Sequential One-Pot Vilsmeier-Haack and Organocatalyzed Mannich Cyclizations to Functionalized Benzoindolizidines and Benzoquinolizidines

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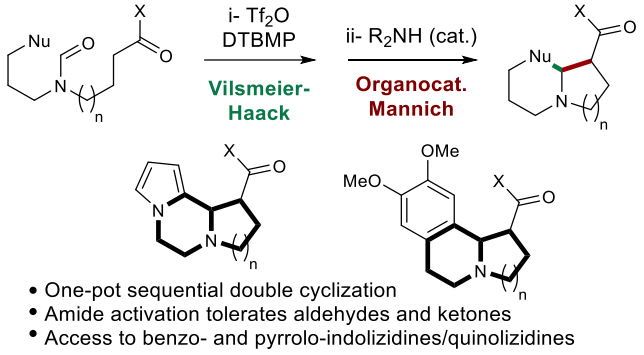


Abstract: The development of a new one-pot sequential cyclizations involving a Vilsmeier-Haack reaction followed by an organocatalyzed Mannich reaction is reported. This synthetic strategy gives access to functionalized indolizidines and quinolizidines in one operation from readily synthesized precursors. Yields and diastereoselectivities are good to excellent when formamides are used to trigger

the key step, bearing either an electron-rich aryl or a pyrrole as the nucleophilic partner in the first cyclization.

Introduction

Substituted indolizidines and quinolizidines are attractive molecular scaffold because of their high occurrence in natural products exhibiting notable biological activity, as represented by the *Erythrina* family (erythraline shown), (+)-oleracein E, (+)-harmicine, (–)-tangutorine, and vincamine (Figure 1).[1] These scaffolds could also be found in several drugs developed by the pharmaceutical industry.

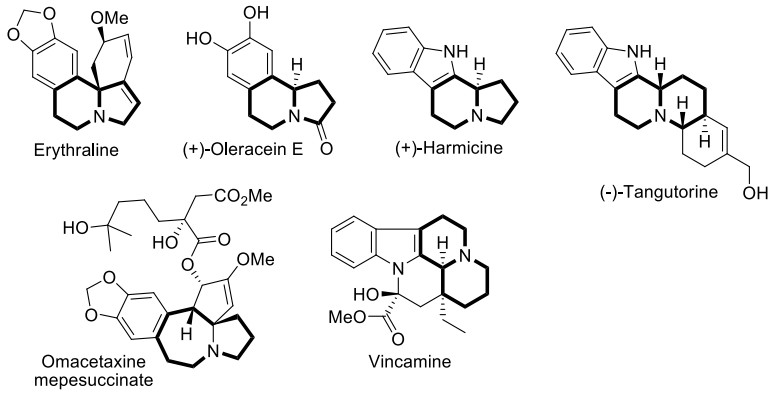
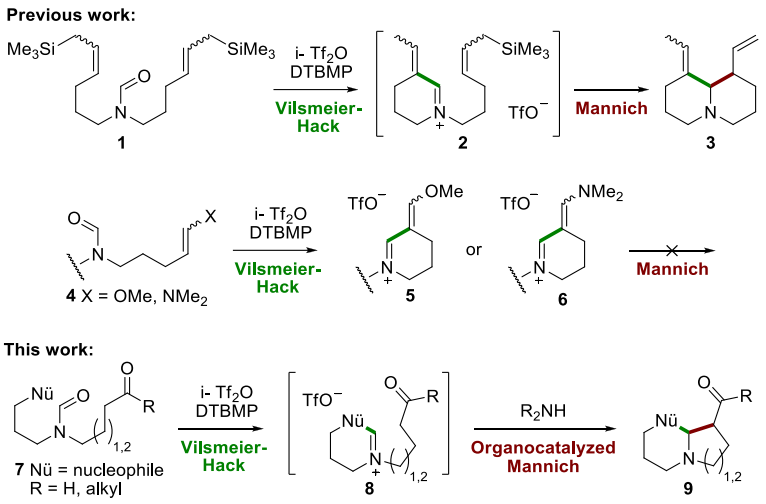


Figure 1. Representative indolizidine, quinolizidine, and cyclohexapiperazine alkaloids and drugs.

In our previous work, we reported an original approach with two consecutive nucleophilic cyclizations onto an activated amide **1** to access quinolizidines **3** (Scheme 1).[2] The originality of such an approach resides in its complementarity with reported double cyclization strategies usually involving C-N bond formation.[3] However, one of the limitations of our initial approach is the second cyclisation (Mannich), suffering from reactivity issues. Indeed, the conjugated iminium intermediate **2** could be trapped only with an allylsilane, an allylstannane, or an indole as the nucleophile. The use of a stronger nucleophile, such as an enol ether or an enamine **4**, is not possible because that nucleophile reacts in the first cyclization, leading to a conjugated iminium intermediate **5**/**6** that is essentially not reactive for the last

cyclization step. Another limitation to this initial work is the poor functionalization of the final quinolizidine **3**, substituted with only alkenes that would need to be differentiated in order to further transform this scaffold into natural products or drugs. Although strategies to increase the reactivity of the iminium ion for the Mannich cyclization were envisaged, a simpler solution is to rather increase the reactivity of the nucleophile. To do so, we need to run the Vilsmeier-Haack cyclization in the presence of a latent nucleophile that would be unveiled after the Vilsmeier-Haack cyclization. One of the best carbon π-nucleophile we thought would fit this requirement is an enamine, prepared in situ from the corresponding aldehyde or ketone **8**. This way, we expect to be able to widen the range of accessible molecular scaffolds containing indolizidines and quinolizidines **9**, with suitable strategic functionalization for synthetic applications.

Scheme 1. Targeted transformation.



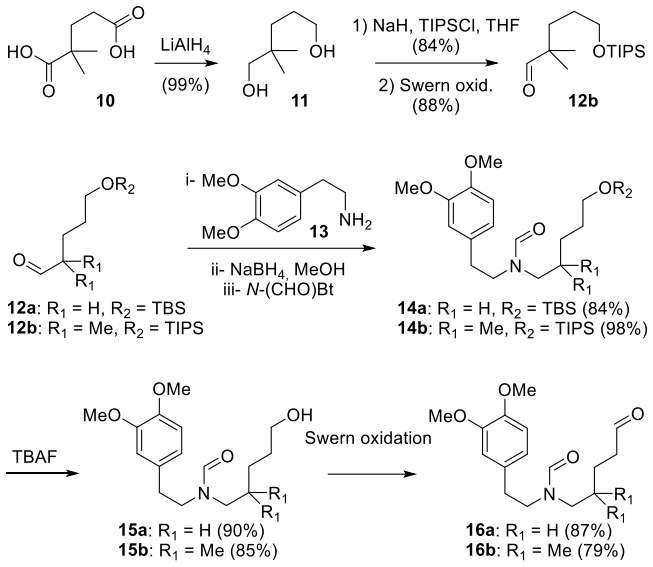
Although organocatalyzed Mannich reactions have been extensively studied,[4,5] using such a reaction in a one-pot sequential process presents significant challenges. Firstly, the amide activation for the Vilsmeier-Haack cyclization needs to be performed chemoselectively in the presence of a ketone or an aldehyde **7**.[6] Secondly, the iminium intermediate **8** has to be stable enough in solution so that a complete

Vilsmeier-Haack cyclization occurs before the addition of amine to launch the intramolecular Mannich reaction. Thirdly, water generated during the amine condensation with the aldehyde or ketone **8** should not hydrolyze the remaining iminium intermediate **8**. Fourthly, the amine added for enamine formation must not react with iminium intermediate **8**, or at least not irreversibly. Lastly, enamine regioisomers resulting from amine condensation with the ketone **8** should reversibly interconvert so that ring size in the organocatalyzed Mannich cyclization could be controlled.

Results and Discussion

We started our investigation by testing the reaction cascade on substrates bearing an aldehyde. Substrates **16a** and **16b** were prepared according to the route detailed in Scheme 2. Quantitative reduction of 2,2-dimethylglutaric acid (**10**) followed by monoprotection and Swern oxidation afforded aldehyde **12b**.[7] Aldehydes **12a**[8] and **12b** were then independently subjected to three consecutive steps performed one-pot, starting with a condensation with amine **13** followed by reduction of the corresponding imine and formylation with *N*-formylbenzotriazole (*N*-(CHO)Bt). After deprotection of silyl ethers **14a**,**b**, a Swern oxidation afforded the desired aldehydes **16a** and **16b**.

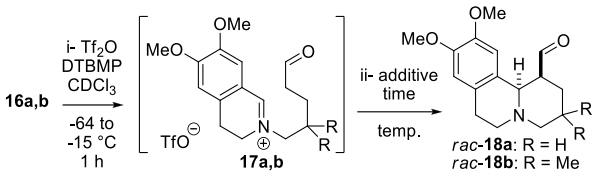
Scheme 2. Synthesis of aldehydes **16a**,**b**.



Upon treatment of substrate **16a** with triflic anhydride, we were pleased to see a complete amide activation and trapping of the resulting triflyliminium ion with the aryle to generate the iminium ion intermediate **17a** with satisfactory preservation of the aldehyde group (Table 1). To the best of our knowledge, this is the first report of a chemoselective amide activation and nucleophilic trapping in the presence of an aldehyde.[6] This Vilsmeier-Haack cyclization was performed at low temperature (–64 to –15 °C) over a period of one hour. Three equivalents of piperidine were added and quinolizidine **18a** was obtained in 30% yield as a single *trans*-diastereomer (entry 1). To ensure that the Mannich cyclization was catalyzed by piperidine, the non-catalyzed background reaction was tested (no piperidine added) and no quinolizidine was observed (entry 2). To discard any catalytic effect of piperidine due to simple enolization of the aldehyde rather than formation of an enamine, the reaction was tested in acidic (CSA, entry 3) or basic (Et_3N, entry 4) conditions. Again, no conversion occurred. Temperature proved to be critical: increasing temperature from –15 °C to rt or to 70 °C resulted in a dramatic yield loss (entries 5, 1, and 6, respectively). To better understand this observation, we activated amide **16a** without treating

with piperidine afterward, and proved by ^{1}H NMR that iminium ion **17a** decomposed at 0 °C in less than 30 min.

Table 1. Development of one-pot Vilsmeier-Haack/organocatalyzed Mannich cyclizations.[a]



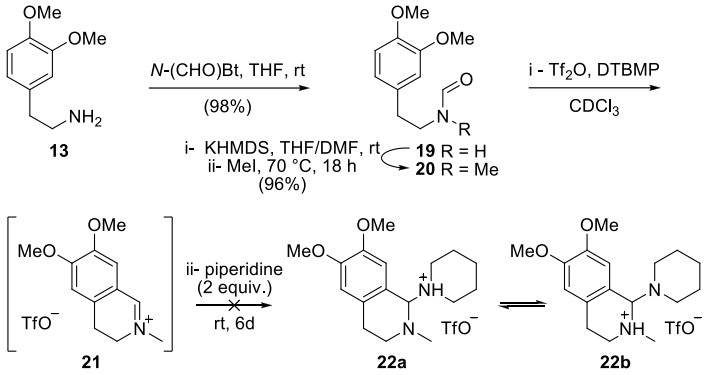
Entry	Substrate	Additive (equiv.)	Time	Temperature (°C)	Product (yield)	d.r.[d]
1	**16a**	Piperidine (3)	3 d	rt	**18a** (30%)	> 19:1
2	**16a**	None	3 d	rt	0	
3	**16a**	CSA (5)	3 d	rt	0	
4	**16a**	Et_3N (3)	3 d	rt	0	
5	**16a**	Piperidine (3)	3 d	–15	40	
6	**16a**	Piperidine (3)	3 d	70	**18a** (< 20%)	> 19:1
7	**16a**	Piperidine (15)[b]	3 d	–15	**18a** (52%)	> 19:1
8	**16a**	Pyrrolidine (3)	18 h	–15	**18a** (45%)	> 19:1
9	**16b**	Piperidine (3)	18 h	–15	**18b** (37%, 63% brsm[c])	7.5:1

[a]Reaction conditions for the Vilsmeier-Haack cyclization (**16** to **17**): i- Tf_2O (1.1 equiv.), DTBMP (1.1equiv.), $CDCl_3$ (0.05 M), –64 °C to –15 °C, 1 h. [b]The reaction mixture was diluted to 0.003 M with $CDCl_3$. [c]Yield based on recovered starting material **16b**. [d]Diastereomeric ratio determined by ^{1}H NMR analysis of crude material.

Besides the poor stability of iminium intermediate **17a**, we thought two other factors could impede the overall conversion. One is a competition between intra- and intermolecular addition of the transient piperidine enamine of aldehyde **17a**. Hence, to favor intramolecular attack of the enamine, dilution of the reaction medium before addition of piperidine was operated and, interestingly, the yield improved

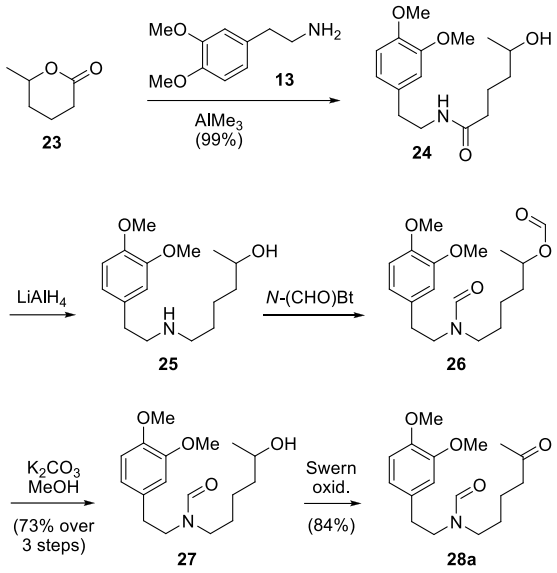
significantly, now up to 52% (entry 7). The second factor is a possible competitive addition of piperidine onto the iminium portion of intermediate **17a** rather than on the aldehyde. If the addition on the iminium ion occurs and is poorly reversible, the final Mannich cyclization would be hampered and intermediate **17a** (or its piperidine adduct) would decompose over time. To verify this last hypothesis, a model substrate lacking the aldehyde portion was synthesized (Scheme 3). Substrate **20** was prepared from amine **13** in two almost quantitative steps. Upon activation, amide **20** was trapped with the aryl group. Piperidine was then added to the resulting iminium ion **21**. After six days at room temperature, analysis of the ^{1}H NMR spectrum showed that integrity of iminium ion **21** was preserved, without any observable addition of piperidine to form ammonium **22a** and/or **22b**. This prove that addition of the secondary amine is either not occurring, or is reversible with a strong preference toward conjugated iminium ion **21** over ammonium ions **22a**,**b**. It should be noted that the observed stability of iminium **21** over six days at rt is a strong indication that the low stability of iminium ion **17a** is due to the aldehyde portion of the molecule. Switching to pyrrolidine (Table 1, entry 8) accelerated the overall process, and the yield was slightly better than with piperidine (entry 5). To increase the yield, it seemed that the possible options were to accelerate the organocatalyzed Mannich reaction or to improve the stability of the iminium intermediate. To accelerate the Mannich reaction, we opted for a Thorpe-Ingold effect by adding a *gem*-dimethyl group on the alkyl chain containing the aldehyde, combined to a reduction of reaction time to limit a possible degradation of iminium intermediate **17b**. The anticipated acceleration did not materialize: roughly the same yield was obtained with substrates **16b** (37%, entry 9) and **16a** (40%, entry 5), with an incomplete conversion for the *gem*-dimethylated substrate **16b** in the former case.[9,10]

Scheme 3. Possible piperidine addition to iminium intermediate.



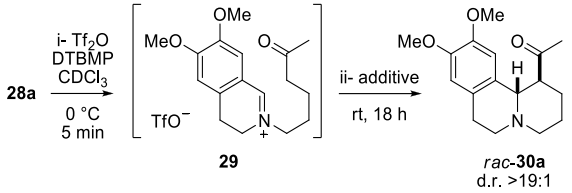
To improve the stability of the iminium intermediate, we decided to switch to ketones instead of aldehydes. Therefore, keto-amide **28a** was prepared following the synthetic sequence presented in Scheme 4. The synthesis started with the quantitative opening of lactone **23** with amine **13** using $AlMe_3$, followed by reduction of the resulting amide **24** to amino alcohol **25**. Attempts to perform a selective formylation of the amine gave mixtures of monoformylated product **27** and *N*,*O*-diformylated congener **26**. We thus decided to perform an extensive formylation to **26** followed by a selective formate methanolysis to successfully afford alcohol **27** in 73% yield over the last three steps. A Swern oxidation furnished the desired keto-amide **28a**.

Scheme 4. Synthesis of ketone **28a**.



After activation of amide **28a** in the usual conditions, we were pleased to observe that iminium intermediate **29** was much more stable than its aldehyde analogue **17a** or **17b**; the Vilsmeier-Haack reaction could now be run at 0 °C for only 5 min, and the integrity of iminium intermediate **29** is preserved at room temperature over at least 18 h (proven by ^{1}H NMR). Preliminary tests with substrate **28a** using three equivalents of pyrrolidine or piperidine afforded the desired compound **30a** as a single diastereomer in good yields (Table 2, entries 1 and 2, respectively), with pyrrolidine being the best catalyst for the ketone substrate as well.

Table 2. Screening of amines.[a]



Entry	Additive	Yield (%)
1	Pyrrolidine	73
2	Piperidine	44
3	None	0
4	CSA	0
5	Et_3N	0
6	Morpholine	51
7	Et_2NH	48
8	Cyclohexylamine	45
9	Pyrrolidine (0.5 equiv.) + DIPEA (2 equiv.)	55

[a] Reaction conditions: i- Tf_2O (1.1 equiv.), DTBMP (1.1equiv.), $CDCl_3$ (0.05 M), 0 °C, 5 min; ii- additive (3 equiv.), rt, 18 h.

Because the condensation of an amine with a ketone may present different kinetics than with an aldehyde, it was necessary to rule out the uncatalyzed Mannich reaction with this ketone substrate as well. Hence, we proved that the secondary amine was necessary for the second cyclisation (entry 3) and that acid or base-promoted enolization of the ketone (and subsequent Mannich) is not operating (entries 4 and 5, respectively). Other secondary (morpholine and diethylamine, entries 6 and 7, respectively) or primary (cyclohexylamine, entry 8) amines all furnished bicyclic product **30a** in similar yields. The amount of needed secondary amine catalyst was determined by ^1H NMR experiment. After amide activation and Vilsmeier-Haack cyclization, there is one equivalent of 2,6-di-*tert*-butyl-4-methylpyridinium triflate

(DTBMP•HOTf) generated. Because the secondary amines tested are more basic than DTBMP, three equivalents of secondary amine were necessary to observe one equivalent of basic amine in solution.[11] Lower amounts of secondary amine (down to 0.5 equiv. of pyrrolidine) still catalyze the reaction, but a tertiary amine (2 equiv. of DIPEA) is usually needed to ensure enough non protonated secondary amine is present in solution (entry 9). Higher amounts of secondary amine (up to 35 equivalents) accelerate the reaction, but ruins any ^{1}H NMR analysis of the progression of the reaction.

When we get a closer look at the major diastereomers of quinolizidines **18a** and **30a** (Figure 2), in the aldehyde and ketone series, respectively, we notice an intriguing opposite diastereomeric relation. We explain this difference with a model presented in Scheme 5. The Mannich cyclization of aldehyde enamine **31** or ketone enamine **32** should process through the least hindered transition state **TS1** also presenting the lowest global dipole. Therefore, the direct diastereomeric product of cyclization should be *cis* and presents an equatorially oriented carbonyl substituent. However, the less congested axially oriented carbonyl in the *trans* isomer should be thermodynamically favored, now allowing a *trans* ring junction in the quinolizidine portion of the molecule (c.f. X-ray structures of **18a** and **30a**, Figure 2).[12,13] Epimerization to the axial carbonyl group necessitates enolization, either to the corresponding enamine (**34**, X = pyrrole) or ketone (**34**, X = O). Such enolization is not likely in the ketone series, presenting severe steric interactions in **34** (R = Me) and this may account for the observed *trans* isomer in the aldehyde series only. This rationale applies to all quinolizidines and indolizidines found in Table 3 (*vide infra*).

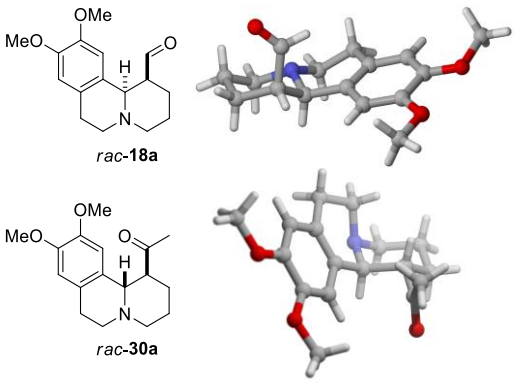
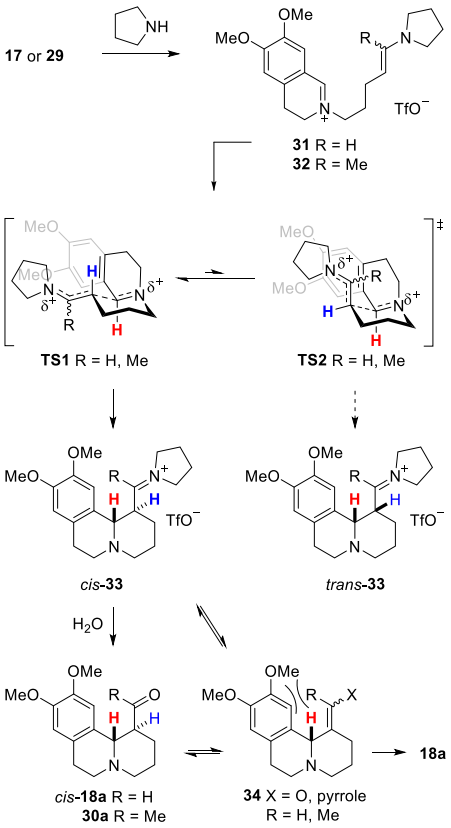


Figure 2. X-ray structures of quinolizidines **18a** and **30a**.[12]

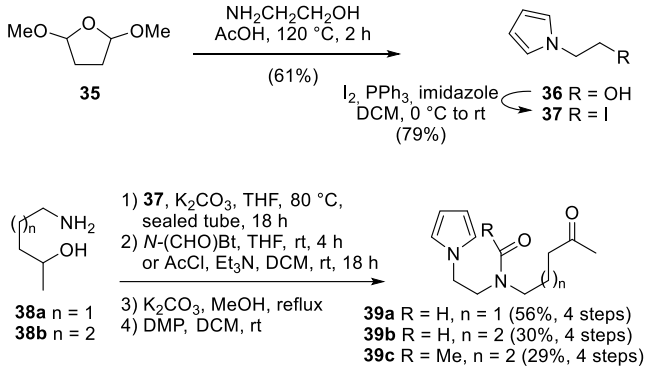
Scheme 5. Mechanistic proposition for diastereoselectivities observed in **18a** and **30a**.



The scope of the reaction was studied with a series of veratrole substrates bearing a formamide or acetamide, linked to a ketone with different tether length. Those substrates (**28b-f**, depicted in Table 3) were synthesized following the strategy described in Scheme 4, starting with lactones of different ring

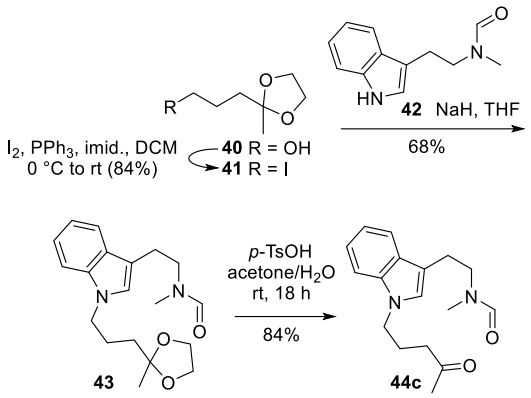
sizes. We also investigated heteroaromatic nucleophiles for the initial Vilsmeier-Haack cyclization. Pyrrole substrates **41a-c** were synthesized according to the route described in Scheme 6. Iodoethylpyrrole **37** was obtained from condensation of commercially available 2,5-dimethoxytetrahydrofuran (**35**) and 2-aminoethanol followed by iodination.[14] Amines **38a**,**b** were then alkylated with iodide **37** and the corresponding amino alcohol were bis-formylated then selectively methanolyzed. The resulting amido alcohols were oxidized using Dess-Martin periodinane to afford the desired compound **39a-c**.

Scheme 6. Preparation of pyrrole substrates.



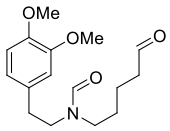
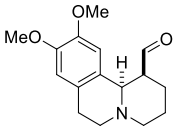
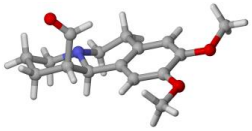
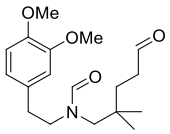
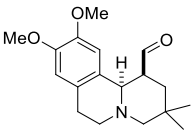
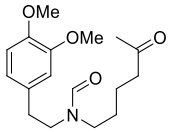
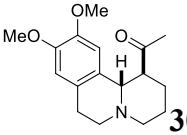
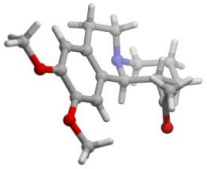
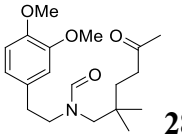
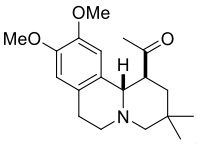
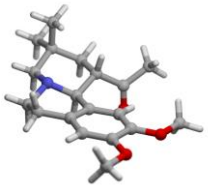
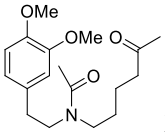
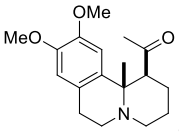
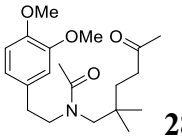
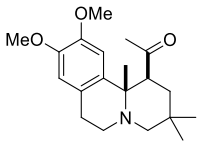
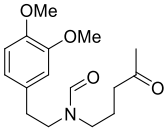
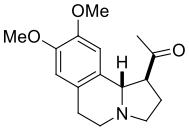
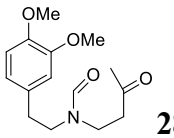
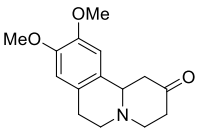
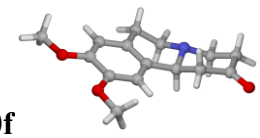
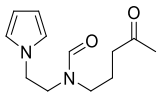
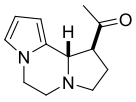
Finally, indole substrates were also prepared. 3-Substituted *N*-methylindoles **44a**,**b** (depicted in Table 3) were obtained from 1-methyltryptamine following the strategy described in Scheme 4, whereas compound **44c** necessitated a different approach (Scheme 7). The ketone chain was prepared from alcohol **40**.[15] Iodination and *N*-alkylation with the anion of indole **42**[16] afforded dioxolane **43**, which was hydrolyzed to the desired ketone **44c**.

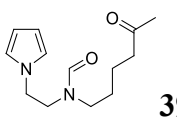
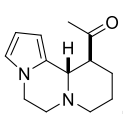
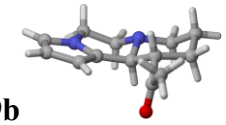
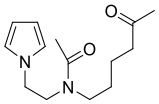
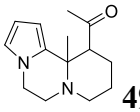
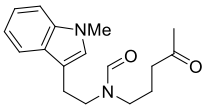
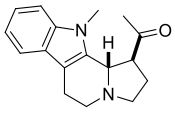
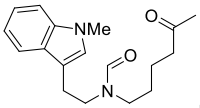
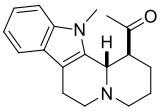
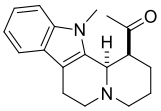
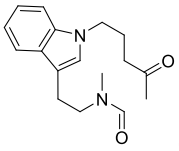
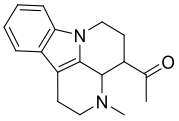
Scheme 7. Preparation of indole substrates.



The Vilsmeier-Haack cyclization is *endo-exo* according to Ben-Ishai nomenclature for sp^2 nucleophiles reacting with sp^2 electrophiles.[17] Hence, the electrophilic triflyliminium ion resulting from amide activation is endocyclic with respect to the ring in formation, and the nucleophile is exocyclic for all substrates of Table 3, except for **28f**, which presents an *endo-endo* cyclization mode.[18] The Vilsmeier-Haack cyclization was run at –15 °C over one hour for aldehyde substrates **16a**,**b**, whereas higher temperature (0 °C) and shorter time (5 min) were sufficient for ketones substrates when formamides (**28a**, **28b**, **28e**, **28f**,**39-c**, and **446a-c**) were activated. In cases of activation of acetamides (**28c** and **28d**), the Vilsmeier-Haack cyclization necessitated prolonged reaction time (4 h) at room temperature. The Mannich cyclization catalyzed by piperidine gave higher yields with aldehydes **16a**,**b**, but in general, pyrrolidine was the best catalyst. In all cases, the secondary amine for the organocatalyzed Mannich cyclization was used in excess (3-6 equivalents), and the best conditions are reported in Table 3. Chloroform and dichloromethane were both good solvents for the sequential one-pot double cyclizations.

Table 3. Substate scope.[a]

Entry	Substrate	Product[12,13]	Yield (%)	d.r.[j]
1[b]	 **16a**	 **18a** 	52[e]	> 19:1
2[b]	 **16b**	 **18b**	37 (63 brsm)[f]	7.5:1
3	 **28a**	 **30a** 	73[g]	> 19:1
4	 **28b**	 **30b** 	73	10.5:1
5[c]	 **28c**	 **30c**	24[h]	> 19:1
6[c]	 **28d**	 **30d**	18	> 19:1
7[d]	 **28e**	 **30e**	95	> 19:1
8[d]	 **28f**	 **30f** 	30[i]	---
9	 **39a**	 **49a**	87	> 19:1

10	 **39b**	 **49b** 	92[h]	> 19:1
11[d]	 **39c**	 **49c**	<5	n.d.
12	 **44a**	 **50a**	18	> 19:1
13	 **44b**	 ***cis*-50b**  ***trans*-50b**	49[h]	***cis*:*trans*** = 1.1:1
14	 **44c**	 **50c**	26	n.d.[k]

[a]Reaction conditions: i- Tf_2O (1.1 equiv.), DTBMP (1.1equiv.), $CDCl_3$ (0.05 M), 0 °C, 5 min; ii- pyrrolidine (3 equiv.), rt, 18 h. [b]The Vilsmeier-Haack cyclization was run at –15° C for 45-60 min. [c]The Vilsmeier-Haack cyclization was run at rt for 4 h. [d]Reaction run in DCM. [e]Reaction medium was diluted with $CDCl_3$ to 0.003 M prior to the addition of piperidine (15 equiv.). The Mannich cyclization was run at –15 C for 3 d. With pyrrolidine (3 equiv.), 45% yield was obtained. [f]Piperidine (3 equiv.) was used for the Mannich cyclization at –15 C for 18 h. [g]With piperidine (3 equiv.), 44% yield was obtained. [h]6 equiv. of pyrrolidine were used. [i]1.5 equiv. of pyrrolidine was used.[j]Diastereomeric ratio determined by ^{1}H NMR analysis of crude material. [k]Major diastereomer not assigned.

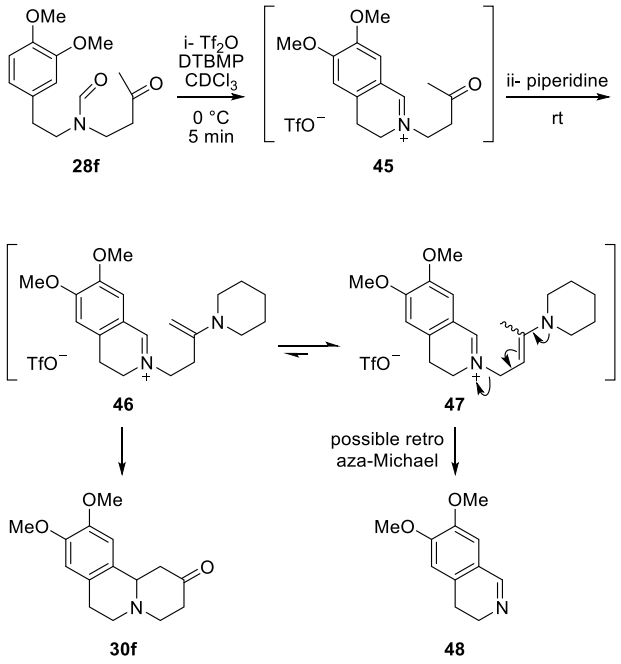
As for aldehydes **16a**,**b** (entries 1 and 2), the *gem*-dimethyl had essentially no effect on the rate and yield for the Mannich cyclization of ketone substrates **28a**,**b** (entries 3 and 4, respectively). For ketone **28a**, we obtained 73% overall yield for the double cyclizations using pyrrolidine in the organocatalyzed Mannich reaction, whereas only 44% yield was obtained when using piperidine. From here, all other substrates were treated with pyrrolidine only.

Formation of a quaternary center at ring junction from the activation of acetamides **28c** and **28d** compared to their formamide congeners **28a** and **28b**, respectively, revealed to be challenging, as expected

(entries 3-6). Here too, no Thorpe-Ingold acceleration was observed with the *gem*-dimethylated substrates **28b** (c.f entries 3 vs 4) or **28d** (c.f entries 5 vs 6).

Formation of a 5-membered ring in the Mannich cyclization was much more efficient (c.f. entries 3 vs 7), with a nearly quantitative overall yield for indolizidine **30e**. It should be noted that in cases depicted in entries 3-7, condensation of the secondary amine with the ketone results in the most substituted, thermodynamically favored enamine for the Mannich cyclization. However, in entry 8, the enamine needs to be formed in the terminal position (see **46**, Scheme 8). If enamines **46** and **47**equilibrate rapidly, low concentration of terminal enamine **46** is expected, thus slowing the Mannich reaction. Hence, side reaction may take place, such as intermolecular addition of thermodynamic enamine **47** onto iminium ion or retro aza-Michael reaction leading to fragmented product **48**, which might account for the low yield observed for quinolizidine **30f** (Table 3, entry 8).

Scheme 8. Possible side reactions with substrate **28f**.



For substrates bearing a pyrrole instead of a veratrole unit as the nucleophilic partner in the Vilsmeier-Haack cyclization, we observed comparable good to excellent yields for the formation of indolizidines (cf. **30e**, entry 7, and**49**, entry 9) and quinolizidines (cf. **30a**, entry 3, and **49b**, entry 10). For pyrrole substrate **49c** (entry 11) as for veratrole substrate **28c** (entry 5), formation of quaternary center at ring junction from activation of an acetamides proved to be difficult.

When indole is used as the initial nucleophile in the Vilsmeier-Haack cyclization, the ensuing organocatalyzed Mannich reaction is much less efficient (see substrates **44a**-**c**, entries 12-14). A greater steric hindrance around the iminium intermediate **53** generated by the *N*-substituted indole ring likely accounts for the low overall yield, when compared to veratrole **51** or pyrrole **52** analogues (Figure 3).

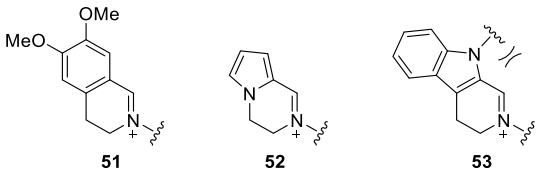


Figure 3. Congestion around iminium ion intermediates **51**, **52**, and **53**.

Conclusion

In conclusion, we successfully developed a new one-pot reaction sequence involving a Vilsmeier-Haack cyclization followed by an organocatalyzed Mannich cyclization as a rapid access to benzo- and pyrrolo-indolizidines and quinolizidines. The Vilsmeier-Haack first cyclization is compatible with electron-rich aryl and pyrrole nucleophiles, as well as with free ketones and even free aldehydes, to a certain extent. Higher yields were obtained when formamides were reacted compared to their acetamide congeners. The iminium intermediate resulting from Vilsmeier-Haack cyclization does not interfere with the enamine formation necessary for the organocatalyzed Mannich cyclization. The latter gave generally higher yields

when pyrrolidine was used as the secondary amine, and proved to be much more efficient in this organocatalyzed variant than in our initially reported allylsilane version. Precursors to the key double cyclizations are easily accessible, and the key transformation gives high diastereoselectivities. This new synthetic strategy is suitable for the preparation of libraries of functionalized indolizidines and quinolizidines as privileged structures to explore new chemical spaces in medicinal chemistry programs.

Experimental Section

General Information. All reactions requiring anhydrous conditions were conducted in flame-dried glassware under a dry nitrogen or argon atmosphere. Compounds lacking experimental details were prepared according to the literature as cited and are in agreement with published spectra. THF was distilled from Na and benzophenone at atmospheric pressure. DCM, toluene, diisopropylethylamine, triethylamine and pyrrolidine were distilled from CaH_2 at atmospheric pressure. Triflic anhydride (Tf_2O), TFAA and chlorobenzene were distilled over a small amount of P_2O_5 at atmospheric pressure prior to use. Methanol was distilled over 4 Å molecular sieves at atmospheric pressure. 2,6-di-*tert*-Butyl-4-methylpyridine (DTBMP) was synthesized following the reported procedure in literature.[19] All other required fine chemicals were used directly without purification. Thin layer chromatography (TLC) was conducted with pre-coated 60 Å 250 μm silica gel plates with F-254 indicator and visualized using a combination of UV and anisaldehyde, ceric ammonium molybdate, iodine on silica, or potassium permanganate staining. Flash column chromatography was performed using silica gel (230–400 mesh). IR spectra were recorded with a FTIR instrument by applying substrates as thin films. ^{1}H and proton-decoupled ^{13}C NMR spectra were recorded on 300 MHz and/or 400 MHz spectrometers. All chemical shifts are referenced to residual non-deuterated solvent. ^{1}H NMR coupling constants are reported in Hertz and refer to apparent multiplicities and not true coupling constants. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)],

integration, coupling constants [Hz]). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm. Mass spectra were recorded with an ESI-Q-TOF instrument.

Usual Reaction Workup and Purification. After addition of the indicated aqueous solution, layers were separated. The aqueous phase was extracted with the indicated solvent, and the combined organic phases were washed with the indicated aqueous solution (if needed), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude material was purified by flash chromatography using silica gel with the indicated eluent.

2,2-Dimethylpentane-1,5-diol (11). A solution of 2,2-dimethylglutaric acid (10, 5.0 g, 31.2 mmol) in Et_2O (12.0 mL) was added dropwise to a solution of $LiAlH_4$ (4.0 g, 106 mmol) in Et_2O (170 mL) at 0 °C and the mixture was refluxed for 18 h. The resulting mixture was cooled at 0 °C and quenched with water (4.0 mL). An aqueous solution of NaOH (15%, 4.0 mL) and water (12.0 mL) were added, and the mixture was stirred vigorously at rt for 3 h. Anhydrous Na_2SO_4 was added and the mixture was stirred for 15 min, filtered over Celite and concentrated under reduced pressure to afford **11** as a colorless oil (4.21 g, 99%). The residue was used directly in the next step. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.64 (t, *J* = 6.3 Hz, 2H), 3.33 (s, 2H), 1.75 (br s, 2H), 1.59 – 1.49 (m, 2H), 1.34 – 1.28 (m, 2H), 0.88 (s, 6H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 71.0 (t), 63.3 (t), 34.9 (s), 34.3 (t), 26.9 (t), 24.3 (q). **IR** (neat) ν (cm^{-1}) 3318 (br), 2943, 2869. **HRMS** (positive ESI) Calcd for $C_7H_{16}O_2Na$ [M*Na*$^+$]: 155.1043, found 155.1044.

2,2-Dimethyl-5-((triisopropylsilyl)oxy)pentanal (12b). A solution of crude **11** (9.54 g, 72.2 mmol) in THF (38 mL) was added dropwise over 20 min to a suspension of NaH (60% dispersion in mineral oil, 5.77 g, 144 mmol) in THF (150 mL) at 0 °C. The mixture was stirred for 30 min at rt then cooled to 0 °C. A solution of TIPSCl (15.6 mL g, 72.8 mmol) in THF (12 mL) was added dropwise and the solution was stirred at 0 °C for 40 min. Water was added and the usual work-up (Et_2O) and purification (2 to 6% EtOAc in hexanes) afforded 2,2-dimethyl-5-((triisopropylsilyl)oxy)pentan-1-ol (17.5 g, 84%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.69 (t, *J* = 6.5 Hz, 2H), 3.35 (d, *J* = 6.0 Hz, 2H), 1.59 – 1.48 (m,

3H), 1.34 – 1.29 (m, 2H), 1.09 (s, 21H), 0.90 (s, 6H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 71.8 (t), 64.3 (t), 35.0 (s), 34.5 (t), 27.5 (t), 24.1(q), 18.1 (q), 12.1 (d). **IR** (neat) ν (cm^{-1}) 3345 (br), 2942, 2891, 2865. **HRMS** (positive ESI) Calcd for $C_{16}H_{36}O_2SiNa$ [M*Na*$^+$]: 311.2377, found 311.2385. DMSO (5.0 mL, 70.3 mmol) was added to a solution of oxalyl chloride (3.43 mL, 40.6 mmol) in DCM (200 mL) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C then a solution of 2,2-dimethyl-5-((triisopropylsilyl)oxy)pentan-1-ol (7.80 g, 27.0 mmol) in DCM (135 mL) was added. Stirring was continued for 1 h at -78 °C then triethylamine (18.7 mL, 135 mmol) was added. The solution was stirred for 1 h at -78 °C then allowed to warm up to rt over 3 h. Water was added and the usual work-up (DCM) and purification (2% EtOAc in hexanes) afforded **12b** (6.84 g, 88%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.43 (s, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 1.56 – 1.38 (m, 4H), 1.03 (s, 27H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 206.3 (d), 63.5 (t), 45.6 (s), 33.5 (t), 27.9 (t), 21.4 (q), 18.1(q), 12.1 (d). **IR** (neat) ν (cm^{-1}) 2959, 2944, 2886, 1724. **HRMS** (positive ESI) Calcd for $C_{16}H_{34}O_2SiNa$ [M*Na*$^+$]: 309.2220, found 309.2222.

***N*-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl)-*N*-(3,4-dimethoxyphenethyl)formamide (14a)**. 2-(3,4-Dimethoxyphenyl)ethylamine (0.91 mL, 5.41 mmol) was added to a solution of 5-((*tert*-butyldimethylsilyl)oxy)pentanal[20](1.17 g, 5.41 mmol) in DCM (11 mL) at rt. The solution was stirred for 1 h at rt then anhydrous $MgSO_4$ (1.30 g, 10.8 mmol) was added. The mixture was stirred for 1 h at rt then filtered and washed with DCM (25 mL). MeOH (15 mL) and sodium borohydride (303 mg, 10.8 mmol) were added. The solution was stirred for 18 h at rt. Water (15 mL) was added and the usual work-up (DCM, brine) afforded a residue that was used directly in the next step. *N*-Formylbenzotriazole (1.06 g, 6.49 mmol) was added to the residue dissolved in THF (27 mL). The solution was stirred for 18 h at rt then the solvent was removed under reduced pressure. The residue was dissolved in DCM and washed with aqueous NaOH (2 M, 2 × 25 mL). The usual work-up (DCM) and purification (20 to 55% EtOAc in hexanes) afforded **14a** (247 mg, 84%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.8 mixture of

rotamers δ (ppm) 8.05 (s) and 7.82 (s) (1H, rotamers), 6.81 – 6.74 (m, 2H), 6.69 – 6.62 (m, 1H), 3.87 (s) and 3.86 (s) (3H, rotamers), 3.62 – 3.57 (m, 2H), 3.52 – 3.47 (m, 2H), 3.41 (t, *J* = 7.0 Hz, 1H, rotamers), 3.35 – 3.30 (m, 1H), 3.11 (t, *J* = 7.0 Hz, 1H, rotamers), 2.82 – 2.73 (m, 2H), 1.63 – 1.46 (m, 4H), 1.39 – 1.25 (m, 2H), 0.89 (s) and 0.88 (s) (9H, rotamers), 0.04 (s) and 0.03 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 162.7, 162.6, 149.0, 148.9, 147.8, 147.6, 131.3, 130.3, 120.8, 120.6, 111.9, 111.4, 111.2, 62.9, 62.7, 55.85, 55.82, 49.1, 47.9, 44.2, 42.3, 35.0, 33.2, 32.4, 32.2, 28.5, 27.2, 25.92, 25.89, 23.2, 22.8, 18.28, 18.26, -5.33, -5.35. **IR** (neat) ν (cm^{-1}) 2930, 2855, 1669, 1515, 1463, 1258, 1236. **HRMS** (positive ESI) Calcd for $C_{22}H_{39}NO_4Si$ [MNa^+]: 432.2541, found 432.2540.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-((triisopropylsilyl)oxy)pentyl)formamide (14b)**. Following the procedure used to prepare **14a**, **12b** (2.22 g, 7.76 mmol) was treated with 2-(3,4-dimethoxyphenyl)ethylamine (1.30 mL, 7.76 mmol) in DCM (15 mL), then with sodium borohydride (0.56 g, 15.5 mmol) in MeOH (20 mL). After the usual work-up (DCM, brine), the residue was treated with *N*-formylbenzotriazole (1.37 g, 9.31 mmol) in THF (40 mL) then with NaOH (2 M). The usual work-up (DCM) and purification (20 to 40% EtOAc in hexanes) afforded **14b** (3.7 g, 98%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1: 0.5 mixture of rotamers δ (ppm) 8.02 (s) and 7.88 (s) (1H, rotamers), 6.78 (d, *J* = 8.5 Hz, 1H), 6.73 – 6.59 (m, 2H), 3.86 (s) and 3.84 (s) (6H, rotamers), 3.66 – 3.47 (m, 4H), 3.14 (s) and 2.88 (s) (2H, rotamers), 2.81 – 2.71 (m, 2H), 1.59 – 1.43 (m, 2H), 1.31 – 1.19 (m, 2H), 1.04 (s, 21H), 0.90 (s) and 0.85 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 163.8 (d), 163.6 (d), 149.0 (s), 148.8 (s), 147.8 (s), 147.5 (s), 131.3 (s), 130.1 (s), 120.8 (d), 120.6 (d), 111.9 (d), 111.3 (d), 111.2 (d), 63.8 (t), 63.5 (t), 58.1 (t), 55.7 (q), 51.6 (t), 51.0 (t), 47.6 (t), 36.8 (t), 36.1(s), 36.0 (t), 35.3 (s), 34.9 (t), 33.0 (t), 27.5 (t) 27.3 (t), 25.8 (q) 25.1 (q), 17.9 (q), 11.8 (d). **IR** (neat) ν (cm^{-1}) 2942, 2892, 2864, 2046, 1673. **HRMS** (positive ESI) Calcd for $C_{27}H_{49}NO_4SiNa$ [MNa^+]: 502.3323, found 502.3325.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(5-hydroxypentyl)formamide (15a)**. A solution of TBAF (1.0 M in THF , 2.84 mL, 2.84 mmol) was added dropwise to a solution of **14a** (972 mg, 2.37 mmol) and glacial acetic acid (0.27 mL, 4.74 mmol) in THF (12 mL). The solution was stirred for 18 h at rt then the solvent was removed under reduced pressure. Usual purification (70 to 100% EtOAc in hexanes then 5% MeOH in DCM) afforded **15a** (631 mg, 90%) as a light brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 8.01 (s) and 7.78 (s) (1H, rotamers), 6.78 – 6.71 (m, 2H), 6.65 – 6.60 (m, 1H), 3.84 (s) and 3.83 (s) (3H, rotamers), 3.82 (s, 3H), 3.61 – 3.56 (m, 2H), 3.49 – 3.44 (m, 1H), 3.39 (t, *J* = 7.0 Hz, 1H, rotamers), 3.32 – 3.27 (m, 1H), 3.09 (t, *J* = 7.0 Hz, 1H, rotamers), 2.79 – 2.70 (m, 2H), 2.30 (br s, 1H), 1.61 – 1.45 (m, 4H), 1.39 – 1.22 (m, 2H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 162.8 (d), 162.7 (d), 148.9 (s), 148.7 (s), 147.7 (s), 147.4 (s), 131.1 (s), 130.1 (s), 120.7 (d), 120.5 (d), 111.81 (d), 111.78 (d), 111.3 (d), 111.1 (d), 62.1 (t), 62.0 (t), 55.8 (q), 49.1 (t), 47.8 (t), 44.1 (t), 42.1 (t), 34.8 (t), 33.1 (t), 32.1 (t), 32.0 (t), 28.3 (t), 27.0 (t), 22.9 (t), 22.6 (t). **IR** (neat) ν (cm^{-1}) 3416 (br), 2932, 2858, 2834, 1655, 1510, 1450, 1260, 1234. **HRMS** (positive ESI) Calcd for $C_{16}H_{25}NO_4Na$ [MNa^+]: 318.1676, found 318.1684.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylpentyl)formamide (15b)**. Following the procedure used to prepare **15a**, **14b** (6.54 g, 13.5 mmol) was treated with TBAF (1.0 M in THF, 4.70 mL, 16.4 mmol) in THF (12 mL). The usual purification (80 to 100% EtOAc in hexanes then 1% MeOH in DCM) afforded **15b** (3.74 g, 85%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.6 mixture of rotamers δ (ppm) 8.03 (s) and 7.88 (s) (1H, rotamers), 6.79 (d, *J* = 8.5 Hz, 1H), 6.74 – 6.60 (m, 2H), 3.86 (s) and 3.85 (s) (3H, rotamers), 3.84 (s, 3H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.55 – 3.48 (m, 2H), 3.13 (s) and 2.89 (s) (2H, rotamers), 2.82 – 2.72 (m, 2H), 1.83 (br s, 1H), 1.64 – 1.46 (m, 2H), 1.31 – 1.20 (m, 2H), 0.92 (s) and 0.87 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 164.2 (d), 149.3 (s), 149.1 (s), 148.1 (s), 147.8 (s), 131.5 (s), 130.3(s), 121.0 (d), 120.8 (d), 112.2 (d), 112.1 (d), 111.6 (d), 111.4 (d), 63.3 (t), 58.5 (t), 56.07 (q), 56.04 (q), 56.03 (q), 56.01 (q), 51.6 (t), 51.5 (t), 48.0 (t),

36.4 (s), 36.3 (t), 36.2 (t), 35.6 (s), 35.3 (t), 33.3(t), 27.3 (t), 27.2 (t), 26.4 (q), 25.3(q). **IR** (neat) ν (cm^{-1}) 3404 (br), 2941, 2872, 2162, 1659. **HRMS** (positive ESI) Calcd for $C_{18}H_{30}NO_4$ [M*H*$^+$]: 324.2169, found 324.2168. Mp 58 – 63 °C.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(5-oxopentyl)formamide (16a)**. DMSO (0.38 mL, 5.33 mmol) was added to a solution of oxalyl chloride (0.26 mL, 3.08 mmol) in DCM (12 mL) at -78 °C. The solution was stirred for 30 min at -78 °C then a solution of **15a** (605 mg, 2.05 mmol) in DCM (8.0 mL) was added. The solution was stirred for 1 at -78 °C then triethylamine (1.44 mL, 10.3 mmol) was added. The solution was stirred for 1 at -78 °C then was allowed to warm up to rt over 45 min. Water was added and the usual work-up (DCM) and purification (60 to 100% EtOAc in hexanes) afforded **16a** (622 mg, 87%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 9.76 (s, 1H), 8.06 (s) and 7.84 (s) (1H, rotamers), 6.82 – 6.74 (m, 2H), 6.69 – 6.63 (m, 1H), 3.88 (s) and 3.87 (s) (3H, rotamers), 3.86 (s, 3H), 3.50 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.43 (t, *J* = 7.0 Hz, 1H), 3.34 (t, *J* = 7.0 Hz, 1H), 3.12 (t, *J* = 6.5 Hz, 1H), 2.83 – 2.74 (m, 2H), 2.52 – 2.44 (m, 2H), 1.63 -1.54 (m, 4H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 201.9 (d), 201.4 (d), 162.7 (d), 162.6 (d), 149.0 (s), 148.9 (s), 147.8 (s), 147.6 (s), 131.2 (s), 130.2 (s), 120.8 (d), 120.6 (d), 111.9 (d), 111.4 (d), 111.2 (d), 55.8 (q), 49.0 (t), 47.6 (t), 44.2 (t), 43.2 (t), 43.1 (t), 41.7 (t), 34.9 (t), 33.1 (t), 28.0 (t), 26.7 (t), 19.1 (t), 18.8 (t). **IR** (neat) ν (cm^{-1}) 2936, 2835, 1718, 1661, 1514, 1260, 1234, 1025. **HRMS** (positive ESI) Calcd for $C_{16}H_{23}NO_4Na$ [M*Na*$^+$]: 316.1519, found 316.1529.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-oxopentyl)formamide (16b)**. Following the procedure used to prepare **16a**, **15b** (3.74 g, 11.6 mmol) was treated with DMSO (2.14 mL, 30.1 mmol), oxalyl chloride (1.47 mL, 17.4 mmol), and triethylamine (8.02 mL, 57.9 mmol) in DCM (87 mL). The usual work-up (DCM) and purification (80% EtOAc in hexanes) afforded **16b** (2.96 g, 79%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.8 mixture of rotamers δ (ppm) 9.68 (s) and 9.67 (s) (1H, rotamers), 7.95 (s) and 7.79 (s) (1H, rotamers), 6.73 – 6.71 (m, 1H), 6.66 – 6.54 (m, 2H), 3.78 (s) and 3.77 (s) (3H,

rotamers), 3.76 (s) and 3.75 (s) (3H, rotamers), 3.50 – 3.41 (m, 2H), 3.05 (s) and 2.82 (s) (2H, rotamers), 2.75 – 2.65 (m, 2H), 2.44 – 2.39 (m, 1H), 2.35 – 2.29 (m, 1H), 1.45 (dd, J = 16.0, 7.5 Hz, 2H), 0.84 (s) and 0.78 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 202.4 (d), 201.4 (d), 163.8 (d), 149.0 (s), 148.8 (s), 147.8 (s), 147.5 (s), 131.2 (s), 130.0 (s), 120.8 (d), 120.6 (d), 111.9 (d), 111.8 (d), 111.4 (d), 111.3 (d), 58.3 (t), 55.9 (q), 55.8 (q), 55.7 (q), 51.3 (t), 51.2 (t), 47.9 (t), 39.0 (t), 38.7 (t), 35.9 (s), 35.2 (s), 34.9 (t), 33.0 (t), 31.7 (t), 31.4 (t), 25.8 (q), 24.6 (q). **IR** (neat) ν (cm^{-1}) 2958 and 2936 (br), 2871, 2835, 2160, 1719, 1663. **HRMS** (positive ESI) Calcd for $C_{18}H_{28}NO_4$ [MH^+]: 322.2013, found 322.2011. Mp 62 - 67 °C.

***trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbaldehyde (18a)**. Triflic anhydride (91 µL, 0.54 mmol) was added dropwise to a solution of **16a** (137 mg, 0.47 mmol) and DTBMP (161 mg, 0.78 mmol) in $CDCl_3$ (9.40 mL) at -60 °C. The reaction mixture was stirred for 45 min at this temperature then at -15 °C for 1 h. ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of iminium ion **17a**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.77 (s, 1H), 9.23 (s, 1H), 7.50 (s, 1H), 6.84 (s, 1H), 4.04 (t, J = 7.3 Hz, 2H), 4.01 (s, 3H), 3.96 (t, J = 8.2 Hz, 2H), 3.92 (s, 3H), 3.23 (t, J = 8.2 Hz, 2H), 2.63 (t, J = 6.7 Hz, 2H), 1.95-1.88 (m, 2H), 1.73-1.64 (m, 2H). Piperidine (140 µL, 1.41 mmol) was added at -15 °C and the reaction was stirred for 3 d at this temperature. Aqueous HCl (1 M, 1 mL) was added and the usual work-up (DCM) and purification (10 to 20% EtOAc in hexanes with 1.5% Et_3N) afforded **18a** (51 mg, 40%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.42 (s, 1H), 6.61 (s, 1H), 6.60 (s, 1H), 3.85 (s 3H), 3.81 (s, 3H), 3.51 (br s, 1H), 3.13 – 2.87 (m, 4H), 2.61 – 2.47 (m, 2H), 2.40 - 2.30 (m, 2H), 1.72 – 1.50 (m, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 206.1, 147.8, 147.7, 128.4, 127.3, 111.8, 108.3, 64.0, 57.2, 56.1, 56.0, 52.7, 49.8, 29.5, 26.1, 22.2. **IR** (neat) ν (cm^{-1}) 2936, 2751, 1717, 1517, 1248, 1144, 1002. **HRMS** (positive ESI) Calcd for $C_{16}H_{22}NO_3$ [MH^+]: 276.1594, found 276.1601. Mp 100 – 104 °C.

***trans*-9,10-Dimethoxy-3,3-dimethyl-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbaldehyde (18b)**. Following the procedure used to prepare **18a**, **16b** (103 mg, 0.32 mmol) was treated with triflic anhydride (59 μL, 0.35 mmol) and DTBMP (72.7 mg, 0.35 mmol) in $CDCl_3$ (6.20 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of iminium ion **17b**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.82 (s, 1H), 9.13 (s, 1H), 7.57 (s, 1H), 6.87 (s, 1H), 4.02 (s, 3H), 3.98 (t, *J* = 8.0 Hz, 2H), 3.94 (s, 3H), 3.87-3.86 (m, 4H), 3.20 (t, *J* = 8.0 Hz, 2H), 2.64-2.60 (m, 2H), 1.07 (s, 6H). Subsequent treatment with piperidine (95 μL, 0.96 mmol) for 18 h at -15 °C followed by the usual work-up (DCM) and purification (10 to 100% EtOAc in hexanes with 1.5% Et_3N) afforded **18b** (36 mg, 37%, 63% brsm) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.57 (s, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.37 (s, 1H), 3.19-3.07 (m, 1H), 2.93-2.79 (m, 2H), 2.64-2.52 (m, 3H), 2.24-2.07 (m, 2H), 1.61–1.55 (m, 1H), 0.92 (s, 3H), 0.90 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 207.2 (d), 147.9 (s), 147.7 (s), 128.6 (s), 127.4 (s), 111.8 (d), 108.6 (d), 68.8 (t), 63.4 (d), 56.1 (q), 56.0 (q), 52.7 (t), 49.2 (d), 41.3 (t), 30.9 (s), 29.7 (t), 29.6 (q), 28.3 (q). **IR** (neat) ν (cm^{-1}) 2950, 2830, 2750, 2164, 2052, 1715, 1518. **HRMS** (positive ESI) Calcd for $C_{18}H_{26}NO_3$ [M*H*$^+$]: 304.1907, found 304.1929.

***N*-(3,4-Dimethoxyphenethyl)formamide (19)**. *N*-Formylbenzotriazole (7.05 g, 43.2 mmol) was added to a solution of 3,4-dimethoxyphenethylamine (**13**, 6.28 mL, 36.1 mmol) dissolved in THF (180 mL) and stirred for 18 h at rt. Then the solvent was removed under reduced pressure, the residue was dissolved in DCM and washed with aqueous NaOH (2 N, 2 × 45 mL). The usual work-up (DCM) and purification (50 to 90% EtOAc in hexanes) afforded **19** (7.40 g, 98%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.2 mixture of rotamers δ (ppm) 8.15 (s) and 7.96 (d, *J* = 12 Hz, 1H, rotamers), 6.82 (d, J = 8.0 Hz, 1H), 6.76 – 6.67 (m, 2H), 5.49 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.57 (q) and 3.46 (q) (2H, *J* = 6.6 Hz, rotamers), 2.80 (t) and 2.76 (t) (2H, *J* = 7.0 Hz, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 164.5 (d), 161.2 (d), 149.1 (s), 147.8 (s), 131.1 (s), 120.7 (d), 112.0 (d), 111.5 (d), 56.0 (q), 55.9

(q), 43.3 (t), 39.4 (t), 37.4 (t), 35.2 (t). **IR** (neat) ν (cm^{-1}) 3316, 3054, 2999, 2936, 2835, 1659, 1513, 1258, 1232, 1024, 766. **HRMS** (positive ESI) Calcd for $C_{11}H_{15}NO_3Na$ [MNa^+]: 232.0944, found 232.0946.

***N*-(3,4-Dimethoxyphenethyl)-*N*-methylformamide (20)**. KHMDS (0.5 M in toluene, 2.40 mL, 1.20 mmol) was added dropwise to a solution of **19** (201 mg, 0.96 mmol) in THF (5.0 mL). The mixture was stirred for 1 h 30 min at rt then DMF (4.80 mL) and MeI (0.24 mL, 3.84 mmol) were added. The solution was refluxed for 18 h then allowed to cool to rt and concentrated under reduced pressure. Water was added and the usual work-up (EtOAc) and purification (50 to 80% EtOAc in hexanes) afforded **20** (206 mg, 96%) as an orange oil. Analytical data were in accordance with those reported in the literature.[21] **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.6 mixture of rotamers δ (ppm) 7.90 (s) and 7.70 (s) (1H, rotamers), 6.71 – 6.55 (m, 3H), 3.76 (s) and 3.75 (s) (3H, rotamers), 3.74 (s, 3H), 3.44 (t) and 3.34 (t) (J = 7.0 Hz, 2H, rotamers), 2.78 (s) and 2.75 (s) (3H, rotamers), 2.72 – 2.65 (m, 2H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 162.4 (d), 162.2 (d), 148.9 (s), 148.7 (s), 147.7 (s), 147.4 (s), 130.9 (s), 130.1 (s), 120.6 (d), 120.5 (d), 111.8 (d), 111.7 (d), 111.3 (d), 111.2 (d), 55.7 (q), 55.6 (q), 51.1 (t), 45.7 (t), 34.8 (q), 34.2 (t), 32.5 (t), 29.5 (q). **IR** (neat) ν (cm^{-1}) 2932, 2835, 1661, 1514, 1259, 1233, 1025.

Iminium ion (21). Following the procedure used to prepare **18a**, **13** was treated with triflic anhydride and DTBMP in $CDCl_3$. ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of iminium ion **21**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.05 (s, 1H), 7.40 (s, 1H), 6.84 (s, 1H), 4.00 (s, 3H), 3.96 (t, J = 8.5 Hz, 2H), 3.90 (s, 3H), 3.78 (s, 3H), 3.24 (t, J = 8.5 Hz, 2H).

***N*-(3,4-Dimethoxyphenethyl)-5-hydroxyhexanamide (24)**. A solution of $AlMe_3$ (2.0 M in toluene, 20.0 mL, 40 mmol) was added to a solution of **13** (6.80 mL, 40 mmol) in DCM (200 mL) at rt. The reaction mixture was stirred for 30 min at rt then a solution of δ-caprolactone (**23**, 2.20 mL, 20 mmol) was added at 0 °C. The solution was stirred for 30 min at 0 °C then for 18 h at rt and finally cooled to 0 °C. Water was slowly added at 0 °C followed by a saturated solution of potassium sodium tartrate and the mixture was stirred vigorously for 4 h at rt. The usual workup (DCM) and purification (70 to 100%

EtOAc in hexanes then 5% MeOH in EtOAc) afforded **24** (5.90 g, 99%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.79 (d, *J* = 8.5 Hz, 1H), 6.72 – 6.70 (m, 2H), 5.68 (br s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 – 3.69 (m, 1H), 3.51 – 3.45 (m, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.20 (br s, 1H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.69 (dt, *J* = 15.0, 7.0 Hz, 2H), 1.45 – 1.37 (m, 2H), 1.15 (d, *J* = 6.0 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.2 (s), 149.1 (s), 147.7 (s), 131.5 (s), 120.7 (d), 112.0 (d), 111.4 (d), 67.3 (d), 56.0 (q), 55.9 (q), 40.7 (t), 38.5 (t), 36.3 (t), 35.3 (t), 23.6 (q), 21.7 (t). **IR** (neat) ν (cm^{-1}) 3304 (br), 2933, 2837, 1645, 1515, 1260, 1235, 1027. **HRMS** (positive ESI) Calcd for $C_{16}H_{25}NO_4Na$ [M*Na*$^+$]: 318.1676, found 318.1678.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(5-hydroxyhexyl)formamide (27)**. $LiAlH_4$ (4.63 g, 122 mmol) was added in small portions to a solution of **24** (18.0 g, 61.0 mmol) in THF (203 mL) at 0 °C and the mixture was refluxed for 18 h. The resulting mixture was cooled at 0 °C and quenched with water (4.6 mL). An aqueous solution of NaOH (15%, 4.6 mL) and water (12.0 mL) were added, and the mixture was stirred vigorously at rt for 5 h. Anhydrous Na_2SO_4 was added and the mixture was filtered over Celite and concentrated under reduced pressure. The residue was used directly in the next step. Following the procedure used to prepare **19**, crude **25** was treated with *N*-formylbenzotriazole (18.8 g, 128 mmol) in THF (244 mL). The residue was used directly in the next step. K_2CO_3 was added to crude **26** dissolved in MeOH (203 mL). The reaction mixture was refluxed for 18 h then cooled to rt. Water (80 mL) was added ant the usual work-up (EtOAc) and purification (30 to 100% EtOAc in hexanes) afforded **27** (13.8 g, 73% over 3 steps) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 8.04 (s) and 7.83 (s) (1H, rotamers), 6.81 – 6.73 (m, 2H), 6.68 – 6.63 (m, 1H), 3.87 (s) and 3.86 (s) (3H, rotamers), 3.85 (s, 3H), 3.81 – 3.73 (m, 1H), 3.52 – 3.47 (m, 1H), 3.41 (t, *J* = 7.0 Hz, 1H), 3.33 (t, *J* = 7.5 Hz, 1H), 3.11 (t, *J* = 7.0 Hz, 1H), 2.82 – 2.73 (m, 2H), 1.59 – 1.24 (m, 7H), 1.17 (d, *J* = 6.0 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 163.0 (d), 162.8 (d), 149.3 (s), 149.1 (s), 148.1 (s), 147.8 (s), 131.5 (s), 130.4 (s), 120.9 (d), 120.8 (d), 112.2 (d), 112.1 (d), 111.6 (d), 111.5 (d), 67.9 (d), 67.8 (d),

56.1 (q), 56.0 (q), 49.3 (t), 48.1 (t), 44.4 (t), 42.3 (t), 38.9 (t), 38.8 (t), 35.2 (t), 33.4 (t), 31.0 (t), 28.9 (t), 27.5 (t), 23.8 (q), 23.7 (q), 23.0 (t), 22.8 (t). **IR** (neat) ν (cm^{-1}) 3413 (br), 2932, 2859, 1653, 1515, 1026. **HRMS** (positive ESI) Calcd for $C_{17}H_{27}NO_4Na$ [M*Na*$^+$]: 332.1832, found 332.1836.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(5-oxohexyl)formamide (28a)**. Following the procedure used to prepare **16a**, **27** (1.02 g, 3.30 mmol) was treated with DMSO (0.61 mL, 8.58 mmol), oxalyl chloride (0.42 mL, 4.95 mmol), and triethylamine (2.30 mL, 16.5 mmol) in DCM (13 mL). The usual work-up (DCM) and purification (40 to 90% EtOAc in hexanes) afforded **28a** (852 mg, 84%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 8.05 (s) and 7.82 (s) (1H, rotamers), 6.81 – 6.73 (m, 2H), 6.68 – 6.62 (m, 1H), 3.87 (s) and 3.86 (s) (3H, rotamers), 3.85 (s, 3H), 3.52 – 3.46 (m, 1H), 3.41 (t, *J* = 7.0 Hz, 1H), 3.32 (t, *J* = 7.0 Hz, 1H), 3.10 (t, *J* = 6.0 Hz, 1H), 2.82 – 2.73 (m, 2H), 2.49 – 2.40 (m, 2H), 2.12 (s, 3H), 1.58 – 1.48 (m, 4H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 208.6 (s), 208.0 (s), 162.9 (d), 162.8 (d), 149.3 (s), 149.1 (s), 148.1 (s), 147.8 (s), 131.4 (s), 130.4 (s), 120.9 (d), 120.8 (d), 112.2 (d), 112.1 (d), 111.6 (d), 111.4 (d), 56.0 (q), 49.2 (t), 48.0 (t), 44.4 (t), 43.0 (t), 42.9 (t), 42.0 (t), 35.2 (t), 33.4 (t), 30.2 (q), 30.1 (q), 28.3 (t), 26.8 (t), 20.9 (t), 20.6 (t). **IR** (neat) ν (cm^{-1}) 2936, 1711, 1665, 1515, 1027. **HRMS** (positive ESI) Calcd for $C_{17}H_{25}NO_4$ [M*Na*$^+$]: 330.1675, found 330.1681.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-oxohexyl)formamide (28b)**. Methylmagnesium bromide (221 µL, 1.91 mmol) was added dropwise to a solution of **16b** (410 mg, 1.27 mmol) in THF (6.0 mL) at -78 °C. The mixture was stirred for 3 h at -78 °C then AcOH was added. The reaction was allowed to warm up at rt and concentrated under reduced pressure. Saturated aqueous NH_4Cl was added. The usual work-up (DCM) and purification (40 to 90% EtOAc in hexanes) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylhexyl)formamide (113 mg, 26%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.6 mixture of rotamers δ (ppm) 8.03 (s) and 7.88 (s) (1H, rotamers), 6.80 (d, *J* = 8.5 Hz, 1H), 6.74 – 6.61 (m, 2H), 3.87 (s) and 3.86 (s) (3H, rotamers), 3.85 (s, 3H), 3.77-3.67 (m,

1H), 3.63-3.48 (m, 2H), 3.14 (s) and 2.89 (s) (2H, rotamers), 2.79-2.75 (m, 2H), 1,73 (br s, 1H), 1.63-1.09 (m, 7H), 0.90 (d, J = 16.0 Hz) and 0.89 (d, J = 16.0 Hz) (6H, rotamers). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 164.2 (d), 149.3 (s), 149.1 (s), 148.1 (s), 147.8 (s), 131.6 (s), 130.3 (s), 121.1 (d), 120.8 (d), 112.2 (d), 112.2 (d), 111.6 (d), 111.5 (d), 68.6 (d), 68.4 (d), 63.3 (t), 58.5 (t), 56.1 (q), 51.5 (t), 48.0 (t), 36.4 (s), 36.2 (s), 35.9 (t), 35.6 (t), 35.3 (t), 33.6 (t), 33.5 (t), 33.3 (t), 26.6 (q), 26.2 (q), 25.4 (q), 25.3 (q), 23.9 (q). **IR** (neat) ν (cm^{-1}) 2958 (br), 2936, 2870, 2162, 2010, 1728, 1660. **HRMS** (positive ESI) Calcd for $C_{19}H_{31}NO_4Na$ [M + Na^+]: 360.2145, found 360.2147. Following the procedure used to prepare **16a**, *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylhexyl)formamide (371 mg, 1.10 mmol) was treated with DMSO (0.20 mL, 2.86 mmol), oxalyl chloride (0.14 mL, 1.65 mmol), and triethylamine (0.76 mL, 5.50 mmol) in DCM (8 + 5.5 mL). The usual work-up (DCM) and purification (40 to 90% EtOAc in hexanes) afforded **28b** (253 mg, 69%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.7 mixture of rotamers δ (ppm) 8.03 (s) and 7.88 (s) (1H, rotamers), 6.80 (d, J = 8.5 Hz, 1H), 6.75 – 6.60 (m, 2H), 6.87 (s, 3H), 6.86 (s, 3H), 3.53 (dt, J = 14.5, 7.0 Hz, 2H), 3.12 (s) and 2.88 (s) (2H, rotamers), 2.83-2.73 (m, 2H), 2.53-2.34 (m, 2H), 2.15 (s, 3H), 1.55 – 1.45 (m, 2H), 0.91 (s, 3H), 0.85 (s, 3H). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 209.1 (s), 208.1 (s), 164.0 (d), 163.9 (d), 149.2 (s), 149.0 (s), 148.0 (d), 147.7 (s), 131.4 (s), 130.2 (s), 120.9 (d), 120.7 (d), 112.1 (d), 112.0 (d), 111.5 (d), 111.4 (d), 58.6 (t), 55.9 (q), 51.4 (t), 51.3 (t), 48.0 (t), 38.7 (t), 38.3 (t), 36.0 (s), 35.3 (s), 35.1 (t), 33.7 (t), 33.7 (t), 33.3 (t), 33.1 (t), 30.0 (q), 26.0 (q), 24.8 (q). **IR** (neat) ν (cm^{-1}) 2960 and 2941 (br), 2871, 2833, 2168, 2032, 1712, 1663. **HRMS** (positive ESI) Calcd for $C_{19}H_{29}NO_4Na$ [M + Na^+]: 358.1989, found 358.1993.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(5-oxohexyl)acetamide (28c)**. Following the procedure to prepare **27**, **24** (5.32 g, 18.0 mmol) was treated with $LiAlH_4$ (1.37 g, 36.0 mmol) in THF (60 mL), then with water (1.37 mL), NaOH (15%, 1.37 mL), and water (4.10 mL) to afford a residue that was used directly in the next step. Et_3N (1.98 mL, 14.2 mmol) and AcCl (0.53 mL, 7.43 mmol) were added to the residue

dissolved in DCM (18 mL) at 0 °C and stirred for 18 h at rt. The residue was washed with a saturated solution of $NaHCO_3$ (2 x 25 mL). The usual work-up (DCM) and purification (40 to 100% EtOAc in hexanes) afforded 6-(*N*-(3,4-dimethoxyphenethyl)acetamido)hexan-2-yl acetate (772 mg, 60% over 2 steps) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 6.82 – 6.75 (m, 2H), 6.73 – 6.65 (m, 1H), 4.93 – 4.83 (m, 1H), 3.87 (s, 3H), 3.86 (s) and 3.85 (s) (3H, rotamers), 3.51 – 3.41 (m, 2H), 3.35 – 3.28 (m, 1H), 3.10 (t, *J* = 7.5 Hz, 1H), 2.82 – 2.75 (m, 2H), 2.09 (s) and 1.90 (s) (3H, rotamers), 2.02 (s, 3H), 1.63 – 1.41 (m, 4H), 1.36 – 1.25 (m, 2H), 1.20 (d, *J* = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 170.8 (s), 170.7 (s), 170.2 (s), 170.1 (s), 149.1 (s), 148.9 (s), 147.9 (s), 147.5 (s), 132.0 (s), 130.7 (s), 120.8 (d), 120.7 (d), 112.1 (d), 112.0 (d), 111.5 (d), 111.3 (d), 70.7 (d), 70.4 (d), 55.9 (q), 55.8 (q), 50.4 (t), 49.4 (t), 48.2 (t), 45.4 (t), 35.7 (t), 35.6 (t), 34.8 (t), 33.6 (t), 28.7 (t), 27.5 (t), 22.8 (t), 22.7 (t), 21.6 (q), 21.4 (q), 21.3 (q), 19.9 (q), 19.8 (q). **IR** (neat) ν (cm^{-1}) 2832, 1864, 1546. **HRMS** (positive ESI) Calcd for $C_{20}H_{31}NO_5Na$ [M + Na^+]: 388.2094, found 388.2102. K_2CO_3 (730 mg, 5.28 mmol) was added to a solution of 6-(*N*-(3,4-dimethoxyphenethyl)acetamido)hexan-2-yl acetate (772 mg, 2.11 mmol) dissolved in MeOH (7.0 mL) and refluxed for 18 h. Water was added and the usual work-up (EtOAc) and purification (60 to 100% EtOAc in hexanes) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxyhexyl)acetamide (662 mg, 97%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 6.82 – 6.64 (m, 3H), 3.87 (s, 3H), 3.86 (s) and 3.85 (s) (3H, rotamers), 3.82 – 3.74 (m, 1H), 3.51 – 3.42 (m, 2H), 3.33 (t, *J* = 7.5 Hz, 1H), 3.12 (t, *J* = 7.5 Hz, 1H), 2.82 – 2.75 (m, 2H), 2.08 (s) and 1.91 (s) (3H, rotamers), 1.57 – 1.31 (m, 7H), 1.19 (d, *J* = 3.0 Hz) and 1.17 (d, *J* = 3.0 Hz) (3H, rotamers). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 170.5 (s), 170.2 (s), 149.1 (s), 148.9 (s), 147.9 (s), 147.5 (s), 132.0 (s), 130.7 (s), 120.8 (d), 120.7 (d), 112.1 (d), 112.0 (d), 111.5 (d), 111.3 (d), 67.6 (d), 67.4 (d), 55.9 (q), 50.5 (t), 49.5 (t), 48.2 (t), 45.5 (t), 38.9 (t), 38.8 (t), 34.8 (t), 33.6 (t), 29.0 (t), 27.6 (t), 23.7 (q), 23.5 (q), 23.0 (t), 21.6 (q), 21.4 (q). **IR** (neat) ν (cm^{-1}) 3301 (br), 2943, 1648. **HRMS** (positive ESI) Calcd for $C_{18}H_{29}NO_4Na$ [M + Na^+]: 346.1989,

found 346.1985. Dess-Martin periodinane (2.78 g, 6.56 mmol) was added to a solution of *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxyhexyl)acetamide (662 mg, 2.05 mmol) in DCM (41 mL). The reaction mixture was stirred for 2 h 30 min then a saturated aqueous solution of $NaHCO_3$ (20 mL) and saturated $Na_2S_2O_3$ (30 mL) were added and the mixture was stirred for 30 min. The usual workup (DCM) and purification (40 to 100% EtOAc in hexanes) afforded **28c** (548 mg, 83%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 6.82 – 6.65 (m, 3H), 3.87 (s, 3H), 3.86 (s) and 3.85 (s) (3H, rotamers), 3.51 – 3.42 (m, 2H), 3.32 (t, *J* = 7.0 Hz, 1H), 3.11 (t, *J* = 7.0 Hz, 1H), 2.81 – 2.76 (m, 2H), 2.49 – 2.42 (m, 2H), 2.13 (s, 3H), 2.08 (s) and 1.90 (s) (3H, rotamers), 1.57 – 1.50 (m, 4H). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 208.8 (s), 208.0 (s), 170.3 (s), 170.1 (s), 149.0 (s), 148.8 (s), 147.8 (s), 147.4 (s), 131.9 (s), 130.7 (s), 120.7 (d), 120.6 (d), 112.0 (d), 111.9 (d), 111.4 (d), 111.2 (d), 55.9 (q), 55.8 (q), 50.4 (t), 49.3 (t), 48.1 (t), 45.1 (t), 43.1 (t), 42.9 (t), 34.7 (t), 33.6 (t), 29.9 (q), 28.4 (t), 27.0 (t), 21.6 (q), 21.3 (q), 20.9 (t), 20.7 (t). **IR** (neat) ν (cm^{-1}) 2834, 1635, 1542. **HRMS** (positive ESI) Calcd for $C_{18}H_{27}NO_4Na$ [M + Na^+]: 344.1832, found 344.1839.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-oxohexyl)acetamide (28d)**. 2-(3,4-Dimethoxyphenyl)ethylamine (4.00 mL, 23.9 mmol) was added to a solution of the aldehyde **12b** (6.84 g, 23.9 mmol) in DCM (50 mL) and stirred for 1 h at rt. Then anhydrous Na_2SO_4 (6.78 g, 47.7 mmol) was added to the reaction and stirred for 1 h 30 min at rt. The resulting mixture was filtered and washed with DCM (30 mL). MeOH (66 mL) and sodium borohydride (1.80 g, 47.7 mmol) were added to the reaction, stirred for 18 h at rt and quenched with water. The usual work-up (DCM, brine) afforded a residue that was used directly in the next step. Pyridine (1.10 mL, 13.2 mmol) was added to the residue dissolved in DCM (133 mL) and cooled to 0 °C. Freshly distilled acetyl chloride (0.47 mL, 6.60 mL) was added to the reaction and stirred for 1 h at 0 °C then allowed to warm up to rt and stirred for 18 h. Then water was added. The usual work-up (DCM) and purification (20 to 40% EtOAc in hexanes) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-((triisopropylsilyl)oxy)pentyl)acetamide (2.69 g, 83%) as a

yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.7 mixture of rotamers δ (ppm) 6.82 – 6.74 (m, 1H), 6.74 – 6.62 (m, 2H), 3.87 (s, 3H), 3.86 (s) and 3.85 (s) (3H, rotamers), 3.64 (t, *J* = 6.5 Hz, 2H), 3.58 – 3.50 (m, 2H), 3.21 (s) and 2.98 (s) (2H, rotamers), 2.83 – 2.73 (m, 2H), 2.10 (s) and 1.99 (s) (3H, rotamers), 1.58 – 1.44 (m, 2H), 1.29 – 1.24 (m, 2H), 1.05 (s, 21H), 0.91 (s) and 0.89 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 171.7 (s), 171.5 (s), 149.2 (s), 149.0 (s), 148.0 (s), 147.6 (s), 132.3 (s), 130.9 (s), 120.9 (d), 120.8 (d), 112.3 (d), 112.1 (d), 111.6 (d), 111.4 (d), 64.2 (t), 63.9 (t), 59.6 (t), 56.1 (q), 56.0 (q), 54.6 (t), 52.5 (t), 50.9 (t), 37.3 (t), 37.1 (t), 36.7 (s), 36.6 (s), 34.7 (t), 33.0 (t), 27.8 (t), 27.6 (t), 26.1(q), 25.9 (q) , 22.5 (q), 21.7 (q), 18.2 (q), 12.2 (d), 12,1 (d). **IR** (neat) ν (cm^{-1}) 2937, 2869, 2147, 1648. **HRMS** (positive ESI) Calcd for $C_{28}H_{51}NO_4SiNa$ [M + Na^+]: 516.3480, found 516.3478. A solution of TBAF (1.0 M in THF, 1.90 mL, 6.54 mmol) was added dropwise to a solution of *N*-(3,4-dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-((triisopropylsilyl)oxy)pentyl)acetamide (2.69 g, 5.45 mmol) in THF (7.0 mL) and stirred for 1 h at rt. The solvent was removed under reduced pressure and purification (100% EtOAc then 2% MeOH in EtOAc) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylpentyl)acetamide (1.62 g, 88%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.4 mixture of rotamers δ (ppm) 6.83 – 6.78 (m, 1H), 6.74 – 6.63 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.65 – 3.51 (m, 4H), 3.20 (s) and 3.00 (s) (2H, rotamers), 2.83 – 2.74 (m, 2H), 2.11 (s) and 2.00 (s) (3H, rotamers), 1.90 (t, *J* = 5.0 Hz, 1H), 1.65 – 1.48 (m, 2H), 1.30 – 1.24 (m, 2H), 0.93 (s) and 0.90 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 172.0 (s), 171.8 (s), 149.2 (s), 149.0 (s), 148.0 (s), 147.6 (s), 132.2 (s), 130.7 (s), 120.8 (d), 120.7 (d), 112.3 (d), 112.1 (d), 111.6 (d), 111.4 (d), 63.3 (t), 63.2 (t), 59.5 (t), 56.1 (q), 56.0 (q), 54.1 (t), 52.7 (t), 51.0 (t), 37.2 (t), 36.7 (s), 36.6 (s), 36.2 (t), 34.6 (t), 33.0 (t), 27.4 (t), 27.2 (t), 26.4 (q), 25.8 (q), 22.5 (q), 21.8 (q). **IR** (neat) ν (cm^{-1}) 3402 (br), 2944, 2150, 2017, 1623. **HRMS** (positive ESI) Calcd for $C_{19}H_{31}NO_4Na$ [M + Na^+]: 360.2145, found 360.2155. Following the procedure used to prepare **16a**, *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylpentyl)acetamide (1.62 g, 4.80 mmol) was treated with DMSO (0.89 mL,

12.5 mmol), oxalyl chloride (0.61 mL, 47.2 mmol), and triethylamine (3.33 mL, 24.0 mmol) in DCM (36 + 24 mL). The usual work-up (DCM) and purification (80% EtOAc in hexanes) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-oxopentyl)acetamide (1.41 g, 88%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.3 mixture of rotamers δ (ppm) 9.76 (t, *J* = 1.5 Hz, 1H), 6.82 – 6.78 (m, 1H), 6.74 – 6.62 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.53 (t, *J* = 7.5 Hz, 2H), 3.20 (s) and 2.99 (s) (2H, rotamers), 2.84 – 2.74 (m, 2H), 2.52 – 2.39 (m, 2H), 2.11 (s) and 2.00 (s) (3H, rotamers), 1.56 – 1.51 (m, 2H), 0.91 (s) and 0.90 (s) (6H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 171.7 (s), 171.6 (s), 149.2 (s), 148.9 (s), 148.0 (s), 147.5 (s), 132.0 (s), 130.6 (s), 120.8 (d), 120.7 (d), 112.2 (d), 112.0 (d), 111.6 (d), 111.3 (d), 59.6 (t), 56.1 (q), 56.0 (q), 54.0 (t), 52.6 (t), 51.1 (t), 39.4 (t), 38.9 (t), 36.3 (s), 34.5 (t), 32.9 (t), 32.4 (t), 32.0 (t), 26.0 (q), 25.4 (q), 22.4 (q), 21.6 (q). **IR** (neat) ν (cm^{-1}) 2955, 2872, 2833, 2057, 1720. **HRMS** (positive ESI) Calcd for $C_{19}H_{29}NO_4Na$ [MNa^+]: 358.1989, found 358.1990. Methylmagnesium bromide (2.90 mL, 2.51 mmol) was added dropwise to a solution of *N*-(3,4-dimethoxyphenethyl)-*N*-(2,2-dimethyl-5-oxopentyl)acetamide (560 mg, 1.67 mmol) in THF (8.0 mL) at -78 °C. The mixture was stirred for 3 h at -78 °C then AcOH was added. The reaction was allowed to warm up at rt and concentrated under reduced pressure. Saturated aqueous NH_4Cl was added. The usual work-up (DCM) and purification (20 to 80% EtOAc in hexanes) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylhexyl)acetamide (237 mg, 40%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 6.82 – 6.63 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.76 – 3.66 (m, 1H), 3.61 – 3.45 (m, 2H), 3.30 – 2.99 (m, 2H), 2.83 – 2.73 (m, 2H), 2.11 (s) and 1.99 (s) (3H, rotamers), 1.72 (br s, 1H), 1.65 – 1.10 (m, 7H), 0.91-0.89 (m, 6H). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 172.0 (s), 171.8 (s), 149.3 (s), 149.1 (s), 148.1 (s), 132.3 (s), 130.8 (s), 120.9 (d), 120.8 (d), 112.3 (d), 112.2 (d), 111.7 (s), 111.4 (s), 68.6 (d), 68.2 (d), 56.1 (q), 53.9 (q),52.8 (t), 37.3 (t), 36.6 (s), 35.7 (t), 34.7 (t), 33.6 (t), 33.5 (t), 33.1 (t), 26.9 (q), 26.5 (q), 26.3 (q), 26.3(q), 25.6 (q), 23.9 (q), 22.5 (q), 21.8 (q). **IR** (neat) ν (cm^{-1}) 2962 (br), 2929, 2868, 2166, 1726, 1628. **HRMS** (positive ESI) Calcd for

$C_{20}H_{33}NO_4Na$ [MNa^+]: 374.2302, found 374.2306. Following the procedure used to prepare **16a**, *N*-(3,4-dimethoxyphenethyl)-*N*-(5-hydroxy-2,2-dimethylhexyl)acetamide (353 mg, 1.00 mmol) was treated with DMSO (0.19 mL, 2.60 mmol), oxalyl chloride (0.13 mL, 1.50 mmol), and triethylamine (0.70 mL, 5.00 mmol) in DCM (8.0 + 5.5 mL). The usual work-up (DCM) and purification (20 to 80% EtOAc in hexanes) afforded **28d** (232 mg, 66%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 6.80 – 6.61 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.56 – 3.49 (m, 2H), 3.16 (s) and 2.06 (s) (2H, rotamers), 2.81 – 2.71 (m, 2H), 2.49-2.33 (m, 2H), 2.13 (s, 3H), 2.09 (s) and 1.97 (s) (3H, rotamers), 1.54 – 1.44 (m, 2H), 0.88 (s, 3H), 0.86 (s, 3H). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 209.4 (s), 202.9 (s), 171.6 (s), 149.2 (s), 149.0 (s), 148.0 (s), 147.6 (s), 130.7 (s), 130.7 (s), 120.8 (d), 112.2 (d), 112.1 (d), 111.6 (d), 111.4 (d), 56.1 (q), 56.0 (q), 54.1 (t), 54.0 (t), 52.7 (t), 52.6 (t), 38.9 (t), 36.3 (s), 34.6 (t), 34.0 (t), 30.1 (q), 30.1 (q), 26.1 (q), 25.4 (q), 21.7 (q). **IR** (neat) ν (cm^{-1}) 2963 and 2939 (br), 2871, 2838, 2166, 1975, 1715, 1634. **HRMS** (positive ESI) Calcd for $C_{20}H_{31}NO_4$ [MNa^+]: 372.2145, found 372.2149.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(4-oxopentyl)formamide (28e)**. Following the procedure used to prepare **24**, **13** (4.05 mL, 24.0 mmol) was treated with $AlMe_3$ (2.0 M in toluene, 12.0 mL, 24.0 mmol) and then γ-valerolactone (**38**, 1.91 mL, 20.0 mmol) in DCM (96 mL). The usual workup (DCM) and purification (70 to 100% EtOAc in hexanes then 2 to 9% MeOH in EtOAc) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(4-hydroxy)pentanamide (4.05 g, 72%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.80 – 6.77 (m, 1H), 6.72 – 6.69 (m, 2H), 5.89 (br s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 – 3.72 (m, 1H), 3.46 (q, *J* = 13.0, 7.0 Hz, 1H), 3.14 (br s, 1H), 2.74 (t, *J* = 7.0 Hz, 1H), 2.28 (t, *J* = 7.0 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.69 – 1.57 (m, 1H), 1.16 (d, *J* = 6.0 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.7 (s), 149.1 (s), 147.8 (s), 131.4 (s), 120.7 (d), 112.0 (d), 111.5 (d), 67.5 (d), 56.1 (q), 56.0 (q), 40.9 (t), 35.3 (t), 34.4 (t), 33.4 (t), 23.7 (q). **IR** (neat) ν (cm^{-1}) 3305 (br), 2976, 1632. **HRMS** (positive ESI) Calcd for $C_{15}H_{23}NO_4Na$ [MNa^+]: 304.1519, found 304.1511. **Mp** 70 – 73 °C. Following

the procedure to prepare **27**, *N*-(3,4-dimethoxyphenethyl)-*N*-(4-hydroxy)pentanamide (2.0 g, 7.11 mmol) was treated with $LiAlH_4$ (539 mg, 14.2 mmol) in THF (24 mL), then with water (0.54 mL), NaOH (15%, 0.54 mL), and water (1.62 mL) to afford a residue that was used directly in the next step. Following the procedure used to prepare **19**, crude the residue was treated with *N*-formylbenzotriazole (562 mg, 3.82 mmol) in THF (6.0 mL) then with NaOH (2 M, 2 × 5 mL). The residue was used directly in the next step. K_2CO_3 (528 mg, 3.82 mmol) was added to the residue dissolved in MeOH (6.0 mL) and refluxed for 18 h. Water was added (10 mL). The usual work-up (EtOAc) and purification (40 to 100% EtOAc in hexanes then 3% MeOH in EtOAc) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(4-hydroxypentyl)formamide (365 mg, 66% over 3 steps) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:1 mixture of rotamers δ (ppm) 8.05 (s) and 7.82 (s) (1H, rotamer), 6.81-6.73 (m, 2H), 6.68-6.62 (m, 1H), 3.87 (s) and 3.86 (s) (3H, rotamers), 3.85 (s, 3H), 3.81-3.72 (m, 1H), 3.53-3.47 (m, 1H), 3.38-3.26 (m, 1H), 3.43 (t, *J* = 7.0 Hz, 1H), 3.38-3.26 (m, 1H), 3.14 (t, *J* = 7.0 Hz, 1H), 2.83-2.74 (m, 2H), 1.90 (br s, 1H), 1.75-1.32 (m, 5H), 1.18 (d, *J* = 6.2 Hz, 1H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 162.7 (d), 162.6 (d), 148.8 (s), 148.6 (s), 147.6 (s), 147.3 (s), 131.0 (s), 130.0 (s), 120.6 (d), 120.4 (d), 111.8 (d), 111.3 (d), 111.1 (d), 66.8 (d), 66.7 (d), 55.6 (q), 55.5 (q), 48.9 (t), 47.8 (t), 43.9 (t), 42.0 (t), 35.7 (t), 35.4 (t), 34.6 (t), 32.9 (t), 24.7 (t), 23.5 (t), 23.4 (q), 23.3 (q). **IR** (neat) ν (cm^{-1}) 3402 (br), 2942, 1644, 1502. **HRMS** (positive ESI) Calcd for $C_{16}H_{25}NO_4$ [M + Na^+]: 318.1676, found 318.1664. Following the procedure to prepare **28c**, *N*-(3,4-dimethoxyphenethyl)-*N*-(4-hydroxypentyl)formamide (365 mg, 1.24 mmol) was treated with Dess-Martin periodinane (1.68 g, 3.97 mmol) in DCM (24 mL) for 18 h. The usual workup (DCM) and purification (40 to 100% EtOAc in hexanes) afforded **28e** (295 mg, 81%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 8.01 (s) and 7.82 (s) (1H, rotamers), 6.80-6.72 (m, 2H), 6.68-6.63 (m, 1H), 3.87 (s) and 3.86 (s) (3H, rotamers), 3.84 (s, 3H), 3.52-3.47 (m, 1H), 3.42 (t, *J* = 7.0 Hz, 1H), 3.34-3.29 (m, 1H), 3.11 (t, *J* = 7.0 Hz, 1H), 2.82-2.74 (m, 2H), 2.46 (t, *J* = 7.0 Hz, 1H), 2.38 (t, *J* = 6.9 Hz, 1H), 2.13 (s) and 2.12 (s) (3H, rotamers), 1.86-1.72 (m, 2H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 208.0 (s), 207.2 (s), 162.9 (d), 162.7 (d), 149.0 (s), 148.9 (s), 147.8 (s), 147.6 (s), 131.1 (s), 130.2 (s), 120.8 (d), 120.7 (d), 111.9 (d), 111.4 (d), 111.3 (d), 55.9 (q), 49.0 (t), 46.9 (t), 44.0 (t), 41.3 (t), 40.4 (t), 39.5 (t), 34.9 (t), 33.1 (t), 30.0 (q), 22.3 (t), 21.3 (t). **IR** (neat) ν (cm^{-1}) 2902, 1701, 1685, 1512. **HRMS** (positive ESI) Calcd for $C_{16}H_{23}NO_4Na$ [M + Na^+]: 316.1519, found 316.1524.

***N*-(3,4-Dimethoxyphenethyl)-*N*-(3-oxobutyl)formamide (28f)**. Following the procedure used to prepare **24**, **13** (2.50 mL, 15.0 mmol) was treated with $AlMe_3$ (2.0 M in toluene, 7.50 mL, 15.0 mmol) and then β-butyrolactone (1.02 mL, 12.5 mmol) in DCM (75 mL). The usual workup (DCM) and purification (50 to 100% EtOAc in hexanes then 1 to 3% MeOH in EtOAc) afforded *N*-(3,4-dimethoxyphenethyl)-3-hydroxybutanamide (3.32 g, 99%) as a yellow oil. **^1H NMR** (300 MHz, $CDCl_3$) 6.81 (d, *J* = 8.5 Hz, 1H), 6.74-6.71 (m, 2H), 5.71 (br s, 1H), 4.21-4.11 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.58 (d, *J* = 3.0 Hz, 1H), 3.56-3.48 (m, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.32-2.17 (m, 2H), 1.20 (d, *J* = 6.5 Hz, 3H). **$^{13}C\{^1H\}$ NMR** (75 MHz, $CDCl_3$) δ (ppm) 172.4 (s), 148.9 (s), 147.6 (s), 131.3 (s), 120.6 (d), 111.9 (d), 111.4 (d), 64.8 (d), 55.9 (q), 55.8 (q), 43.9 (t), 40.6 (t), 35.1 (t), 22.8 (q). **IR** (neat) ν (cm^{-1}) 3333 (br), 2932, 2833, 1642, 1514, 1259, 1024. **HRMS** (positive ESI) Calcd for $C_{14}H_{21}NO_4Na$ [M + Na^+]: 290.1363, found 290.1368. Following the procedure to prepare **27**, *N*-(3,4-dimethoxyphenethyl)-3-hydroxybutanamide (3.37 g, 12.6 mmol) was treated with $LiAlH_4$ (956 mg, 25.2 mmol) in THF (42 mL), then with water (0.96 mL), NaOH (15%, 0.96 mL), and water (2.88 mL). The usual purification (60 to 100% EtOAc in hexanes then 3 to 6% MeOH in EtOAc with 1.5% Et_3N) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-methyl-5-oxohexanamide (3.0 g, 94%) as a yellow oil. **^1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.80 (d, *J* = 8.0 Hz, 1H), 6.74-6.71 (m, 2H), 4.02-3.92 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.67 (br s, 2H), 3.02-2.72 (m, 6H), 1.63-1.41 (m, 2H), 1.16 (d, *J* = 6.0 Hz, 3H). **$^{13}C\{^1H\}$ NMR** (75 MHz, $CDCl_3$) δ (ppm) 149.1 (s), 147.7 (s), 132.1 (s), 120.7 (d), 112.0 (d), 111.5 (d), 69.6 (d), 56.1 (q), 56.0 (q), 50.9 (t), 48.8 (t), 36.6 (t), 35.7 (t), 23.7 (q). **IR** (neat) ν (cm^{-1}) 3348 (br), 2960, 2932, 2836,

1514, 1260. **HRMS** (positive ESI) Calcd for $C_{14}H_{24}NO_3$ [M + H^+]: 254.1751, found 254.1755. Following the procedure used to prepare **19**, *N*-(3,4-dimethoxyphenethyl)-*N*-methyl-5-oxohexanamide (1.48 g, 5.84 mmol) was treated with *N*-formylbenzotriazole (1.81 g, 12.3 mmol) in THF (19 mL) then with NaOH (2 M, 2 × 25 mL). The usual work-up (DCM) and purification (50 to 100% EtOAc in hexanes then 1 to 4% MeOH in EtOAc) afforded *N*-(3,4-dimethoxyphenethyl)-*N*-(3-hydroxybutyl)formamide (1.63 g, 99%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.3 mixture of rotamers δ (ppm) 8.10 (s) and 7.84 (s) (1H, rotamers), 6.82-6.62 (m, 3H), 3.96-3.90 (m, 1H), 3.88 (s) and 8.87 (s) (3H, rotamers), 3.86 (s, 3H), 3.77 (br s, 1H), 3.65-3.55 (m, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 3.39-3.02 (m, 1H), 2.84-2.77 (m, 2H), 1.59-1.43 (m, 1H), 1.22-1.18 (m, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 163.6 (d), 163.0 (d), 149.0 (s), 148.8 (s), 147.8 (s), 147.5 (s), 131.2 (s), 129.9 (s), 120.7 (d), 120.6 (d), 111.9 (d), 111.8 (d), 111.4 (d), 111.2 (d), 64.1 (d), 63.8 (d), 55.8 (q), 55.7 (q), 49.4 (t), 44.6 (t), 44.1 (t), 39.4 (t), 37.5 (t), 36.7 (t), 34.8 (t), 33.1 (t), 23.8 (q), 22.7 (q). **IR** (neat) ν (cm^{-1}) 3402 (br), 2946, 2841, 1651, 1515, 1025. **HRMS** (positive ESI) Calcd for $C_{15}H_{23}NO_4Na$ [M + Na^+]: 304.1519, found 304.1518. Following the procedure used to prepare **16a**, *N*-(3,4-dimethoxyphenethyl)-*N*-(3-hydroxybutyl)formamide (1.63 g, 5.79 mmol) was treated with DMSO (1.07 mL, 15.0 mmol), oxalyl chloride (0.75 mL, 8.69 mmol), and triethylamine (4.04 mL, 29.0 mmol) in DCM (43 + 23 mL). The usual work-up (DCM) and purification (40 to 100% EtOAc in hexanes then 1 to 4% MeOH in EtOAc) afforded **28f** (1.51 g, 93%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.6 mixture of rotamers δ (ppm) 8.06 (s) and 7.71 (s) (1H, rotamers), 6.75 (d, *J* = 8.0 Hz, 1H), 6.60-6.60 (m, 2H), 3.82 (s) and 3.81 (s) (3H, rotamers), 3.79 (s, 3H), 3.50-3.34 (m, 4H), 2.77-2.69 (m, 3H), 2.53 (t, *J* = 6.5 Hz, 1H), 2.10 (s) and 2.06 (s) (3H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 206.9 (s), 205.6 (s), 163.1 (d), 162.8 (d), 149.0 (s), 148.8 (s), 147.7 (s), 147.5 (s), 131.1 (s), 130.1 (s), 120.8 (d), 120.6 (d), 111.9 (d), 111.8 (d), 111.4 (d), 111.2 (d), 55.8 (q), 49.9 (t), 44.5 (t), 42.1 (t), 42.0 (t), 41.4 (t), 37.8 (t),

35.0 (t), 33.0 (t), 30.2 (q), 29.9 (q). **IR** (neat) ν (cm^{-1}) 3507, 2934, 2836, 1710, 1655, 1514, 1025. **HRMS** (positive ESI) Calcd for $C_{15}H_{21}NO_4Na$ [M + Na^+]: 302.1363, found 302.1364. **Mp** 75 – 77 °C.

***cis*-1-(9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-1-yl)ethan-1-one (30a)**. Following the procedure used to prepare **18a**, **28a** (107.6 mg, 0.35 mmol) was treated with triflic anhydride (66 μL, 0.39 mmol) and DTBMP (80 mg, 0.39 mmol) in $CHCl_3$ (7.0 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of iminium ion **29**. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ (ppm) 8.97 (s, 1H), 7.39 (s, 1H), 6.85 (s, 1H), 3.97-3.77 (m, 10H), 3.21 (t, *J* = 8.0 Hz, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.11 (s, 3H), 1.91-1.81 (m, 2H), 1.65-1.58 (m, 2H). Subsequent treatment with pyrrolidine (88 μL, 1.05 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (8 to 70% EtOAc in hexanes with 1.5% Et_3N) afforded **30a** (74 mg, 73%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.57 (s, 1H), 6.43 (s, 1H), 3.96 (d, *J* = 10.0 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.26 – 3.18 (m, 1H), 3.06 – 2.89 (m, 3H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.77 – 2.70 (m, 1H), 2.04 (s, 3H), 1.90 – 1.45 (m, 4H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 213.6 (s), 147.8 (s), 146.8 (s), 129.1 (s), 126.7 (s), 111.7 (d), 110.2 (d), 61.7 (d), 55.9 (q), 55.8 (q), 54.7 (t), 51.5 (d), 46.9 (t), 32.5 (q), 29.1 (t), 29.0 (t), 20.2 (t). **IR** (neat) ν (cm^{-1}) 2930, 2856, 1701, 1516, 1265, 1227, 1019. **HRMS** (positive ESI) Calcd for $C_{17}H_{24}NO_3$ [MH^+]: 290.1750, found 290.1756. Mp 98 – 101 °C.

***cis*-1-(9,10-Dimethoxy-3,3-dimethyl-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-1-yl)ethan-1-one (30b)**. Following the procedure used to prepare **18a**, **28b** (117. mg, 0.35 mmol) was treated with triflic anhydride (66 μL, 0.39 mmol) and DTBMP (80 mg, 0.39 mmol) in $CHCl_3$ (7.0 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of an iminium ion resulting from the Vilsmeier-Haack cyclization. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.94 (s, 1H), 7.47 (s, 1H), 6.90 (s, 1H), 4.01 (s, 3H), 4.00-3.94 (m, 2H), 3.91 (s, 3H), 3.86-3.80 (m, 2H), 3.19 (t, *J* = 8.0 Hz, 2H), 2.59-2.54 (m, 2H), 2.18 (s, 3H), 1.65-1.60 (m, 2H), 1.04 (s, 6H). Subsequent treatment with pyrrolidine (175 μL, 2.10 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up

(DCM) and purification (5 to 20% EtOAc in hexanes with 1.5% Et_3N) afforded **30b** (81 mg, 73%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.56 (s, 1H), 6.48 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.62 (d, *J* = 10.0 Hz, 1H), 3.07-2.87 (m, 3H), 2.65-2.50 (m, 3H), 2.36-2.32 (m, 1H), 2.25 (s, 3H), 1.62-1.56 (m, 1H), 1.47-1.39 (m, 1H), 1.08 (s, 3H), 0.92 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 214.0 (s), 147.4 (s), 146.7 (s), 129.3 (s), 128.4 (s), 111.8 (d), 109.6 (d), 67.6 (t), 63.9 (d), 55.9 (q), 55.8 (q), 53.1 (d), 52.5 (t), 43.2 (t), 31.7 (q), 30.4 (s), 30.0 (t), 29.4 (q), 25.3 (q). **IR** (neat) ν (cm^{-1}) 2943, 1704, 1516, 1256. **HRMS** (positive ESI) Calcd for $C_{19}H_{28}NO_3$ [M + H^+]: 318.2064, found 318.2068. **Mp** 98 – 100 °C.

***cis*-1-(9,10-Dimethoxy-11b-methyl-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-1-yl)ethan-1-one (30c)**. Following the procedure used to prepare **18a**, **28c** (97 mg, 0.30 mmol) was treated with triflic anhydride (56 µL, 0.33 mmol) and DTBMP (68 mg, 0.33 mmol) in $CHCl_3$ (6.0 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of an iminium ion resulting from the Vilsmeier-Haack cyclization. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.23 (s, 1H), 6.82 (s, 1H), 4.00-3.87 (m, 10H), 3.12 (t, *J* = 7.5 Hz, 2H), 2.82 (s, 3H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.16 (s, 3H), 1.92-1.81 (m, 2H), 1.72-1.65 (m, 2H). Subsequent treatment with pyrrolidine (0.15 mL, 1.80 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (5 to 35% EtOAc in hexanes with 1.5% Et_3N) afforded **30c** (22 mg, 24%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.54 (s, 1H), 6.53 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.45 – 3.29 (m, 2H), 3.26 – 2.16 (m, 2H), 2.91 – 2.72 (m, 4H), 2.17 (s, 3H), 3.09 (s, 3H), 1.64 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 214.1 (s), 147.4 (s), 146.8 (s), 134.8 (s), 126.6 (s), 111.6 (d), 109.7 (d), 59.6 (s), 55.9 (q), 55.8 (q), 54.0 (d), 49.4 (t), 45.9 (t), 34.1 (q), 30.0 (t), 25.6 (t), 21.0 (t), 19.1 (q). **IR** (neat) ν (cm^{-1}) 2929, 2845, 1701, 1514, 1254. **HRMS** (positive ESI) Calcd for $C_{18}H_{26}NO_3$ [M + H^+]: 304.1907, found 304.1910.

***cis*-1-(9,10-Dimethoxy-3,3,11b-trimethyl-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-1-yl)ethan-1-one (30d)**. Following the procedure used to prepare **18a**, **28d** (76.5 mg, 0.22 mmol) was

treated with triflic anhydride (40 µL, 0.24 mmol) and DTBMP (49 mg, 0.24 mmol) in DCM (4.4 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of an iminium ion resulting from the Vilsmeier-Haack cyclization. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.51 (s, 1H), 6.84 (s, 1H), 4.02-4.00 (m, 5H), 3.94 (s, 3H), 3.89-3.81 (m, 2H), 3.14-3.09 (m, 2H), 2.86 (s, 3H), 2.60-2.54 (m, 2H), 2.20 (s, 3H), 1.72-1.67 (m, 2H), 1.15 (s, 3H), 1,09 (s, 3H). Subsequent treatment with pyrrolidine (55 µL, 0.66 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (2 to 10% EtOAc in hexanes with 1.5% Et_3N) afforded **30d** (13 mg, 18%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.59 (s, 1H), 6.54 (s, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.10 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.05-2.83 (m, 3H), 2.61-2.46 (m, 2H), 2.18 (dd, *J* = 12.0, 2.0 Hz, 1H), 2.12 (s, 3H), 1.70 (t, *J* = 13.5 Hz, 1H), 1.46 (s, 3H), 1.34-1.25 (m, 1H), 1.09 (s, 3H), 0.91 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 214.7 (s), 147.2 (s), 146.8 (s), 136.0 (s), 127.8 (s), 111.7 (d), 109.8 (d), 61.5 (t), 60.8 (s), 55.9 (q), 55.8 (q), 55.4 (d), 47.4 (t), 39.9 (t), 33.9 (q), 31.2 (t), 30.3 (s), 29.4 (q), 26.2 (q), 13.4 (q). **IR** (neat) ν (cm^{-1}) 2948, 2823, 1703, 1514, 1254. **HRMS** (positive ESI) Calcd for $C_{20}H_{30}NO_3$ [M + H^+]: 332.2220, found 332.2221.

***cis*-1-(8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-1-yl)ethan-1-one (30e)**. Following the procedure used to prepare **18a**, **28e** (88 mg, 0.30 mmol) was treated with triflic anhydride (56 µL, 0.33 mmol) and DTBMP (68 mg, 0.33 mmol) in DCM (6.0 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of an iminium ion resulting from the Vilsmeier-Haack cyclization. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.04 (s, 1H), 7.41 (s, 1H), 6.86 (s, 1H), 4.00-3.94 (m, 7H), 3.90 (s, 3H), 3.23 (t, *J* = 8.5 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.14 (s, 3H), 2.13-2.06 (m, 2H). Subsequent treatment with pyrrolidine (75 µL, 0.90 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (10 to 70% EtOAc in hexanes with 1.5% Et_3N) afforded **30e** (79 mg, 95%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.58 (s, 1H), 6.45 (s, 1H), 4.15 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.13-3.01 (m, 3H), 2.96-2.69 (m, 4H), 2.42-2.32

(m, 1H), 2.29 (s, 3H), 1.97-1.85 (m, 1H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 210.5 (s), 147.7 (s), 147.5 (s), 129.5 (s), 126.2 (s), 111.5 (d), 109.1 (d), 63.6 (d), 57.9 (d), 56.1 (q), 56.0 (q), 52.7 (t), 47.5 (t), 30.1 (q), 28.8 (t), 27.4 (t). **IR** (neat) ν (cm^{-1}) 2928, 2831, 1703, 1511, 1255, 1013. **HRMS** (positive ESI) Calcd for $C_{16}H_{22}NO_3$ [M + H^+]: 276.1594, found 276.1598.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (30f). Following the procedure used to prepare **18a**, **28f** (100 mg, 0.36 mmol) was treated with triflic anhydride (67 µL, 0.40 mmol) and DTBMP (82 mg, 0.40 mmol) in DCM (7.2 mL). Subsequent treatment with pyrrolidine (45 µL, 0.54 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (5 to 90% EtOAc in hexanes with 1.5% Et_3N) afforded **30f** (28 mg, 30%) as a orange solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.61 (s, 1H), 6.53 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.60-3.53 (m, 1H), 3.34-3.24 (m, 1H), 3.15-3.13 (m, 2H), 2.91 (d, *J* = 14.0 Hz, 1H), 2.81-2.42 (m, 6H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 208.5 (s), 148.0 (s), 147.7 (s), 128.3 (s), 126.1 (s), 111.6 (d), 107.9 (d), 61.6 (d), 56.1 (q), 56.0 (q), 54.8 (t), 50.9 (t), 47.5 (t), 41.1 (t), 29.2 (t). **IR** (neat) ν (cm^{-1}) 2924, 1712, 1514. **HRMS** (positive ESI) Calcd for $C_{15}H_{20}NO_3$ [M + H^+]: 262.1438, found 262.1439. **Mp** 148 – 151 °C.

2-(1*H*-Pyrrol-1-yl)ethan-1-ol (36). Ethanolamine (66 mL, 1.09 mmol) was added to glacial acetic acid (120 mL) at 0 °C a rate such that the temperature was maintained at 15-25 °C. Then, 2,5-dimethoxytetrahydrofuran (32 mL, 0.25 mmol) was added in one portion and the reaction was stirred at 110-120 °C, at which point distillation of a liquid commenced. After 1 h 30 min at that temperature, 25 mL of a distillate was collected. The residual liquid in the reaction vessel was cooled to rt and water was added. The usual work-up (DCM, brine, saturated aqueous Na_2CO_3) afforded a residue that was dissolved in MeOH (67 mL). NaOH (20 wt %, 33 mL) was added and the solution was stirred at rt for 1 h, then poured into brine and extracted with DCM. The solvent was removed under reduced pressure to afford **36** (17 g, 61%) as a yellow oil. Analytical data were in accordance with those reported in the literature.[22] **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.71-6.70 (m, 2H), 6.19-6.18 (m, 2H), 4.02 (t, *J* = 5.0

Hz, 2H), 3.84 (t, *J* = 5.0 Hz, 2H), 1.73 (s, 1H). **$^{13}C\{^{1}H\}$ NMR** (75 MHz, $CDCl_3$) δ (ppm) 120.8 (d), 108.2 (d), 62.5 (t), 51.7 (t). **IR** (neat) ν (cm^{-1}) 3401 (br), 2927, 2881. **HRMS** (positive ESI) Calcd for C_6H_9NONa [M*Na*$^+$]: 134.0576, found 134.0571.

1-(2-Iodoethyl)-1*H*-pyrrole (37). Iodide (1.40 g, 5.50 mmol) was added in three portions to a solution of triphenylphosphine (1.43 g, 5.45 mmol) and imidazole (450 mg, 6.60 mmol) in DCM (55 mL) at 0 °C, protected from the light. The mixture was stirred for 30 min at 0 °C then a solution of **36** (611 mg, 5.50 mmol) in DCM (6.0 mL) was added. The reaction mixture was stirred for 18 h at rt then saturated aqueous $Na_2S_2O_3$ was added. The usual work-up (DCM) and purification (10 to 20% DCM in hexanes) afforded **37** (968 mg, 79%) as a yellow oil. Analytical data were in accordance with those reported in the literature.[23] **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.71-6.70 (m, 2H), 6.22-6.21 (m, 2H), 4.27 (t, *J* = 7.5 Hz, 2H), 3.41 (t, *J* = 7.5 Hz, 2H). **$^{13}C\{^{1}H\}$ NMR** (75 MHz, $CDCl_3$) δ (ppm) 120.4 (d), 108.8 (d), 51.9 (t), 3.4 (t). **IR** (neat) ν (cm^{-1}) 1495, 1276, 721. **HRMS** (positive ESI) Calcd for C_6H_9NI [M*H*$^+$]: 221.9774, found 221.9764.

***N*-(2-(1*H*-Pyrrol-1-yl)ethyl)-*N*-(4-oxopentyl)formamide (39a)**. K_2CO_3 (4.50 g, 32.4 mmol) was added to a solution of **37** (2.38 g, 10.8 mmol) and **38a** (1.11 g, 10.8 mmol) in THF (36 mL) in a sealed tube. The reaction mixture was stirred for 18 h at 90 °C, then K_2CO_3 was filtered and solvent was removed under reduced pressure to afford crude alkylated amine that was used directly in the next step. Following the procedure used to prepare **19**, the residue was treated with *N*-formylbenzotriazole (3.18 g, 21.6 mmol) in THF (27 mL) then with NaOH (2 M). The usual work-up (DCM) afforded a crude *N,O*-bisformylated product that was used directly in the next step. K_2CO_3 (4.48 g, 32.4 mmol) was added to a solution of the residue in MeOH (35 mL). The reaction mixture was refluxed for 2 h then allowed to cool to rt. Water was added and the usual work-up (EtOAc) afforded crude hydroxy-formamide that was used directly in the next step. Following the procedure to prepare **28c**, the residue was treated with Dess-Martin periodinane in DCM (20 mL) for 18 h. The usual workup (DCM) and purification (20 to 80% EtOAc in

hexanes) afforded **39a** (354 mg, 56% over 4 steps) as an orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.6 mixture of rotamers δ (ppm) 8.04 (s) and 7.53 (s) (1H, rotamers), 6.64-6.57 (m, 2H), 6.16-6.12 (m, 2H), 4.09 (t, *J* = 6.0 Hz, 1H), 4.02-3.99 (m, 1H), 3.57-3.49 (m, 2H), 3.26-3.21 (m, 1H), 2.81-2.76 (m, 1H), 2.45 (t, *J* = 7.0 Hz, 1H), 2.30 (t, *J* = 7.0 Hz, 1H), 2.14 (s) and 2.11 (s) (3H, rotamers), 1.83-1.74 (m, 1H), 1.67-1.57 (m, 1H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 207.9 (s), 207.1 (s), 162.9 (d), 162.7 (d), 120.6 (d), 120.4 (d), 109.2 (d), 108.7 (d), 48.6 (t), 48.0 (t), 47.2 (t), 46.9 (t), 44.5 (t), 41.3 (t), 40.2 (t), 39.5 (t), 30.1 (q), 30.0 (q), 22.2 (t), 21.2 (t). **IR** (neat) ν (cm^{-1}) 3458 (br), 1707, 1652, 730. **HRMS** (positive ESI) Calcd for $C_{12}H_{18}N_2O_2Na$ [M*Na*$^+$]: 245.1260, found 245.1267.

***N*-(2-(1*H*-Pyrrol-1-yl)ethyl)-*N*-(5-oxohexyl)formamide (39b)**. Following the procedure used to prepare **39a**, **38b** (1.22 g, 10.4 mmol) was treated with K_2CO_3 (4.30 g, 31.2 mmol) and **37** (2.29 g, 10.4 mmol) in THF (35 mL) to afford a crude alkylated amine that was used directly in the next step. The residue was then treated with *N*-formylbenzotriazole (3.06 g, 20.8 mmol) in THF (26 mL) to afford crude *N,O*-bisformylated product that was used directly in the next step. The residue then treated with K_2CO_3 (4.31 g, 31.2 mmol) in MeOH (35 mL) and the usual work-up (EtOAc) and purification (20 to 100% EtOAc in hexanes with 1.5% Et_3N, then 5% MeOH in EtOAc with 1.5% Et_3N) afforded *N*-(2-(1*H*-pyrrol-1-yl)ethyl)-*N*-(5-hydroxyhexyl)formamide (1.52 g, 61% over 3 steps) as an orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.5 mixture of rotamers δ (ppm) 8.07 (s) and 7.57 (s) (1H, rotamers), 6.64-6.58 (m, 2H), 6.18-6.14 (m, 2H), 4.11-3.97 (m, 2H), 3.82-3.69 (m, 1H), 3.57-3.48 (m, 2H), 3.28-3.23 (m, 1H), 2.81 (t, *J* = 7.0 Hz, 1H), 1.55-1.25 (m, 7H), 1.18 (d, *J* = 6.0 Hz) and 1.17 (d, *J* = 6.0 Hz) (3H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 163.0 (d), 162.7 (d), 120.6 (d), 120.5 (d), 109.3 (d), 108.8 (d), 67.6 (d), 67.5 (d), 48.8 (t), 48.3 (t), 48.2 (t), 47.0 (t), 44.7 (t), 42.3 (t), 38.7 (t), 38.5 (t), 28.6 (t), 27.4 (t), 23.6 (q), 23.5 (q), 22.9 (t), 22.6 (t). **IR** (neat) ν (cm^{-1}) 3410 (br), 2934, 2860, 1657, 724. **HRMS** (positive ESI) Calcd for $C_{13}H_{22}N_2O_2Na$ [M*Na*$^+$]: 261.1573, found 261.1576. Following the procedure to prepare **28c**, *N*-(2-(1*H*-pyrrol-1-yl)ethyl)-*N*-(5-hydroxyhexyl)formamide (83 mg,

0.35 mmol) was treated with Dess-Martin periodinane (297 mg, 0.70 mmol) in DCM (7.0 mL) for 18 h. The usual workup (DCM) and purification (20 to 80% EtOAc in hexanes) afforded **39b** (41 mg, 49%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.6 mixture of rotamers δ (ppm) 8.06 (s) and 7.55 (s) (1H, rotamers), 6.63-6.57 (m, 2H), 6.17-6.13 (m, 2H), 4.09 (t, *J* = 6.0 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 1H), 3.56-3.48 (m, 2H), 3.23 (t, *J* = 6.5 Hz, 1H), 2.78 (t, *J* = 7.0 Hz, 1H), 2.46 (t, *J* = 6.5 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 1H), 2.13 (s) and 2.11 (s) (3H, rotamers), 1.54-1.19 (m, 4H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 208.6 (s), 208.0 (s), 163.1 (d), 162.8 (d), 120.8 (d), 120.6 (d), 109.5 (d), 108.9 (d), 48.9 (t), 48.4 (t), 48.3 (t), 47.2 (t), 45.0 (t), 42.9 (t), 42.8 (t), 42.1 (t), 30.2 (q), 30.1 (q), 28.1 (t), 26.9 (t), 20.8 (t), 20.5 (t). **IR** (neat) ν (cm^{-1}) 2938, 2866, 1711, 1664, 727. **HRMS** (positive ESI) Calcd for $C_{13}H_{20}N_2O_2Na$ [M*Na*$^+$]: 259.1417, found 259.1418.

***N*-(2-(1*H*-pyrrol-1-yl)ethyl)-*N*-(5-oxohexyl)acetamide (39c)**. Following the procedure used to prepare **39a**, **38b** (870 mg, 7.42 mmol) was treated with K_2CO_3 (3.08 g, 22.3 mmol) and **37** (1.64 g, 7.42 mmol) in THF (25 mL) to afford a crude alkylated amine that was used directly in the next step. The residue was dissolved in DCM (37 mL) at 0 °C and Et_3N (4.14 mL, 29.7 mmol) was added, followed by a dropwise addition of acetyl chloride (1.11 mL, 15.6 mmol). The reaction mixture was stirred for 18 h at rt then quenched and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 25 mL). The usual workup (DCM) afforded crude *N,O*-bisacetylated product that was used directly in the next step. Following the procedure used to prepare **39a**, the residue then treated with K_2CO_3 (3.08 g, 22.3 mmol) in MeOH (25 mL) and the usual work-up (EtOAc) and purification (20 to 100% EtOAc in hexanes with 1.5% Et_3N, then 5% MeOH in EtOAc with 1.5% Et_3N) afforded crude hydroxy-acetamide that was used directly in the next step. Following the procedure to prepare **28c**, the residue was treated with Dess-Martin periodinane (1.0 g, 2.36 mmol) in DCM (16 mL) and the usual workup (DCM) and purification (10 to 100% EtOAc in hexanes with 1.5% Et_3N) afforded **39c** (142 mg, 29% over 4 steps) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.4 mixture of rotamers δ (ppm) 6.62-6.57 (m, 2H), 6.16-6.12 (m, 2H),

4.08 (t, J = 6.0 Hz) and 4.01 (t, J = 6.0 Hz) (2H, rotamers), 3.53 (t, J = 6.0 Hz, 2H), 3.25 (t, J = 7.0 Hz, 1H), 2.80-2.75 (m, 1H), 2.46 (t, J = 6.5 Hz, 1H), 2.38 (t, J = 7.0 Hz, 1H), 2.13 (s) and 2.12 (s) (3H, rotamers), 2.08 (s) and 1.63 (s) (3H, rotamers), 1.54-1.25 (m, 4H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 208.5 (s), 207.9 (s), 170.7 (s), 170.4 (s), 120.6 (d), 109.1 (d), 108.5 (d), 49.9 (t), 49.6 (t), 48.3 (t), 47.8 (t), 47.3 (t), 44.8 (t), 42.9 (t), 42.7 (t), 29.9 (q), 27.9 (t), 26.8 (t), 21.4 (q), 20.8 (t), 20.6 (t), 20.5 (q). **IR** (neat) ν (cm^{-1}) 2941, 1709, 1636, 1419. **HRMS** (positive ESI) Calcd for $C_{14}H_{22}N_2O_2Na$ [MNa^+]: 273.1573, found 273.1572.

2-(3-Iodopropyl)-2-methyl-1,3-dioxolane (41). Iodide (327 mg, 1.29 mmol) was added in three different portions to a solution of triphenylphosphine (336 mg, 1.28 mmol) and imidazole (106 mg, 1.55 mmol) in DCM (13 mL) at 0 °C, protected from the light. After stirring for 30 min at 0 °C, a solution of **40** (188 mg, 1.29 mmol) in DCM (1.5 mL) was added. The reaction was stirred for 18 h at rt. Saturated aqueous $NaHSO_3$ was added. The usual work-up (Et_2O) and purification (50 to 100% EtOAc in hexanes) afforded **41** (276 mg, 84%) as a colorless oil. Analytical data were in accordance with those reported in the literature.[24] **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.96-3.91 (m, 4H), 3.21 (t, J = 7.0 Hz, 2H), 2.00-1.90 (m, 2H), 1.77-1.72 (m, 2H), 1.32 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 109.5 (s), 64.8 (t), 39.9 (t), 28.4 (t), 24.1 (q), 7.1 (t). IR (neat) ν (cm^{-1}) 2978, 2364.

***N*-Methyl-*N*-(2-(1-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)-1*H*-indol-3-yl)ethyl)formamide (43)**. Following the procedure used to prepare **27**, ethyl (2-(1*H*-indol-3-yl)ethyl)carbamate[25] (300 mg, 1.29 mmol) was first treated with $LiAlH_4$ (147 mg, 3.87 mmol) in THF (6.5 mL), then with water (0.1 mL), NaOH (15%, 0.1 mL), and water (0.3 mL) to afford a crude amino-alcohol that was used directly in the next step. Following the procedure used to prepare **19**, crude amino-alcohol was treated with *N*-formylbenzotriazole (228 mg, 1.55 mmol) in THF (6.0 mL) and the usual work-up (DCM) and purification (60 to 100% EtOAc in hexanes then 2% MeOH in EtOAc) afforded *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-methylformamide (**42**, 220 mg, 84% over 2 steps) as a white solid. Analytical data were in

accordance with those reported in the literature.[26] **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.5 mixture of rotamers δ (ppm) 8.19 (br s, 1H), 8.06 (s) and 7.77 (s) (1H, rotamers), 7.65 (d, *J* = 8.0 Hz) and 7.56 (d, *J* = 8.0 Hz) (1H, rotamers), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24-7.11 (m, 2H), 7.06 (s) and 6.96 (s) (1H, rotamers), 3.70-3.65 (m) and 3.57-3.52 (m) (2H, rotamers), 3.06-2.99 (m, 2H), 2.94 (s) and 2.89 (s) (3H, rotamers). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 163.0 (d), 162.7 (d), 136.5 (s), 136.4 (s), 127.4 (s), 126.9 (s), 122.7 (d), 122.1 (d), 122.0 (d), 119.5 (d), 119.3 (d), 118.6 (d), 118.2 (d), 111.6 (d), 111.4 (d), 50.2 (t), 45.0 (t), 35.1 (q), 29.8 (q), 24.4 (t), 22.8 (t). **IR** (neat) ν (cm^{-1}) 3287, 2918, 2855, 1653. **HRMS** (positive ESI) Calcd for $C_{12}H_{14}N_2ONa$ [M*Na*$^+$]: 225.0998, found 225.0998. Mp 71 – 74 °C. A solution of **42** (218 mg, 1.08 mmol) in THF (0.54 mL) was added to a suspension of NaH (60% in min. oil, 86 mg, 2.16 mmol) in THF (2.2 mL). The reaction mixture was stirred for 15 min at rt then **41** (276 mg, 1.08 mmol) was added. The resulting mixture was stirred for 3 h at rt then water was added. The usual work-up (DCM) and purification (70 to 100% EtOAc in hexanes then 2% MeOH in EtOAc) afforded **43** (242 mg, 68%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.5 mixture of rotamers δ (ppm) 8.06 (s) and 7.83 (s) (1H, rotamers), 7.63 (d, *J* = 8.0 Hz) and 7.54 (d, *J* = 8.0 Hz) (1H, rotamers), 7.34 (d, *J* = 3.5 Hz) and 7.31 (d, *J* = 3.5 Hz) (1H, rotamers), 7.24-7.18 (m, 1H), 7.14-7.08 (m, 1H), 6.97 (s) and 6.88 (s) (1H, rotamers), 4.09 (t, *J* = 7.0 Hz, 2H), 3.97-3.86 (m, 4H), 3.67-3.62 (m) and 3.55-3.50 (m) (2H, rotamers), 3.03-2.97 (m, 2H), 2.93 (s) and 2.88 (s) (3H, rotamers), 1.92 (dt, *J* = 12.0, 7.5 Hz, 2H), 1.66 (dd, *J* = 10.0, 6.0 Hz, 2H), 1.29 (s) and 1.28 (s) (3H, rotamers). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 162.6 (d), 162.3 (d), 136.3 (s), 136.2 (s), 127.7 (s), 127.3 (s), 125.8 (d), 125.5 (d), 121.6 (d), 121.4 (d), 118.8 (d), 118.7 (d), 118.3 (d), 111.1 (s), 110.1 (s), 109.6 (d), 109.5 (s), 109.3 (d), 64.5 (t), 50.0 (t), 46.1 (t), 46.0 (t), 44.9 (t), 36.2 (t), 36.1 (t), 34.8 (q), 29.5 (q), 24.7 (t), 24.3 (t), 23.8 (q), 22.6 (t). **IR** (neat) ν (cm^{-1}) 2944, 2877, 1667, 1063. **HRMS** (positive ESI) Calcd for $C_{19}H_{26}N_2O_3Na$ [M*Na*$^+$]: 353.1836, found 353.1835.

***N*-(2-(1-Methyl-1*H*-indol-3-yl)ethyl)-*N*-(4-oxopentyl)formamide (44a)**. Trifluroroacetic acid (1.5 mL, 19.4 mmol) was added to a solution of *tert*-butyl (2-(1-methyl-1*H*-indol-3-yl)ethyl)carbamate (886 mg, 3.23 mmol) in DCM (16 mL) at 0 °C. The solution was stirred for 18 h at rt then a saturated aqueous solution of Na_2CO_3 (20 mL) was added. The usual workup (DCM) afforded the crude primary amine (338 mg, 1.94 mmol) that was used directly in the next step. Following the procedure used to prepare **24**, crude primary amine was treated with $AlMe_3$ (2.0 M in toluene, 0.97 mL, 1.94 mmol) and γ-valerolactone (0.15 mL, 1.62 mmol) in DCM (13 mL). The usual workup (DCM) and purification (50 to 100% EtOAc in hexanes then 1% MeOH in EtOAc) afforded 4-hydroxy-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)pentanamide (405 mg, 91%) as an orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.59 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.90 (s, 1H), 5.66 (br s, 1H), 3.83-3.78 (m, 1H), 3.76 (s, 3H), 3.59 (dd, *J* = 13.0, 6.5 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.80 (br s, 1H), 2.27 (dd, *J* = 10.5, 4.0 Hz, 2H), 1.83-1.58 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.8 (s), 137.2 (s), 127.9 (s), 126.9 (d), 121.8 (d), 119.0 (d), 118.9 (d), 111.5 (s), 109.4 (d), 67.4 (d), 40.1 (t), 34.4 (t), 33.3 (t), 32.7 (q), 25.2 (t), 23.6 (q). **IR** (neat) ν (cm^{-1}) 3305 (br), 2922, 1639, 1549, 739. **HRMS** (positive ESI) Calcd for $C_{16}H_{22}N_2O_2Na$ [M*Na*$^+$]: 297.1573, found 297.1579. Following the procedure used to prepare **27**, 4-hydroxy-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)pentanamide (405 mg, 1.48 mmol) was first treated with $LiAlH_4$ (112 mg, 2.96 mmol) in THF (5.0 mL), then with water (0.11 mL), NaOH (15%, 0.11 mL), and water (0.33 mL) to afford a crude amino-alcohol that was used directly in the next step. Following the procedure used to prepare **19**, crude amino-alcohol was treated with *N*-formylbenzotriazole (458 mg, 3.11 mmol) in THF (5 mL) to afford crude *N,O*-bisformylated product that was used directly in the next step. The residue then treated with K_2CO_3 (430 mg, 3.11 mmol) in MeOH (10 mL) and the usual work-up (EtOAc) and purification (40 to 100% EtOAc in hexanes then 1 to 3% MeOH in EtOAc) afforded *N*-(4-hydroxypentyl)-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)formamide (252 mg, 59% over 3 steps) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$)

1:0.8 mixture of rotamers δ (ppm) 8.09 (s) and 7.82 (s) (1H, rotamers), 7.64 (d, *J* = 8.0 Hz) and 7.53 (d, *J* = 8.0 Hz) (1H, rotamers), 7.31 (d, *J* = 3.5 Hz) and 7.29 (d, *J* = 3.5 Hz) (1H rotamers), 7.25-7.20 (m, 1H), 7.15-7.09 (m, 1H), 6.91 (s) and 6.82 (s) (1H, rotamers), 3.89-3.79 (m, 1H), 3.74 (s, 3H), 3.63-3.58 (m, 1H), 3.51 (t, *J* = 7.0 Hz, 1H), 3.49-3.31 (m, 1H), 3.18 (t, *J* = 7.1 Hz, 1H), 3.00 (dt, *J* = 11.0, 8.0 Hz, 2H).1.84-1.31 (m, 5H), 1.19 (d, *J* = 6.0 Hz) and 1.16 (d, *J* = 6.0 Hz) (3H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 163.1 (d), 162.9 (d), 137.2 (s), 137.0 (s), 127.8 (s), 127.4 (s), 127.2 (d), 126.9 (d), 121.9 (d), 121.7 (d), 119.1 (d), 118.9 (d), 118.8 (d), 118.4 (d), 111.4 (s), 110.2 (s), 109.5 (d), 109.3 (d), 67.5 (d), 67.4 (d), 48.1 (t), 48.0 (t), 43.4 (t), 42.3 (t), 36.1 (t), 35.8 (t), 32.8 (q), 32.7 (q), 25.2 (t), 25.1 (t), 23.9 (t), 23.8 (q), 23.7 (q), 23.2 (t). **IR** (neat) ν (cm^{-1}) 3390 (br), 2928, 1650, 738. **HRMS** (positive ESI) Calcd for $C_{17}H_{24}N_2O_2Na$ [M*Na*$^+$]: 311.1730, found 311.1728. *N*-(4-hydroxypentyl)-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)formamide (84 mg, 0.29 mmol) was then treated with Dess-Martin periodinane (246 mg, 0.58 mmol) in DCM (2.0 mL) and the usual workup (DCM) and purification (60 to 100% EtOAc in hexanes then 1% MeOH in EtOAc) afforded **44a** (56 mg, 67%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.7 mixture of rotamers δ (ppm) 8.05 (s) and 7.80 (s) (1H, rotamers), 7.65 (d, *J* = 8.0 Hz) and 7.54 (d, *J* = 8.0 Hz) (1H, rotamers), 7.31-7.20 (m, 2H), 7.12 (t, *J* = 7.0 Hz, 1H), 6.91 (s) and 6.82 (s) (1H, rotamers), 3.73 (s, 3H), 3.62-3.57 (m, 1H), 3.50 (t, *J* = 7.0 Hz, 1H), 3.37 (t, *J* = 7.0 Hz, 1H), 3.16 (t, *J* = 7.0 Hz, 1H), 3.03-2.95 (m, 2H), 2.46 (t, *J* = 7.0 Hz) and 2.36 (t, *J* = 7.0 Hz) (2H, rotamers), 2.13 (s) and 2.10 (s) (3H, rotamers), 1.92-1.72 (m, 2H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 208.0 (s), 207.3 (s), 163.2 (d), 162.8 (d), 137.2 (s), 137.0 (s), 127.8 (s), 127.4 (s), 127.2 (d), 126.8 (d), 121.9 (d), 121.7 (d), 119.1 (d), 119.0 (d), 118.9 (d), 118.4 (d), 111.3 (s), 110.2 (s), 109.5 (d), 109.3 (d), 47.9 (t), 46.9 (t), 43.3 (t), 41.4 (t), 40.6 (t), 39.7 (t), 32.8 (q), 32.7 (q), 30.1 (q), 30.0 (q), 25.0 (t), 23.2 (t), 22.4 (t), 21.4 (t). **IR** (neat) ν (cm^{-1}) 2932, 1711, 1662, 740. **HRMS** (positive ESI) Calcd for $C_{17}H_{22}N_2O_2Na$ [M*Na*$^+$]: 309.1573, found 309.1579.

***N*-(2-(1-Methyl-1*H*-indol-3-yl)ethyl)-*N*-(5-oxohexyl)formamideformamide (44b)**. Following the procedure used to prepare **44a**, *tert*-butyl (2-(1-methyl-1*H*-indol-3-yl)ethyl)carbamate (886 mg, 3.23 mmol) was treated with trifluroroacetic acid (1.5 mL, 19.4 mmol) in DCM (16 mL) to afford the crude primary amine (218 mg, 1.25 mmol) that was used directly in the next step. Following the procedure used to prepare **24**, crude primary amine was treated with $AlMe_3$ (2.0 M in toluene, 0.63 mL, 1.25 mmol) and **23** (0.11 mL, 1.04 mmol) in DCM (8.3 mL). The usual workup (DCM) and purification (80 to 100% EtOAc in hexanes then 2% MeOH in EtOAc) afforded 5-hydroxy-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)hexanamide (298 mg, 99%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.59 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.89 (s, 1H), 5.57 (br s, 1H), 3.76 (s, 3H), 3.73-3.69 (m, 1H), 3.59 (dd, *J* = 12.5, 6.5 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.14 (td, *J* = 7.0, 2.5 Hz, 2H), 1.84 (br s, 1H), 1.73-1.63 (m, 2H), 1.45-1.38 (m, 2H), 1.16 (d, *J* = 6.0 Hz, 3H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.2 (s), 137.2 (s), 127.9 (s), 126.9 (d), 121.9 (d), 119.0 (d), 118.9 (d), 111.6 (s), 109.4 (d), 67.4 (d), 40.0 (t), 38.7 (t), 36.4 (t), 32.7 (q), 25.3 (t), 23.6 (q), 21.7 (t). **IR** (neat) ν (cm^{-1}) 3294 (br), 2928, 1641, 1550. **HRMS** (positive ESI) Calcd for $C_{17}H_{24}N_2O_2Na$ [M*Na*$^+$]: 311.1730, found 311.1735. Following the procedure used to prepare **27**, 5-hydroxy-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)hexanamide (332 mg, 1.15 mmol) was first treated with $LiAlH_4$ (87 mg, 2.30 mmol) in THF (8.3 mL), then with water (0.09 mL), NaOH (15%, 0.09 mL), and water (0.27 mL) to afford a crude amino-alcohol that was used directly in the next step. Following the procedure used to prepare **19**, crude amino-alcohol was treated with *N*-formylbenzotriazole (244 mg, 1.66 mmol) in THF (2.6 mL) to afford crude *N,O*-bisformylated product that was used directly in the next step. The residue then treated with K_2CO_3 (229 mg, 1.66 mmol) in MeOH (2.6 mL) and the usual work-up (EtOAc) and purification (60 to 100% EtOAc in hexanes then 3% MeOH in EtOAc) afforded *N*-(5-hydroxyhexyl)-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)formamide (171 mg, 72% over 3 steps) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.9 mixture of rotamers δ (ppm) 8.09 (s) and 7.82 (s) (1H, rotamers),

7.64 (d, *J* = 8.0 Hz) and 7.53 (d, *J* = 8.0 Hz) (1H, rotamers), 7.32 (d, *J* = 3.5 Hz) and 7.29 (d, *J* = 3.5 Hz) (1H, rotamers), 7.23 (dd, *J* = 3.5, 1.0 Hz) and 7.21 (dd, *J* = 3.5, 1.0 Hz) (1H, rotamers), 7.15-7.09 (m, 1H), 6.91 (s) and 6.83 (s) (1H, rotamers), 3.83-3.78 (m, 1H), 3.75 (s, 3H), 3.63-3.68 (m, 1H), 3.51 (t, *J* = 7.0 Hz, 1H), 3.38 (t, *J* = 7.5 Hz, 1H), 3.16 (t, *J* = 7.0 Hz, 1H), 2.99 (dt, *J* = 10.0, 7.5 Hz, 2H), 1.65-1.26 (m, 7H), 1.19 (d, *J* = 4.5 Hz) and 1.17 (d, *J* = 4.5 Hz) (3H, rotamers). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 163.0 (d), 162.8 (d), 137.1 (s), 137.0 (s), 127.8 (s), 127.3 (s), 127.1 (d), 126.8 (d), 121.8 (d), 121.6 (d), 119.0 (d), 118.9 (d), 118.8 (d), 118.3 (d), 111.3 (s), 110.2 (s), 109.5 (d), 109.2 (d), 67.6 (d), 67.5 (d), 48.0 (t), 47.9 (t), 43.3 (t), 42.1 (t), 38.7 (t), 38.6 (t), 32.7 (q), 32.6 (q), 28.7 (t), 27.4 (t), 25.0 (t), 23.6 (q), 23.5 (q), 23.2 (t), 23.0 (t), 22.7 (t). **IR** (neat) ν (cm^{-1}) 3407 (br), 2930, 2861, 1652. **HRMS** (positive ESI) Calcd for $C_{18}H_{26}N_2O_2Na$ [M*Na*$^+$]: 325.1886, found 325.1890. Following the procedure to prepare **28c**, *N*-(5-hydroxyhexyl)-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)formamide (86 mg, 0.28 mmol) was treated with Dess-Martin periodinane (178 mg, 0.42 mmol) in DCM (5.6 mL) and the usual workup (DCM) and purification (40 to 100% EtOAc in hexanes) afforded **44b** (53 mg, 63%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.8 mixture of rotamers δ (ppm) 8.08 (s) and 7.81 (s) (1H, rotamers), 7.63 (d, *J* = 8.0 Hz) and 7.53 (d, *J* = 8.0 Hz) (1H, rotamers), 7.31 (d, *J* = 3.5 Hz) and 7.28 (d, *J* = 3.5 Hz) (1H, rotamers), 7.25-7.20 (m, 1H), 7.12 (ddd, *J* = 8.5, 3.0, 1.5 Hz, 1H), 6.91 (s) and 6.83 (s) (1H, rotamers), 3.74 (s, 3H), 3.60 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.50 (t, *J* = 7.0 Hz, 1H), 3.37 (t, *J* = 7.0 Hz, 1H), 3.14 (t, *J* = 6.5 Hz, 1H), 2.99 (m, 2H), 2.49-2.35 (m, 2H), 2.13 (s) and 2.11 (s) (3H, rotamers), 1.60-1.46 (m, 4H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 208.7 (s), 208.1 (s), 163.0 (d), 162.8 (d), 137.2 (s), 137.1 (s), 127.8 (s), 127.4 (s), 127.2 (d), 126.9 (d), 121.9 (d), 121.7 (d), 119.1 (d), 119.0 (d), 118.8 (d), 118.4 (d), 111.4 (s), 110.2 (s), 109.6 (d), 109.3 (d), 48.0 (t), 47.9 (t), 43.4 (t), 43.0 (t), 42.9 (t), 41.8 (t), 32.8 (q), 32.7 (q), 30.1 (q), 30.0 (q), 28.3 (t), 26.8 (t), 25.1 (t), 23.3 (t), 20.9 (t), 20.6 (t). **IR** (neat) ν (cm^{-1}) 2936, 2871, 1710, 1659. **HRMS** (positive ESI) Calcd for $C_{18}H_{24}N_2O_2Na$ [M*Na*$^+$]: 323.1730, found 323.1730.

***N*-Methyl-*N*-(2-(1-(4-oxopentyl)-1*H*-indol-3-yl)ethyl)formamide (44c)**. *p*-TsOH (42 mg, 0.22 mmol) was added to a solution of **43** (242 mg, 0.73 mmol) in acetone/H_2O (1:1, 4.0 mL). The solution was stirred for 18 h at rt then a saturated solution of $NaHCO_3$ was added. The usual workup (Et_2O) and purification (50 to 100% EtOAc in hexanes then 2% MeOH in EtOAc) afforded **44c** (175 mg, 84%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 1:0.5 mixture of rotamers δ (ppm) 8.06 (s) and 7.74 (s) (1H, rotamers), 7.63 (d, *J* = 8.0 Hz) and 7.54 (d, *J* = 8.0 Hz) (1H, rotamers), 7.33 (d, *J* = 4.0 Hz) and 7.30 (d, *J* = 4.0 Hz) (1H, rotamers), 7.25-7.18 (m, 1H), 7.15-7.09 (m, 1H), 6.94 (s) and 6.83 (s) (1H, rotamers), 4.11 (t, *J* = 7.0 Hz, 2H), 3.68-3.63 (m) and 3.55-3.50 (m) (2H, rotamers), 3.03-2.97 (m, 2H), 2.93 (s) and 2.91 (s) (3H, rotamers), 2.39-2.32 (m, 2H), 2.12-2.03 (m, 5H). **^{13}C{^{1}H} NMR** mixture of rotamers (75 MHz, $CDCl_3$) δ (ppm) 207.8 (s), 207.7 (s), 162.7 (d), 162.4 (d), 136.4 (s), 136.3 (s), 127.8 (s), 127.3 (s), 126.0 (d), 125.5 (d), 121.9 (d), 121.7 (d), 119.1 (d), 118.9 (d), 118.8 (d), 118.5 (d), 111.5 (s), 110.4 (s), 109.6 (d), 109.4 (d), 50.0 (t), 44.9 (t), 39.9 (t), 39.8 (t), 34.9 (q), 30.0 (q), 29.5 (q), 24.2 (t), 24.1 (t), 24.0 (t), 22.6 (t). **IR** (neat) ν (cm^{-1}) 2932, 1711, 1666. **HRMS** (positive ESI) Calcd for $C_{17}H_{22}N_2O_2Na$ [M*Na*$^+$]: 309.1573, found 309.1571.

***cis*-1-(1,2,3,5,6,10b-Hexahydrodipyrrolo[1,2-*a*:2',1'-*c*]pyrazin-1-yl)ethan-1-one (49a)**. Following the procedure used to prepare **18a**, **39a** (67 mg, 0.30 mmol) was treated with triflic anhydride (56 µL, 0.33 mmol) and DTBMP (68 mg, 0.33 mmol) in DCM (6.0 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of an iminium ion resulting from the Vilsmeier-Haack cyclization. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.70 (s, 1H), 7.38 (s, 1H), 7.27 (s, 1H), 6.48 (dd, *J* = 4.5, 2.5 Hz, 1H), 4.49-4.45 (m, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.91 (t, *J* = 7.0 Hz, 2H), 2.68-2.63 (m, 2H), 2.12 (s, 3H), 2.11-2.01 (m, 2H). Subsequent treatment with pyrrolidine (75 µL, 0.90 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (5 to 80% EtOAc in hexanes with 1.5% Et_3N) afforded **49a** (53 mg, 87%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.57-6.55 (m, 1H), 6.14-6.12 (m, 1H), 5.81-5.80 (m, 1H), 4.09-4.01 (m, 2H), 3.92 (dt, *J* = 12.0, 4.0

Hz, 1H), 3.22-3.13 (m, 2H), 3.08-2.93 (m, 2H), 2.87-2.79 (m, 1H), 2.29 (s, 3H), 2.08-1.92 (m, 2H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 209.2 (s), 129.8 (s), 119.1 (d), 108.1 (d), 103.3 (d), 61.2 (d), 56.8 (d), 51.9 (t), 47.5 (t), 43.0 (t), 30.0 (q), 28.1 (t). **IR** (neat) ν (cm^{-1}) 2921, 1706, 720. **HRMS** (positive ESI) Calcd for $C_{12}H_{17}N_2O$ [M + H^+]: 205.1335, found 205.1340.

***cis*-1-(5,6,9,10,11,11a-Hexahydro-8*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-11-yl)ethan-1-one (49b)**. Following the procedure used to prepare **18a**, **39b** (14 mg, 0.06 mmol) was treated with triflic anhydride (12 µL, 0.07 mmol) and DTBMP (14 mg, 0.07 mmol) in $CDCl_3$ (1.2 mL). ^{1}H NMR analysis of a small sample of the reaction mixture revealed the presence of an iminium ion resulting from the Vilsmeier-Haack cyclization. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.72 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 6.48 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.47 (t, *J* = 6.5 Hz, 2H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.92 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 6.5 Hz, 2H), 2.12 (s, 3H), 1.87-1.77 (m, 2H), 1.67-1.61 (m, 2H). Subsequent treatment with pyrrolidine (30 µL, 0.36 mmol) added at 0 °C then stirred at rt for 3 h followed by the usual work-up (DCM) and purification (2 to 50% EtOAc in hexanes with 1.5% Et_3N) afforded **49b** (53 mg, 87%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.52-6.47 (m, 1H), 6.07-6.05 (m, 1H), 5.57 (d, *J* = 3.5 Hz, 1H), 4.09 (td, *J* = 12.0, 5.0 Hz, 1H), 3.90 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.62 (d, *J* = 10.0 Hz, 1H), 3.02-2.75 (m, 4H), 2.42-2.37 (m, 1H), 2.32 (s, 3H), 2.00-1.95 (m, 1H), 1.77-1.63 (m, 2H), 1.50-1.36 (m, 1H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 211.6 (s), 129.4 (s), 119.0 (d), 108.2 (d), 103.8 (d), 60.9 (d), 55.0 (t), 54.6 (d), 52.7 (t), 44.8 (t), 30.3 (q), 28.8 (t), 24.7 (t). **IR** (neat) ν (cm^{-1}) 2923, 2790, 1705. **HRMS** (positive ESI) Calcd for $C_{13}H_{19}N_2O$ [M + H^+]: 219.1492, found 219.1503. **Mp** 104 – 107 °C.

***cis*-1-(11-Methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)ethan-1-one (50a)**. Following the procedure used to prepare **18a**, **44a** (52 mg, 0.18 mmol) was treated with triflic anhydride (34 µL, 0.20 mmol) and DTBMP (41 mg, 0.20 mmol) in DCM (3.6 mL). Subsequent treatment with pyrrolidine (45 µL, 0.54 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (5 to 70% EtOAc in hexanes with 1.5% Et_3N) afforded **50a** (9.0 mg, 19%) as a

yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.49 (d, *J* = 8.0 Hz, 1H), 7.24-7.07 (m, 3H), 4.94 (d, *J* = 5.0 Hz, 1H), 3.50 (s, 3H), 3.29-2.89 (m, 6H), 2.71-2.62 (m, 1H), 2.31 (s, 3H), 2.08-1.98 (m, 2H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 208.6 (s), 137.5 (s), 135.9 (s), 126.8 (s), 121.5 (d), 119.3 (d), 118.3 (d), 108.9 (d), 107.5 (s), 57.3 (d), 56.6 (d), 50.2 (t), 46.0 (t), 30.5 (q), 29.9 (t), 28.9 (q), 17.5 (t). **IR** (neat) ν (cm^{-1}) 2921, 1707, 748. **HRMS** (positive ESI) Calcd for $C_{17}H_{21}N_2O$ [M + H^+]: 269.1648, found 269.1652.

1-(12-Methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)ethan-1-one (50b). Following the procedure used to prepare **18a**, **44b** (99 mg, 0.33 mmol) was treated with triflic anhydride (61 μL, 0.36 mmol) and DTBMP (74 mg, 0.36 mmol) in $CHCl_3$ (6.6 mL). Subsequent treatment with pyrrolidine (0.17 mL, 1.98 mmol) added at 0 °C then stirred at 0 °C for 2 h then at rt for 18 h followed by concentration under reduce pressure and the usual purification (2 to 80% EtOAc in hexanes with 1.5% Et_3N) afforded ***cis*-50b** (22 mg) and ***trans*-50b** (20 mg) (49%) as yellow oils. ***cis*-50b: ^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.50 (d, *J* = 8.0 Hz, 1H), 7.23-7.17 (m, 2H), 7.13-7.07 (m, 1H), 4.12 (d, *J* = 10.0 Hz, 1H), 3.63-3.52 (m, 1H), 3.39 (s, 3H), 3.31-3.21 (m, 3H), 3.00-2.89 (m, 3H), 2.04-1.86 (m, 3H), 1.83 (s, 3H), 1.46-1.39 (m, 1H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 212.6 (s), 138.5 (s), 136.3 (s), 127.5 (s), 121.8 (d), 119.4 (d), 118.4 (d), 109.7 (d), 108.2 (s), 56.5 (d), 54.5 (t), 49.6 (d), 43.9 (t), 32.4 (q), 30.9 (q), 27.8 (t), 21.6 (t), 18.3 (t). **IR** (neat) ν (cm^{-1}) 2933, 2857, 1701, 1467, 737. **HRMS** (positive ESI) Calcd for $C_{18}H_{23}N_2O$ [M + H^+]: 283.1805, found 283.1802. **Rf** = 0.49, 70% EtOAc/Hexanes with Et_3N). ***trans*-50b: ^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.50 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.14-7.10 (m, 1H), 3.79 (d, *J* = 2.0 Hz, 1H), 3.75 (s, 3H), 3.18-3.16 (m, 1H), 3.12-2.89 (m, 3H), 2.76-2.69 (m, 1H), 2.63-2.51 (m, 2H), 2.41-2.37 (m, 1H), 2.18-2.00 (m, 1H), 1.70 (s, 3H), 1.67-1.55 (m, 2H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 209.7 (s), 138.2 (s), 134.9 (s), 126.6 (s), 121.6 (d), 119.5 (d), 118.3 (d), 110.8 (s), 109.1 (d), 62.2 (d), 57.3 (t), 53.4 (t), 51.1 (d), 31.7 (q), 30.2 (q),

27.5 (t), 22.3 (t), 22.0 (t). **IR** (neat) ν (cm^{-1}) 2942, 2918, 1699, 1468, 736. **Rf** = 0.82, 70% EtOAc/Hexanes with Et_3N). **HRMS** (positive ESI) Calcd for $C_{18}H_{23}N_2O$ [M + H^+]: 283.1805, found 283.1808.

***cis*-1-(3-Methyl-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-yl)ethan-1-one (50c)**. Following the procedure used to prepare **18a**, **44c** (66 mg, 0.23 mmol) was treated with triflic anhydride (42 µL, 0.25 mmol) and DTBMP (51 mg, 0.25 mmol) in DCM (4.6 mL). Subsequent treatment with DIPEA (80 µL, 0.46 mmol) and L-prolinamide (6.0 mg, 0.05 mmol) added at 0 °C then stirred at rt for 18 h followed by the usual work-up (DCM) and purification (5 to 70% EtOAc in hexanes with 1.5% Et_3N) afforded **50c** (30 mg, 48%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.50 (d, *J* = 7.5 Hz, 1H), 7.28 (m, 1H), 7.20-7.09 (m, 2H), 4.32-4.23 (m, 1H), 4.21 (d, *J* = 11.0 Hz, 1H), 3.76-3.66 (m, 1H), 3.24-2.67 (m, 6H), 2.39 (s, 3H), 2.29 (s, 3H), 2.26-2.17 (m, 1H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ (ppm) 209.8, 137.1, 132.7, 128.0, 121.2, 119.8, 118.5, 109.4, 106.3, 59.8, 53.7, 50.1, 41.8, 38.6, 29.6, 27.2, 18.8. **IR** (neat) ν (cm^{-1}) 2956, 1732, 1402. **HRMS** (positive ESI) Calcd for $C_{17}H_{21}N_2O$ [M + H^+]: 269.1648, found 269.1660.

Supporting Information Available. Copies ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Note

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