which highlights not only the benefits offered by flow reactors but also the current limits of this approach.

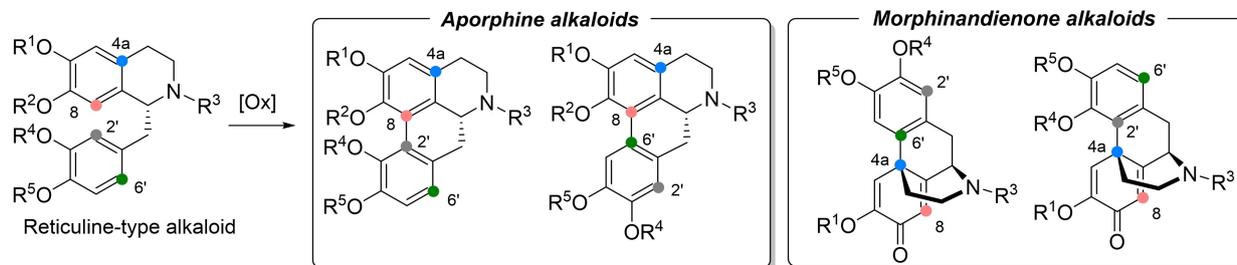
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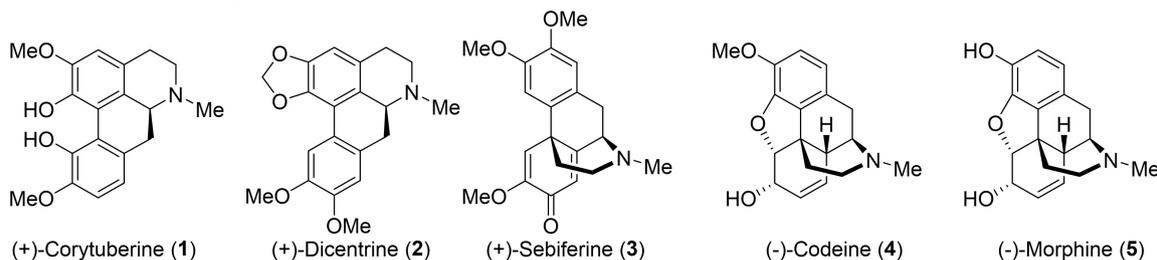
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A - Oxidative coupling of reticuline-type alkaloids



B - Natural products sharing the aporphine and morphinane skeleton

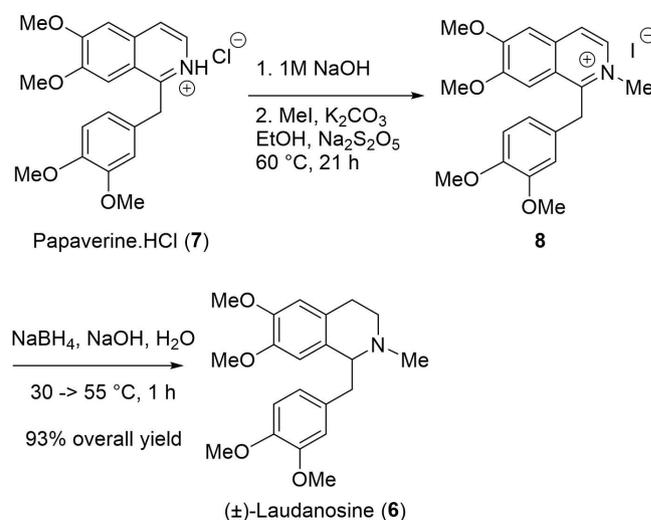


Scheme 1. (A) Oxidative coupling of reticuline-type alkaloids. (B) Selection of natural products sharing the aporphine or morphinane skeleton.

Results and Discussion

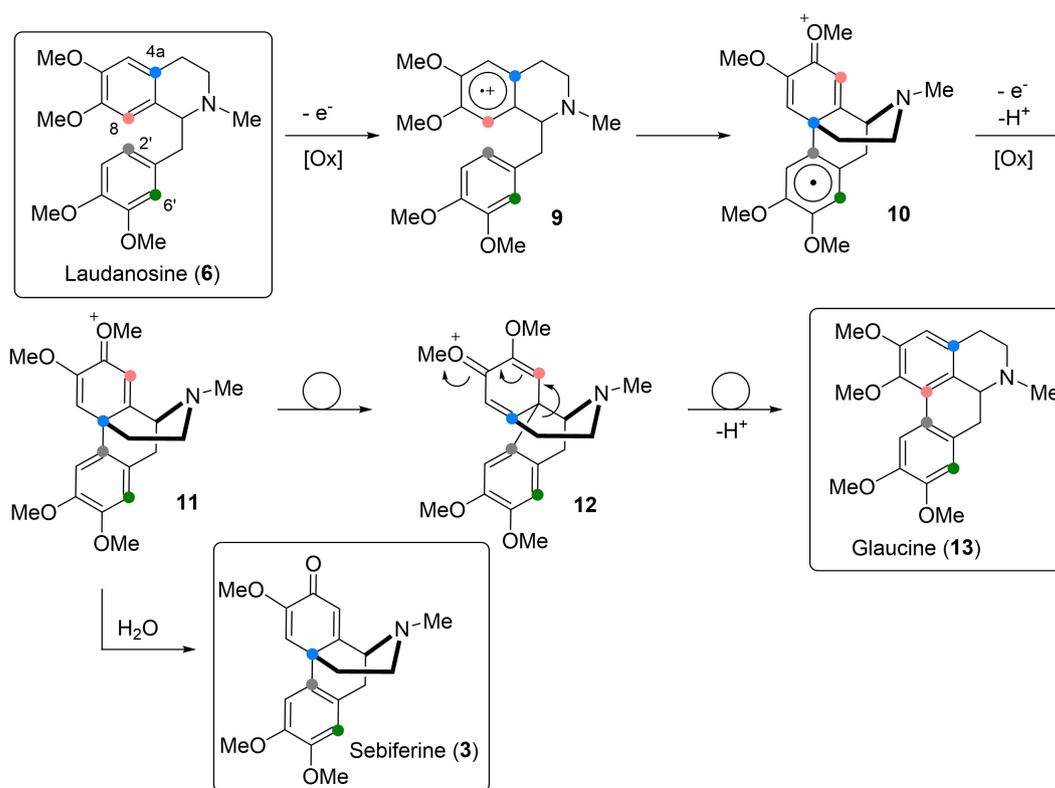
Optimization studies – Understanding the aporphine vs. morphinandienone selectivity. Our initial objectives in this work were to identify the factors governing the selectivity of the oxidative addition toward aporphine versus morphinandienone alkaloids through the development of robust, original and room temperature experimental conditions compatible with a continuous flow process. While continuous flow processes possess several assets compared to traditional batch approaches, they require homogeneous conditions, and therefore soluble reagents, to prevent clogging issues. This point alone justifies the use of hypervalent iodine(III) reagents, which are soluble in many organic solvents, to the detriment of poorly soluble oxidizing heavy metals. In order to address our initial objectives, we explored the reactivity of laudanosine (6) under various experimental conditions. Laudanosine (6) was prepared from commercially available papaverine hydrochloride (7) in three steps by modification of literature procedures (Scheme 2).^[29,30] Papaverine hydrochloride (7) was neutralized with sodium hydroxide and methylated with MeI to give N-methylisoquinolinium (8) which was reduced *in situ* with sodium borohydride to give laudanosine (6).

It is well known from literature precedents that laudanosine (6) can only be converted to either glaucine (13) or sebiferine (3) through 8–2' or 4a–2' bond formation, respectively (Scheme 3).^[13] Alkaloids resulting from the formation of 8–6' and 4a–6' bonds are strongly disfavored due to steric constraints induced by methoxy groups. In order to design original and efficient reaction conditions, compatible with a flow process, we adopted an unusual methodological approach. Traditionally, reaction mechanisms are established following



Scheme 2. Synthesis of (±)-laudanosine (6).

the determination of the optimal experimental conditions. In this work, we followed a reverse strategy since we capitalized on previously reported mechanistic investigations^[13,31,32] to establish pathways depicted in Scheme 3 and to design experimental conditions that regioselectively lead to either glaucine (13) or sebiferine (3). We reasoned that compound 11 obtained by a two electrons oxidation of laudanosine (6) is a common intermediate to glaucine (13) and sebiferine (3). In this frame we also assumed that 11 can rearrange to glaucine (13) through the erythrinandienone intermediate 12. On the other hand, in the presence of water, intermediate 11 is likely hydrolyzed to sebiferine (3). From the mechanistic hypothesis



Scheme 3. Possible reaction pathways leading to glaucine (13) and sebiferine (3).

depicted in Scheme 3 we realized that the exclusive formation of glaucine (13) is expected under strictly anhydrous conditions while the formation of sebiferine (3) should be favored, or at least possible, under aqueous conditions.

Synthesis of glaucine (13). The hypervalent iodine(III)-mediated oxidative cyclization of laudanosine (6) to glaucine (13) has been reported on several occasions in batch under experimental conditions requiring the use of $\text{PhI}(\text{OCOCF}_3)_2$ as the oxidizing agent and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, which is expected to favor the cyclization and prevent the tertiary amine from oxidation, in CH_2Cl_2 at low temperatures, *ca.*, ranging from -20 to -40°C .^[13,33–35] Surprisingly, contrasted reaction yields were accounted, ranging from 33 to 75%, despite similar experimental conditions, suggesting reproducibility issues. With the objective of developing a robust flow process working at room temperature, we initially assessed the solubility of laudanosine (6) in CH_2Cl_2 in the presence of $\text{PhI}(\text{OCOCF}_3)_2$ and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in test vials. Disappointingly, we observed the rapid formation of large amounts of tar-like solids which would inevitably lead to clogging problems in the event of a continuous flow transfer of these experimental conditions. This phenomenon, never mentioned in previous reports, might also explained the variable yields reported in the literature since we observed that the addition rate of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to a solution of laudanosine (6) and $\text{PhI}(\text{OCOCF}_3)_2$ in CH_2Cl_2 severely impacted the amount of tar solids. We interpreted this observation as the result of the low stability of radical cation intermediates 9–10 in CH_2Cl_2 . We reasoned that the ability of hexafluoroisopropanol (HFIP) to

stabilize aromatic radical cations^[36,37] while increasing the oxidizing capacity of hypervalent iodine(III) reagents^[38,39] might prevent the formation of tar solids. In addition, the strong hydrogen-bond donating ability of HFIP would reduce the risk of oxidation of the tertiary amine.

With these considerations in mind, we started our investigations using a two-stream flow platform equipped with injection loops delivering the reagents (Table 1). The reaction occurred in a reactor coil at room temperature and the crude mixture was collected in vials. The reaction conversion was assessed by ^1H NMR on the crude mixture after a standard work up. A selection of the most representative reactions conducted during the optimization campaign are reported in Table 1. For the initial test, loop 1 was loaded with a solution of laudanosine (6) [28 mM] and PIFA [42 mM] in HFIP, while loop 2 delivered a solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [140 mM]. Both streams were mixed in a T-shaped piece and the reaction occurred in a peek coil reactor (5 mL, 0.75 mm id) at a 0.166 ml/min flow rate corresponding to 30 min of residence time. Under such initial conditions, we were unable to identify glaucine (13) and laudanosine (6) was quantitatively recovered (entry 1). Suspecting that the high viscosity of HFIP could alter the mass transfer between the two streams due to an inefficient mixing, we switched the standard T-shaped piece for a T-mixer equipped with a 250 μL frit to improve the turbulent mixing. With such modifications of the flow setup, the conversion spectacularly increased to 50% confirming the decisive effect of the mixing event on the reaction outcome (entry 2). Increasing the residence time to 60

Table 1. Optimization of the oxidative cyclization of laudanosine (**6**) to glaucine (**13**).

Entry	Loop 1	Loop 2	Mixer	RT [min]	Conv. [%] ^[a]
1	6 [28 mM] PIFA [42 mM]	BF ₃ [140 mM]	T-mixer	30	0
2	6 [28 mM] PIFA [42 mM]	BF ₃ [140 mM]	T-mixer with frit	30	50
3	6 [28 mM] PIFA [42 mM]	BF ₃ [140 mM]	T-mixer with frit	60	84
4	6 [28 mM]	BF ₃ [140 mM] PIFA [42 mM]	T-mixer with frit	60	73
5	6 [28 mM] BF ₃ ·Et ₂ O [140 mM]	PIFA [42 mM]	T-mixer with frit	60	100 (82)
6	6 [28 mM]	PIFA [42 mM]	T-mixer with frit	60	0
7	6 [28 mM]	BF ₃ [140 mM]	T-mixer with frit	60	0

[a] Conversions determined by ¹H NMR on the crude mixture. Isolated yield in bracket.

minutes using a larger peek coil reactor (20 mL, 0.75 mm id) at 0.333 ml/min flow rate further improved the reaction conversion to 84 % (entry 3). Interestingly, we observed an important effect of the composition of solutions injected in loops 1 and 2. When loop 1 was loaded with a solution laudanosine (**6**) while loop 2 contained a mixture of PIFA and BF₃·Et₂O, the conversion decreased to 73 % (entry 4). By contrast, feeding the first stream with a mixture of laudanosine (**6**) and BF₃·Et₂O while the second stream was fed with a solution of PIFA led to the complete disappearance of (**6**) and the formation of glaucine (**13**) in 82% isolated yield (entry 5). Finally, the omission of either BF₃·Et₂O or PIFA did not allow the formation of glaucine (**13**) (entries 6–7).

Synthesis of sebiferine (3). For the synthesis of sebiferine (**3**) which shares the morphinandienone backbone we followed the same conceptual approach than the one developed for glaucine (**13**). Following the mechanism hypothesis depicted in Scheme 3, we anticipated that the use of a hygroscopic solvent containing a more or less important amount of water would favor the hydrolysis of intermediate **11** leading to sebiferine (**3**). From a selection of solvents partially miscible with water (CH₃CN, THF and acetone), we identified, in preliminary study, CH₃CN as the only solvent able to solubilize both laudanosine (**6**) and hypervalent iodine (III) reagents (PIDA or PIFA). With these considerations in mind, we started our investigations using the same two-stream flow platform used for the glaucine (**13**) synthesis (Table 2). The reaction occurred in a reactor coil at room temperature and the crude mixture was collected in

Table 2. Optimization of the oxidative cyclization of laudanosine (**6**) to Sebiferine (**3**).

Entry	Loop 1	Loop 2	RT [min]	Conv. [%] ^[a]
1	6 [28 mM] PIFA [28 mM]	BF ₃ [56 mM]	15	0
2	6 [28 mM] PIDA [28 mM]	BF ₃ [56 mM]	15	0
3	6 [28 mM] PIFA [28 mM]	TMSOTf [56 mM]	15	^b
4	6 [28 mM] PIDA [28 mM]	TMSOTf [56 mM]	15	75
5	6 [28 mM] PIDA [28 mM]	TMSOTf [56 mM]	15	100 (82)
6	6 [28 mM] PIDA [84 mM]	TMSOTf [56 mM]	15	^[b]
7	6 [28 mM] PIDA [84 mM]	TMSOTf [84 mM]	15	64
8	6 [28 mM] PIDA [56 mM]	TMSOTf [56 mM]	15	100 ^[c]
9	6 [28 mM] PIDA [56 mM]	TMSOTf [56 mM]	15	17 ^[d]

[a] Conversions determined by ¹H NMR on the crude mixture. Isolated yield in bracket. [b] Degradation of starting material. [c] 10 equivalents of water were added. [d] 40 equivalents of water were added.

vials. The reaction conversion was assessed by ¹H NMR on the crude mixture after a standard work up. A selection of the most representative reactions conducted during the optimization campaign are reported in Table 2. For the initial test, loop 1 was loaded with a solution of laudanosine (**6**) [28 mM] and PIFA [28 mM] in undistilled CH₃CN, while loop 2 delivered a solution of BF₃·Et₂O [56 mM]. Both streams were mixed in a T-shaped piece and the reaction occurred in a peek coil reactor (5 mL, 0.75 mm id) at a 0.332 ml/min flow rate corresponding to 15 min of residence time. Under such initial conditions, we were unable to identify sebiferine (**3**) and laudanosine (**6**) was quantitatively recovered (entry 1). A similar result was obtained when PIFA was substituted for PIDA (entry 2). Considering that the methoxy hydrolysis of intermediate **11** is likely assisted by the Lewis acid, we switched BF₃·Et₂O for TMSOTf whose Lewis acidity is increased. While the association of PIFA/TMSOTf completely degraded laudanosine (**6**) (entry 3), a sharply different reaction outcome was observed with PIDA/TMSOTf for which a clean conversion for sebiferine (**3**) (75 %) was observed (entry 4). Gratifyingly, increasing the concentration of PIDA from 28 mM to 56 mM fully converted laudanosine (**6**) and sebiferine (**3**) was isolated in 82% yield (entry 5). A further increase of the stoichiometry for either PIDA or TMSOTf led to

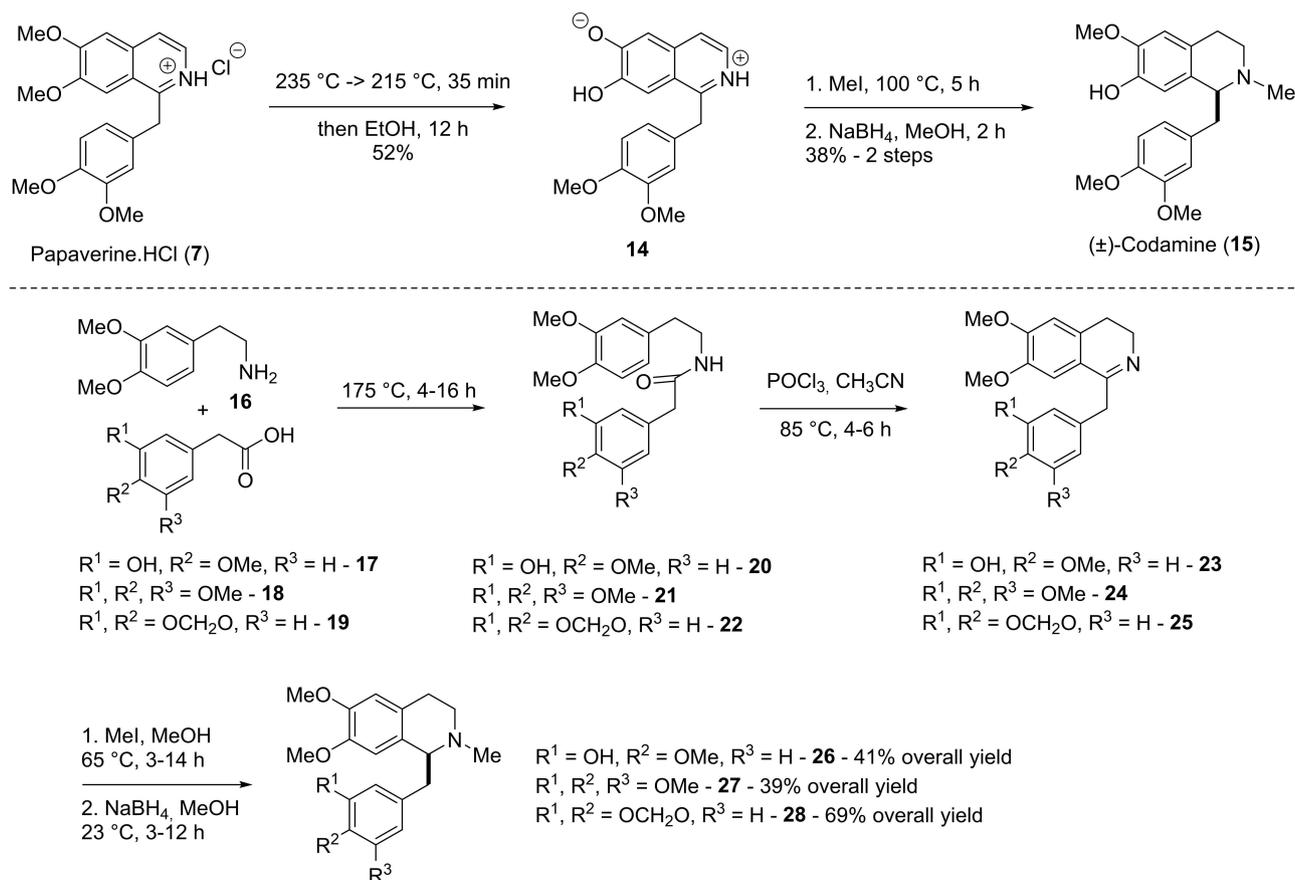
unsatisfactory results (entries 6–7). The addition of 10 equivalents of water did not significantly modify the reaction outcome while a further addition to 40 equivalents sharply altered the conversion which dropped to 17% (entries 8–9).

From these results we learned that PIDA was the oxidant of choice for the synthesis of sebiferine (**3**). This unexpected result contrasts with literature precedents which reported, quasi exclusively, the use of PIFA while PIDA was considered to be inactive. This apparent discrepancy might result from the convergence of several beneficial factors. First, batch synthesis of sebiferine (**3**) from laudanosine (**6**) using hypervalent iodine(III) reagents was reported at low temperature (-20°C) while our flow process proceeded at room temperature (23°C).^[13] This increase of temperature by more than 40°C likely increase the oxidation rate. Second, to our knowledge, the use of TMSOTf as Lewis acid has never been reported for the oxidative cyclization of reticuline-type alkaloids to morphinan-dienone compounds. We suspect that, in this reaction, the role of TMSOTf might be more complex than just being a simple Lewis acid assisting the cyclization. It has been recently demonstrated, through theoretical and spectroscopic investigations, that PIDA in the presence of 2 equivalents of TMSOTf gives $\text{PhI}(\text{OTf})(\text{OAc})$, a iodine(III) species.^[40,41] We assume that the increased oxidative capacity of $\text{PhI}(\text{OTf})(\text{OAc})$ allowed the cyclization of laudanosine (**6**) to sebiferine (**3**).

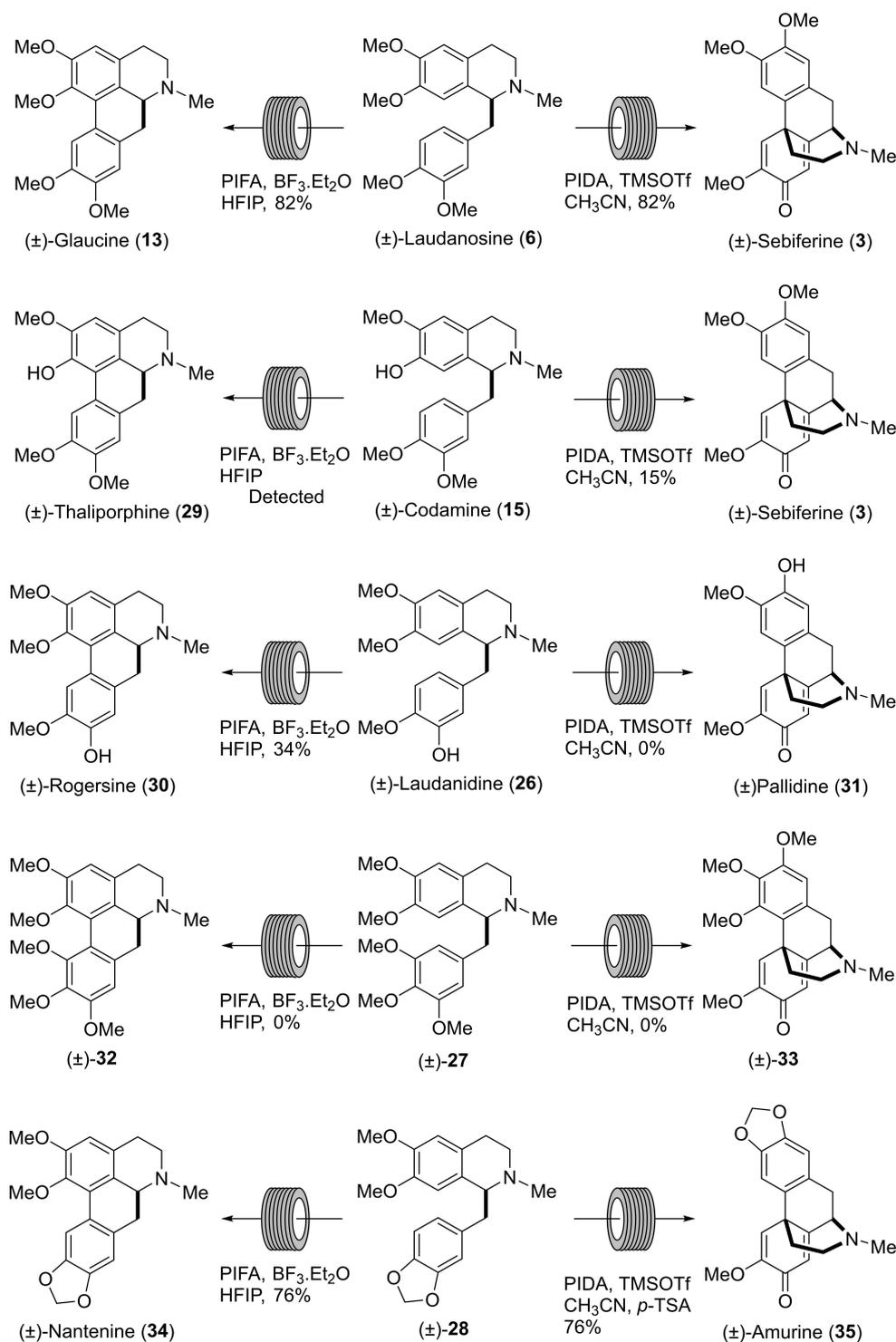
Our results also revealed the dual action of water on the reaction outcome. While a small amount of water was necessary for the hydrolysis of intermediate **11**, the use of >10 equivalents H_2O sharply inhibited the oxidation likely due to the hydrolysis of PIDA and/or $\text{PhI}(\text{OTf})(\text{OAc})$ to unreactive $\text{PhI}(\text{OH})_2$ (entries 5, 8 *versus* 9).

Identifying the limits. From laudanosine (**6**) we identified two robust flow processes leading to either glaucine (**13**) with PIFA/ $\text{BF}_3\cdot\text{Et}_2\text{O}$ in HFIP or sebiferine (**3**) in PIDA/TMSOTf in CH_3CN . In order to establish a first structure-reactivity relationship and to assess the current limits of such oxidative processes, we prepared a series of variously substituted reticuline-type alkaloids. Codamine **15** was prepared in three steps from papaverine hydrochloride **7** in modest overall yield while alkaloids **26–28** were assessed by adaptation of literature precedents in four steps from readily available starting materials in overall yields ranging from 39 to 69% (Scheme 4).

With *N*-methylisoquinolines **15** and **26–28** in hands, we evaluated the flow processes leading to either aporphine or morphinandienone alkaloids. Results collected from this product diversification campaign are summarized in Scheme 5. Surprisingly, codamine **15**, which differs from laudanosine **6** only by the phenol function at C7, led to sebiferine **3** with a modest yield of 15%; the reaction crude showing several unidentified side-products and tar material. The same behavior



Scheme 4. Preparation of reticuline-type alkaloids.



Scheme 5. Scope of the flow processes leading to either aporphine or morphinandienone alkaloids.

was also observed for the cyclization of 15 to thaliporphine 29 which could be detected in the complex crude mixture but not isolated in pure form after chromatography on silica gel. We attributed these disappointing results to the ease of free phenol groups, under highly oxidative conditions, to produce highly sensitive *p*-quinol intermediates that can react and

degrade.^[42–45] This assumption was confirmed with the oxidative cyclization of Laudanidine 26 which completely degraded in the conditions required to access pallidine 31 while the aporphine alkaloids rogersine 30 was isolated in 34% yield. While still modest, this latter result significantly improved literature precedents since the cyclization of laudanidine 26 to

rogersine **30** was described to only proceed with $\text{Pb}(\text{OAc})_4$ in 17–23% yield.^[46] The cyclization process is also highly sensitive to steric constraints since the presence of a methoxy group at C5' completely inhibited the formation of both aporphine and morphinandienone alkaloids and *N*-methylisoquinoline **27** was quantitatively recovered. An increase of the residence time did not modify the reaction outcome while an increase of oxidants (PIFA or PIDA) led to degradation products. The switch of methoxy groups at C3' and C4' by a more acid sensitive dioxolane group did not lead to the formation of degradation products and two natural products, *i.e.* nantenine **34** and amurine **35** sharing a morphinandienone and aporphine skeleton, respectively, were isolated with good yields (*ca.* 76%). Regarding the synthesis of amurine **35** we observed that the cyclization only occurred in the presence of *p*-TSA (3 equivalents). While the exact role of *p*-TSA was unclear at this stage, we suspected that it favored the activation of the dioxolane ring to promote the cyclization. We should add that the beneficial effect of *p*-TSA was not observed for the synthesis of morphinandienones **3**, **31** and **33**.

Conclusion

In this work we described the first oxidative cyclization of reticuline-type alkaloids in flow using hypervalent iodine(III) reagents. Based on mechanistic assumptions, we designed original and robust flow conditions selectively leading to either aporphine or morphinandienone alkaloids. Highlights of this work include (i) the development of fast (15–30 minutes) and room temperature processes (ii) the unusual use of HFIP as solvent for the stabilization of radical cation intermediates and the activation of PIFA in the selective preparation of aporphine alkaloids and (iii) the unusual use of TMSOTf in association with PIDA for the selective preparation of morphinandienone alkaloids. In addition, we established the very first structure-reactivity relationship to assess the current limits of such oxidative processes. The results obtained from this scope study provide essential information for the future improvement of these transformations and make it possible to solve reproducibility issues in oxidation processes which are recurrent well beyond the current study.^[47] In the quest of mimicking nature, we are currently working on the development flow processes compatible with free phenol groups.

Experimental Section

General information

All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification, unless otherwise noted. High-field ^1H and ^{13}C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz, respectively. ^1H and ^{13}C NMR spectra were referenced to the internal deuterated solvent (CDCl_3) at 7.26 and 77.16 ppm, respectively and Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference

standard. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m= multiplet, br=broad. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance (ν_{max}) are shown in wave numbers (cm^{-1}). High resolution mass spectrometry (HRMS) was recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254), and visualization was accomplished with UV light at 254 nm. Flash column chromatography was performed using silica gel 60 (40–63 μm).

Experimental procedures and characterization data

Laudanosine (6). Papaverine.HCl (**7**) (10 g, 26.6 mmol) was dissolved in a mixture of 1 M aqueous NaOH (approx. 60 mL) and saturated aqueous Na_2CO_3 (approx. 150 mL) and extracted with EtOAc (3 \times 50 mL). The collected organic layers were dried over anhydrous MgSO_4 and concentrated under vacuum to give papaverine (6.38 g, 71%) as a white solid. In a sealed tube, a solution of papaverine (1 g, 2.95 mmol) in EtOH (3 mL) was treated with K_2CO_3 (100 mg, 0.72 mmol), $\text{Na}_2\text{S}_2\text{O}_5$ (5 mg, 0.026 mmol) and MeI (720 μL , 11.56 mmol). The tube was sealed and heated at 60 °C for 21 hours. Volatiles were removed under a stream of N_2 . An additional 1 mL of EtOH was added and evaporated under a stream of N_2 . The solid residue **8** was treated with NaBH_4 (112 mg, 2.95 mmol) dissolved in 50% aqueous NaOH solution (1 mL) at 30 °C and the solution was heated at 55 °C for 1 hour. The initial dark orange mixture vigorously foamed and progressively turned pale green upon completion of the reaction after 1 hour of stirring. The resulting mixture was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 \times 5 mL). The collected organic layers were dried over anhydrous MgSO_4 , concentrated under vacuum and purified by flash chromatography on silica gel (99% EtOAc–1% Et_3N) to give laudanosine (**6**) (983 mg, 93% from papaverine) as a beige solid. mp 117–120 °C [lit.^[30] 114–116 °C]. IR (ATR) ν 2915, 2837, 2786, 1606, 1511, 1446, 1258, 1223, 1135, 1103, 1015, 856, 815 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 6.76 (d, 1H, $J=8.0$ Hz), 6.62 (dd, 1H, $J=1.9$, 8.0 Hz), 6.60 (d, 2H, $J=1.9$ Hz), 6.56 (s, 1H), 6.03 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.71 (dd, 1H, $J=4.8$, 7.7 Hz), 3.56 (s, 3H), 3.13–3.21 (m, 2H), 2.74–2.89 (m, 3H), 2.55–2.64 (m, 1H), 2.55 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 148.6, 147.4, 147.3, 146.4, 132.6, 129.3, 126.1, 121.9, 113.0, 111.2, 111.1, 111.0, 65.0, 56.0, 55.9, 55.9, 55.6, 47.1, 42.8, 41.0, 25.6. HRMS (ASAP+) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_4$ 358.2018; Found 358.2014.

Codamine (15). Papaverine.HCl (**7**) (6.88 g, 18.3 mmol) was melted at ca. 235 °C under stirring in a 100 mL round bottom flask. When the fusion was complete, the temperature was adjusted to ca. 215 °C for 35 minutes until bubbling ceased. The flask was cooled to room temperature and the residue was suspended in EtOH (70 mL) and stirred overnight until dissolution. The ethanol solution was cooled to 0 °C and was stand for 12 hours in the fridge. The precipitate was filtered and dried under vacuum to give protopapaverine **14** as a yellow solid (3.23 g, 52%). In a sealed tube, protopapaverine (**14**) (1 g, 3.1 mmol) was dissolved in methyl iodide (3.3 mL, 53 mmol) and stirred at 100 °C for 5 hours. Excess of methyl iodide was removed under a stream of N_2 and the resulting solid was dissolved in warm water (50 °C). After filtration, the filtrate was concentrated to dryness under vacuum to give a yellow oil (635 mg). The latter was dissolved in MeOH (140 mL), cooled to 0 °C and treated with NaBH_4 (635 mg, 16.71 mmol). The resulting mixture was stirred for 2 hours at 23 °C. Volatiles were removed under vacuum and the solid residue was diluted in 1 M aqueous NaOH solution (6 mL) and extracted with EtOAc (6 mL). The aqueous phase was adjusted to pH 8 with 2 M aqueous HCl and

back extracted with CH_2Cl_2 (3×6 mL). The collected organic layers were dried over anhydrous MgSO_4 , concentrated under vacuum and purified by flash chromatography on silica gel (10% MeOH – 90% CH_2Cl_2) to give codamine (**15**) as a yellow oil (400 mg, 38%). IR (ATR) ν 2934, 1591, 1510, 1446, 1259, 1233, 1135, 1023, 725 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 6.71 (d, 1H, $J=8.1$ Hz), 6.64 (dd, 1H, $J=1.6, 8.2$ Hz), 6.56 (d, 1H, $J=1.6$ Hz), 6.51 (s, 1H), 6.33 (s, 1H), 6.14 (br s, 1H), 3.80 (s, 6H), 3.73 (s, 3H), 3.69–3.78 (m, 1H), 3.06–3.15 (m, 2H), 2.71–2.88 (m, 3H), 2.48–2.58 (m, 1H), 2.48 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 148.4, 147.3, 145.6, 143.7, 131.9, 129.1, 124.9, 121.7, 114.0, 112.8, 110.9, 110.7, 64.6, 55.8, 55.8, 55.7, 46.9, 42.3, 41.0, 24.9. HRMS (ASAP+) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4$ 344.1862; Found 344.1863.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-hydroxy-4-methoxybenzeneacetamide 20. A mixture of 3-hydroxy-4-methoxyphenylacetic acid **17** (2 g, 11 mmol) and 3,4-dimethoxyphenethylamine **16** (1.85 mL, 11 mmol) was stirred at 175 °C in a 100 mL round bottom flask for 4 hours under nitrogen. After cooling, the residue was dissolved in EtOAc (20 mL) under sonication and the resulting solution was washed with 1 M aqueous HCl (30 mL) and saturated aqueous NaHCO_3 (40 mL). The aqueous phase was extracted three times with EtOAc (3×50 mL). The organic layer was dried over anhydrous MgSO_4 , concentrated under vacuum to give **20** as a beige solid (3.09 g) which was used in the next step without further purification.

5-[(3,4-Dihydro-6,7-dimethoxy-1-isoquinolinyl)methyl]-2-methoxyphenol 23. In a 100 mL round bottom flask, a solution of amide **20** (3.09 g, 8.96 mmol) in CH_3CN (45 mL) was treated with POCl_3 (850 μl , 8.96 mmol) and stirred at 85 °C for 4 hours. Volatiles were removed under vacuum, the solid residue was partitioned in CH_2Cl_2 (50 mL) and saturated aqueous NaHCO_3 (40 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (2×50 mL). The organic layer was dried over anhydrous MgSO_4 , concentrated under vacuum to give **23** as a yellow foam (3.11 g) which was used in the next step without further purification.

Laudanidine (26). A solution of **23** (3.11 g, 9.57 mmol) in MeOH (12 mL) was treated with Mel (596 μl , 9.57 mmol) and stirred at 65 °C for 3 hours. Volatiles were removed under vacuum to give a yellow foam (3.88 g, 8.31 mmol) which was diluted in MeOH (60 mL) and treated with NaBH_4 (338 mg, 8.89 mmol) at 0 °C. The mixture was warmed to 23 °C and stirred for 14 hours. Volatiles were removed under vacuum, the solid residue was partitioned in CH_2Cl_2 (40 mL) and H_2O (40 mL) and the aqueous phase was extracted two times with CH_2Cl_2 (2×50 mL). The collected organic layers were dried over anhydrous MgSO_4 , concentrated under vacuum and purified by flash chromatography on silica gel (80% EtOAc – 19% cyclohexane – 1% ammonia) to give **26** as a beige solid (1.53 g, 41% from **17**). mp 149.5–153.5 °C [lit.^[48] 156–157 °C]. IR (ATR) ν 2949, 1585, 1508, 1277, 1217, 1133, 1110, 1014, 859, 592 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 6.77 (d, 1H, $J=2.1$ Hz), 6.72 (d, 1H, $J=8.2$ Hz), 6.55 (s, 1H), 6.52 (dd, 1H, $J=2.1, 8.2$ Hz), 6.05 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.68 (dd, 1H, $J=5.2, 7.8$ Hz), 3.56 (s, 3H), 3.08–3.23 (m, 2H), 2.57–2.90 (m, 4H), 2.50 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 147.3, 146.4, 145.6, 145.2, 133.4, 129.4, 125.8, 121.3, 115.9, 111.2, 111.1, 110.6, 64.9, 56.1, 55.8, 55.6, 46.6, 42.6, 40.9, 25.3. HRMS (ASAP+) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4$ 344.1862; Found 344.1860.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4,5-trimethoxybenzeneacetamide 21. A mixture of 3,4,5-trimethoxyphenylacetic acid **18** (2 g, 8.85 mmol) and 3,4-dimethoxyphenethylamine **16** (1.49 mL, 8.85 mmol) was stirred at 175 °C in a 100 mL round bottom flask for 16 hours under nitrogen. After cooling, the residue was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was washed with 1 M aqueous HCl (40 mL) and saturated aqueous NaHCO_3 (40 mL). The aqueous layers were

extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over anhydrous MgSO_4 , concentrated under vacuum to give **21** as a beige solid (3.46 g) which was used in the next step without further purification.

6,7-Dimethoxy-1-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline 24. In a 100 mL round bottom flask, a solution of amide **21** (3.46 g, 9.28 mmol) in CH_3CN (55 mL) was treated with POCl_3 (887 μl , 9.28 mmol) and stirred at 85 °C for 6 hours. Volatiles were removed under vacuum, the solid residue was partitioned in CH_2Cl_2 (50 mL) and saturated aqueous NaHCO_3 (40 mL) and the aqueous phase was extracted two times with CH_2Cl_2 (2×50 mL). The organic layer was dried over anhydrous MgSO_4 , concentrated under vacuum to give **25** as a yellow foam (3.49 g) which was used in the next step without further purification.

6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (27)

A solution of **24** (3.49 g, 9.88 mmol) in MeOH (12 mL) was treated with Mel (616 μl , 9.88 mmol) and stirred at 65 °C for 14 hours. Volatiles were removed under vacuum to give a yellow foam (4.05 g, 8.18 mmol) which was diluted in MeOH (65 mL) and treated with NaBH_4 (311 mg, 8.18 mmol) at 0 °C. The mixture was warmed to 23 °C and stirred for 3 hours. Volatiles were removed under vacuum, the solid residue was partitioned in CH_2Cl_2 (50 mL) and H_2O (40 mL) and the aqueous phase was extracted two times with CH_2Cl_2 (2×50 mL). The collected organic layers were dried over anhydrous MgSO_4 , concentrated under vacuum and purified by flash chromatography on silica gel (99% EtOAc – 1% ammonia) to give **27** as a yellow oil (1.32 g, 39% from **18**). IR (ATR) ν 2934, 2833, 1588, 1507, 1455, 1419, 1227, 1120, 1007 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ 6.55 (s, 1H), 6.29 (s, 2H), 6.04 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 6H), 3.69 (dd, 1H, $J=5.0, 8.0$ Hz), 3.56 (s, 3H), 3.11–3.18 (m, 2H), 2.70–2.86 (m, 3H), 2.53–2.61 (m, 1H), 2.53 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 153.0, 153.0, 147.5, 146.5, 136.5, 135.7, 129.2, 126.1, 111.4, 111.3, 106.9, 106.9, 64.8, 60.9, 56.2, 56.2, 55.9, 55.6, 47.0, 42.8, 41.7, 25.6. HRMS (ES+) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_5$ 388.2124; Found 388.2123.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-1,3-benzodioxole-5-acetamide 22. A mixture of 3,4-(methylenedioxy)phenylacetic acid **19** (2 g, 11.11 mmol) and 3,4-dimethoxyphenethylamine **16** (1.87 mL, 11.11 mmol) was stirred at 175 °C in a 100 mL round bottom flask for 14 hours under nitrogen. After cooling, the residue was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was washed with 1 M aqueous HCl (40 mL) and saturated aqueous NaHCO_3 (40 mL). The aqueous layers were extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over anhydrous MgSO_4 , concentrated under vacuum to give **22** as a beige solid (3.89 g) which was used in the next step without further purification.

1-(1,3-Benzodioxol-5-ylmethyl)-3,4-dihydro-6,7-dimethoxyisoquinoline 25. In a 100 mL round bottom flask, a solution of amide **22** (3.89 g, 11.34 mmol) in CH_3CN (40 mL) was treated with POCl_3 (1.08 mL, 11.34 mmol) and stirred at 85 °C for 6 hours. Volatiles were removed under vacuum, the solid residue was partitioned in CH_2Cl_2 (50 mL) and saturated aqueous NaHCO_3 (40 mL) and the aqueous phase was extracted two times with CH_2Cl_2 (2×50 mL). The organic layer was dried over anhydrous MgSO_4 , concentrated under vacuum to give **25** as a yellow foam (3.34 g) which was used in the next step without further purification.

6,7-Dimethoxy-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (28). A solution of **25** (3.34 g, 10.34 mmol) in MeOH (12 mL) was treated with Mel (644 μl , 10.34 mmol) and stirred at

65 °C for 14 hours. Volatiles were removed under vacuum to give a yellow foam (4.80 g) which was diluted in MeOH (50 mL) and treated with NaBH₄ (393 mg, 10.34 mmol) at 0 °C. The mixture was warmed to 23 °C and stirred for 14 hours. Volatiles were removed under vacuum, the solid residue was partitioned in CH₂Cl₂ (50 mL) and H₂O (40 mL) and the aqueous phase was extracted two times with CH₂Cl₂ (2×50 mL). The collected organic layers were dried over anhydrous MgSO₄, concentrated under vacuum and purified by flash chromatography on silica gel (99% EtOAc-1% ammonia) to give **28** as a beige solid (2.61 g, 69% from **19**). mp 117.5–120 °C. IR (ATR) ν 2938, 1609, 1497, 1437, 1360 1251, 1227, 1100, 1030, 920, 845 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 6.69 (d, 1H, *J*=7.9 Hz), 6.63 (d, 1H, *J*=1.6 Hz), 6.55 (s, 1H), 6.53 (dd, 1H, *J*=1.6, 7.9 Hz), 6.11 (s, 1H), 5.89 (dd, 2H, *J*=1.4, 2.8 Hz), 3.83 (s, 3H), 3.62–3.68 (m, 1H), 3.62 (s, 3H), 3.06–3.21 (m, 2H), 2.71–2.88 (m, 3H), 2.55–2.62 (m, 1H), 2.50 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 147.4, 147.3, 146.5, 145.8, 133.9, 129.2, 126.0, 122.7, 111.2, 111.0, 110.2, 108.0, 100.8, 65.0, 55.8, 55.7, 46.9, 42.7, 41.1, 25.4. HRMS (ES+) *m/z* [M+H]⁺ Calcd for C₂₀H₂₄NO₄ 342.1705; Found 342.1707.

General experimental setup for the synthesis of aporphine alkaloids 13, 30 and 34 in flow. The experimental setup consisted of two stream as depicted in Table 1. The first stream (flow rate: 166 μ L/min) equipped with a stainless-steel injection loop (2 mL) loaded with a solution of *N*-methylisoquinoline **6**, **26** or **28** (28 mM) and BF₃·Et₂O (140 mM), meet in a PEEK T-shaped mixer equipped with a 250 μ L frit a second stream (flow rate: 166 μ L/min) consisting of a solution of PIFA (42 mM) in HFIP loaded in a second loop (2 mL). The mixed stream entered in a PEEK coil reactor (20 mL, 0.75 mm id, 23 °C) at a flow rate of 332 μ L/min and the resulting aporphine alkaloids were collected in a flask containing 1 mL of MeOH and 6 mL of CH₂Cl₂. The resulting mixture was hydrolyzed with saturated aqueous NaHCO₃ and extracted three times with CH₂Cl₂ (3×20 mL). The collected organic layers were dried over anhydrous MgSO₄, concentrated under vacuum and purified by flash chromatography on silica gel.

Glaucine (13). Purification by flash chromatography on silica gel (89% EtOAc – 10% MeOH – 1% ammonia) gave **13** as a yellow oil (16.3 mg, 82%). IR (ATR) ν 2933, 2842, 2786, 1633, 1597, 1511, 1458, 1253, 1111, 1088 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (s, 1H), 6.78 (s, 1H), 6.59 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.64 (s, 3H), 2.99–3.23 (m, 4H), 2.48–2.72 (m, 3H), 2.48 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 151.9, 148.0, 147.5, 144.3, 129.3, 128.9, 127.1, 126.9, 124.5, 111.6, 110.8, 110.4, 62.6, 60.2, 55.9, 55.8, 55.8, 53.3, 44.0, 34.6, 29.3. HRMS (ES+) *m/z* [M+H]⁺ calcd for C₂₁H₂₆NO₄ 356.1862; Found 356.1858.

Rogersine (30). Purification by flash chromatography on silica gel (99% EtOAc – 1% ammonia) gave **30** as a yellow oil (6.5 mg, 34%). IR (ATR) ν 2922, 2852, 1510, 1457 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.05 (s, 1H), 6.81 (s, 1H), 6.58 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.64 (s, 3H), 2.94–3.22 (m, 5H), 2.50–2.71 (m, 2H), 2.50 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 152.1, 145.4, 145.0, 144.3, 130.0, 128.8, 127.2, 124.0, 114.1, 111.3, 110.3, 87.6, 62.6, 60.3, 56.1, 55.9, 53.4, 43.8, 34.2, 29.1. HRMS (ASAP+) *m/z* [M+H]⁺ Calcd for C₂₀H₂₄NO₄ 342.1705; Found 342.1703.

Nantenine (34). Purification by flash chromatography on silica gel (94% CH₂Cl₂ – 5% MeOH – 1% Et₃N) gave **34** as a yellow oil (14.5 mg, 76%). IR (ATR) ν 2906, 1589, 1474, 1241, 1179, 1037, 736 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 7.93 (s, 1H), 6.75 (s, 1H), 6.59 (s, 1H), 5.96 (dd, 2H, *J*=1.4, 4.8 Hz), 3.87 (s, 3H), 3.65 (s, 3H), 2.94–3.19 (m, 5H), 2.63–2.70 (m, 1H), 2.52 (s, 3H), 2.46–2.56 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 152.0, 146.6, 146.4, 144.5, 131.0, 128.7, 127.4, 127.1, 125.7, 110.7, 109.0, 108.4, 101.0, 62.6, 60.3, 55.9, 53.3, 44.1, 35.3, 29.3. HRMS (ASAP+) *m/z* [M+H]⁺ Calcd for C₂₀H₂₂NO₄ 340.1549; Found 340.1551.

General experimental setup for the synthesis of morphinane-dione alkaloids 3 and 35 in flow. The experimental setup consisted of two stream as depicted in Table 2. The first stream (flow rate: 166 μ L/min) equipped with a stainless-steel injection loop (5 mL) loaded with a solution of *N*-methylisoquinoline **6**, **15** or **28** (28 mM) and PIDA (28 mM) in CH₃CN meet in a PEEK T-shaped piece (internal volume 0.57 μ L) a second stream (flow rate: 166 μ L/min) consisting of a solution of TMSOTf (56 mM) [and *p*-TSA (84 mM) in the case of **35**] loaded in a second loop (5 mL). The mixed stream entered in a PEEK coil reactor (5 mL, 0.75 mm id, 23 °C) at a flow rate of 332 μ L/min and the resulting morphinane-dione alkaloids were collected in a flask containing 10 mL of saturated aqueous NaHCO₃. The resulting mixture was diluted with CH₂Cl₂ (20 mL) and extracted three times with CH₂Cl₂ (2×20 mL). The collected organic layers were dried over anhydrous MgSO₄, concentrated under vacuum and purified by flash chromatography on silica gel.

Sebiferine (3). Purification by flash chromatography on silica gel (94% CH₂Cl₂ – 5% MeOH – 1% ammonia) gave **3** as a red oil (38.9 mg, 82% from **6** and 7.5 mg, 15% from **15**). IR (ATR) ν 2926, 1665, 1641, 1617, 1512, 1448, 1219, 1167, 1100, 1005 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 6.80 (s, 1H), 6.63 (s, 1H), 6.35 (s, 1H), 6.33 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.70 (d, 1H, *J*=6.0 Hz), 3.34 (d, 1H, *J*=17.9 Hz), 3.04 (dd, 1H, *J*=6.0, 17.9 Hz), 2.56–2.60 (m, 2H), 2.46 (s, 3H), 1.82–1.99 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 181.1, 161.8, 151.5, 148.5, 148.1, 130.1, 128.9, 122.4, 118.9, 110.5, 108.7, 61.0, 56.4, 56.0, 55.2, 45.8, 42.4, 41.8, 41.3, 32.8. HRMS (ASAP+) *m/z* [M+H]⁺ Calcd for C₂₀H₂₄NO₄ 342.1705; Found 342.1704.

Amurine (35). Purification by flash chromatography on silica gel (94% CH₂Cl₂ – 5% MeOH – 1% Et₃N) gave **35** as a yellow oil (34.6 mg, 76%). IR (ATR) ν 2923, 1667, 1642, 1483, 1221, 1174, 1034 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 6.83 (s, 1H), 6.61 (s, 1H), 6.32 (s, 1H), 6.29 (s, 1H), 5.93 (dd, 2H, *J*=1.4, 10.0 Hz), 3.79 (s, 3H), 3.68 (d, 1H, *J*=6.0 Hz), 3.32 (d, 1H, *J*=18.0 Hz), 3.01 (dd, 1H, *J*=6.0, 18.0 Hz), 2.57–2.61 (m, 2H), 2.46 (s, 3H), 1.79–1.94 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 181.0, 161.2, 151.5, 147.0, 146.9, 131.1, 129.6, 122.5, 118.8, 107.7, 105.3, 101.4, 60.8, 55.2, 45.8, 42.5, 41.8, 41.2, 33.0. HRMS (ASAP+) *m/z* [M+H]⁺ Calcd for C₁₉H₂₀NO₄ 326.1392; Found 326.1389.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Alkaloids · Flow chemistry · Hypervalent iodine · Natural products · Oxidation

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