The Formal [3+2+1] Cyclisation of Cyclopropylamines with Carboxylic Anhydrides: A Quick Access to Polysubstituted 2,3,3a,4-Tetrahydro-6(5*H*)-indolone Ring Systems

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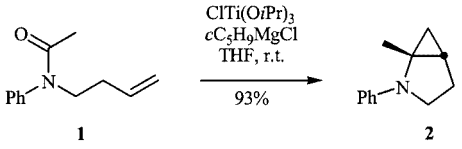
Several 2-azabicyclo[3.1.0]hexanes were synthesised using the intramolecular version of the Kulinkovich–de Meijere cyclopropanation reaction. Upon heating in the presence of a carboxylic anhydride, the cyclopropane rings of these systems open up to afford vinylogous amides. Depending on the reaction conditions used, the monoacylated compounds may be the major products, or subsequent acylation may take place to afford cyclic diketones. The method is flexible, and it is possible to incorporate different acyl groups in a two-step sequence. The diketones are easily converted into 2,3,3a,4-tetrahydro-6(5*H*)-indolone derivatives by intramolecular aldolisation. The products, which are highly functionalised alcohols, are obtained as single diastereoisomers.

Introduction

The de Meijere variation of the Kulinkovich cyclopropanation[1,2] provides a quick and general access to a variety of cyclopropylamines.[2a,3] Bicyclic molecules are obtained when this reaction is performed in the intramolecular mode.[4] The synthesis of 1-methyl-2-phenyl-2-azabicyclo[3.1.0]hexane (**2**) is the first reported example that uses the ligand-exchange method (Scheme 1).[4b]



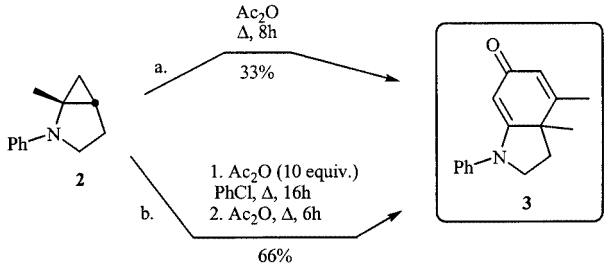
Scheme 1

Such compounds are especially interesting. Relatively few studies have been carried out to describe the reactivity of cyclopropylamines since they were previously not so easily accessible.[5] However, it is known that under thermal conditions they may undergo ring-opening to iminium or enamine species.[6] With an increase in reactivity due to additional ring strain, bicyclic molecules like **2** could thus be valuable intermediates in the synthesis of a number of attractive chemical structures. We now wish to report some results involving their reactions with carboxylic anhydrides.

Results and Discussion

Initial Results

When the cyclopropylamine **2** was heated in acetic anhydride at reflux for 8 h, the tetrahydroindolone **3** was obtained in 33% yield (Scheme 2, a).



Scheme 2

In the course of the reaction, TLC analysis revealed the initial formation of two other compounds. Reducing the amount of acetic anhydride to 10 equiv. with chlorobenzene as the solvent allowed for the isolation of these products in good yields. They were assigned as the vinylogous amide structures **4** and **5** (Scheme 3). Their intermediacy in the mechanism of formation of **3** is supported by the fact that heating of **4** in acetic anhydride cleanly converted it into **3**,

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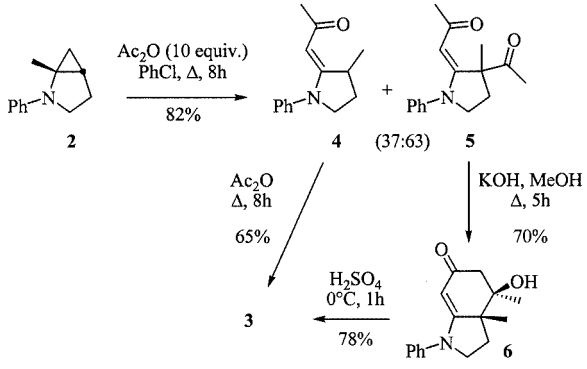
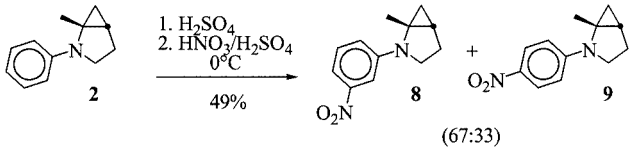
with the transient formation of **5** as observed by TLC analysis. Moreover, intramolecular aldolisation of diketone **5** occurs by simply heating it in a methanolic solution of potassium hydroxide[7] to afford a highly functionalised tertiary alcohol **6** bearing two contiguous quaternary centres.[8] Dehydration of **6** by treatment with sulfuric acid furnishes **3**. We also improved the formation of **3** from **2** using a two-step procedure where the intermediates are not purified (Scheme 2, b).



Scheme 3

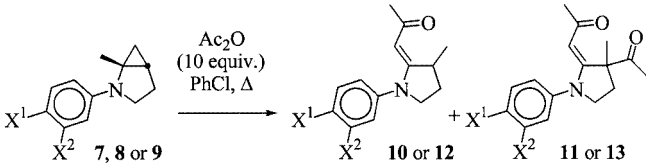
Mechanistic Study

It is worth noting that the cyclopropane ring-opening is highly regioselective. No product resulting from cleavage of the carbon−carbon bond fusing the two cycles has ever been observed by us for any of our compounds.[9] To gain further insight into the mechanism, we also studied the reactivity of the substituted derivatives **7**−**9**. The *p*-phenoxy-substituted compound **7** was prepared in a few steps from *p*-phenoxyaniline with the same reaction sequence as for the synthesis of **2**. Cyclopropylamines **8** and **9** were prepared by nitration of **2** (Scheme 4).



Scheme 4

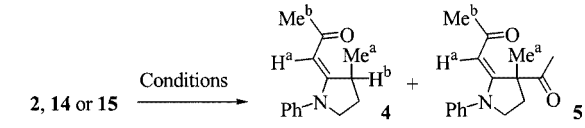
Although no significant rate enhancement was observed with the electronically enriched **7**, the reaction performed at least equally well as that with **2**. In contrast, the nitro compounds **8** and **9** displayed very low reactivities (Scheme 5). This observation supports the hypothesis of the formation of a species with a positive charge in the rate-determining step (vide infra).



X^1	X^2	Starting material	Time	Yield	Products (ratio)
OPh	H	**7**	14h	79%	**10** and **11** (23:77)
H	NO_2	**8**	57h	14%	**12** and **13** (57:43)
NO_2	H	**9**	48h	no reaction	

Scheme 5

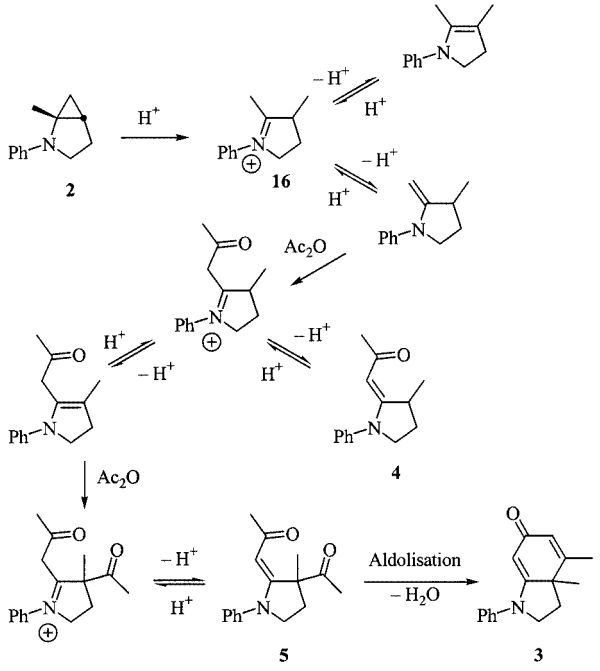
When the cyclopropylamine **2** is converted into vinylogous amides **4** and **5**, the CH_2 group of the cyclopropane moiety becomes a methyl group (Scheme 3). A few experiments were carried out to establish whether the newly introduced hydrogen atom was coming from compound **2** itself, or from the reaction medium. Deuterated cyclopropylamines **14** and **15** were synthesised for this purpose from the corresponding deuterated amides.[10] When chlorobenzene solutions of **14** and **15** were refluxed in the presence of acetic anhydride, no incorporation of deuterium was observed at the carbon atom of the methyl group originally belonging to the cyclopropane ring in the isolated products **4** and **5**. The products were partially deuterated at some other sites, which is in agreement with the possibility of proton exchange at these positions in the reaction intermediates. In contrast, when the non-deuterated cyclopropylamine **2** was treated with[D_6]acetic anhydride in chlorobenzene, the above-mentioned methyl group was slightly deuterated, and when a 5:1 mixture of [D_6]acetic anhydride and [D_4]acetic acid was used, deuterium incorporation was high (Scheme 6). It is also worth noting that in the latter case, the presence of acetic acid significantly increased the rate of the reaction.



Starting material	Conditions; yield (**4** : **5** ratio)	% [D] in **4** H^a	H^b	Me^a	Me^b	% [D] in **5** H^a	Me^a	Me^b
14	Ac_2O (16 equiv.) PhCl, Δ, 5h 74% (30:70)	22	33	**0**	28	17	**0**	20
15	Ac_2O (16 equiv.) PhCl, Δ, 3h 70% (50:50)	20	35	**0**	n.d.	n.d.	**0**	n.d.
2	[D_6]Ac_2O (16 equiv.) PhCl, Δ, 11h 65% (11:89)	40	70	**10**	100	46	**13**	100
2	[D_6]Ac_2O/[D_4]AcOH (5:1) Δ, 20 min 75% (29:71)	20	90	**90**	100	25	**87**	100

Scheme 6

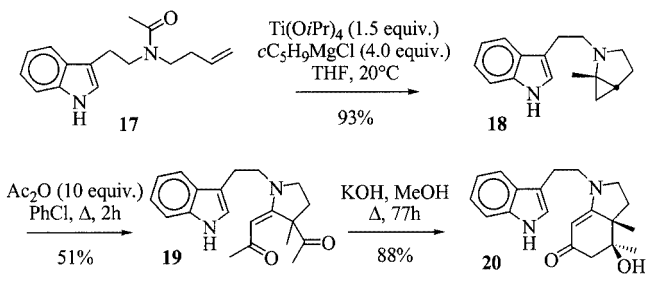
Taking these various observations into account, the following mechanism may be proposed tentatively, where the rate-determining step would be the formation of the iminium ion **16** (Scheme 7). This species could be formed by the direct protonation of the cyclopropane ring by a trace amount of acid,[11] or by the rearrangement of an initially formed cyclopropylammonium ion. An alternative possibility would be a process where the three-membered ring would open reversibly in a heterolytic fashion under the action of heat.[5] Protonation of the opened form would lead to **16**. Once formed, the iminium ion should be in equilibrium with the corresponding enamines. Acylation by acetic anhydride would then provide the intermediate vinylogous amides **4** and **5**. Finally, intramolecular aldolisation of **5** followed by dehydration would deliver **3**.



Scheme 7

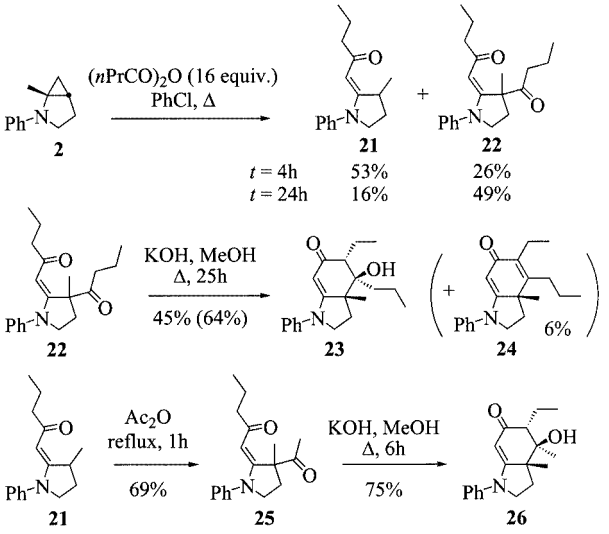
Further Developments

Next, the method was successfully extended to the indole derivative **18**, which is easily synthesised from tryptamine in three steps. The highly functionalised alcohol **20** was thus obtained, again as a single diastereoisomer (Scheme 8).[8] This example shows that an aromatic group on the nitrogen atom is not required for this kind of intramolecular Kulinkovich–de Meijere reaction, or for the subsequent ring-opening in the presence of acetic anhydride.



Scheme 8

The example depicted in Scheme 9 further demonstrates the potential of our method since it is not limited to the use of acetic anhydride. Moreover and most interestingly, two non-identical acyl functions can be incorporated sequentially (Scheme 9, bottom). Once again, the alcohols **23** and **26** thus synthesised are isolated as single diastereoisomers.[8]

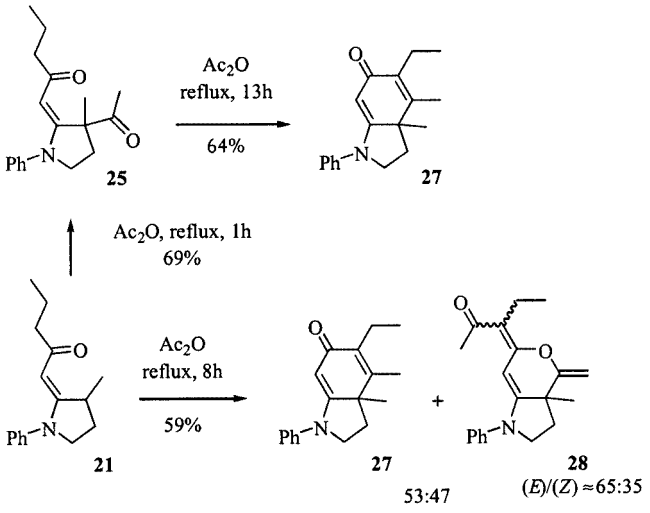


Scheme 9

Limitations and "Anomalous" Results

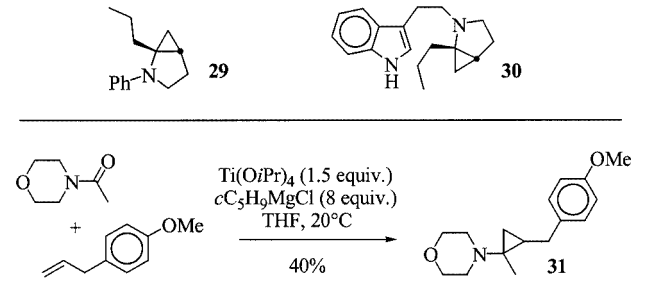
When heated in acetic anhydride at reflux, the diketone **25** cyclised to afford the expected tetrahydroindolone **27** (Scheme 10). Since **25** had been obtained cleanly from the vinylogous amide **21** under the same conditions, it seemed possible to convert **21** into **27** directly, in one step. This proved to be the case, but surprisingly, two unexpected compounds were also isolated in significant yields. They were assigned as the diastereoisomeric structures **28** on the basis of COSY, NOESY, HMQC and HMBC 2D NMR spectroscopic experiments (Scheme 10).

With the full characterisation and identification of **28**, it appeared in retrospect that some of it had been formed as well when **27** had been prepared from **25**, albeit in a much smaller amount. Since acetic acid is produced during the conversion of **21** to **25**, the formation of **28** may tentatively be rationalised by an acid-catalysed acetylation of **25**. We also attempted to extend the herein described method to cyclopropylamines **29** and **30**, which are higher analogues of **2** and **18** (Scheme 11, top). When they were heated in chlorobenzene in the presence of an excess of acetic anhydride, complex mixtures were obtained. Finally, it is worth noting that compound **31**, obtained as a single diastereoisomer from *N*-acetylmorpholine and *p*-allylanisole (Scheme 11, bottom), failed to react under the conditions described above. This indicates that the strain induced by



Scheme 10

the five-membered rings of **2**, **7**, **8** and **18** is essential for the ring-opening to proceed at this temperature.



Scheme 11

Conclusion

In summary, we have developed a quick and flexible method for the preparation of various 2,3,3a,4-tetrahydro-6(5*H*)-indolones using inexpensive reagents and starting from readily available cyclopropylamines. So far, this method is limited to bicyclic cyclopropylamines bearing a methyl group at the ring junction next to the nitrogen atom. Since these compounds appear to behave as 1,3-dinucleophilic species equivalents in the process described here, the scope of the possible applications could be much more general. The use of electrophiles other than carboxylic anhydrides is currently under study in our laboratory.

Experimental Section

General Remarks: NMR spectra were recorded with AC 250 (^{1}H at 250 MHz, ^{13}C at 62.9 MHz), AM 300, AVANCE 300 (^{1}H at 300 MHz, ^{13}C at 75.5 MHz) and AMX 400 (^{1}H at 400 MHz) Bruker spectrometers. Chemical shifts are given in ppm, referenced to the peak of tetramethylsilane, defined at δ = 0.00 (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at δ = 77.1 (^{13}C NMR). Infrared spectra were recorded with a Perkin−Elmer BX FT-IR spectrometer. Mass spectra were obtained using HP MS 5972 (CI), Thermofinigan Automass (EI), LC/MS Thermoquest Navigator (ES^+) and LCT Micromass (low- and high-resolution ES^+) spectrometers. Melting points were determined using a Büchi BS540 apparatus and are not corrected. Flash column chromatography was performed on SDS Chromagel silica gel 60 (35−70 μm). All reactions were carried out under argon unless otherwise stated. The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Analytical grade diethyl ether, DMF and toluene were purchased from SDS and used as received. Acetic anhydride, butyric anhydride, aniline and chlorobenzene were distilled before use. Chloroform was passed through a column containing a 10 cm high amount of silica gel of the type specified above. THF was distilled from sodium/benzophenone under argon. Cyclopentylmagnesium chloride solution in diethyl ether was purchased from Sigma−Aldrich or Fluka and titrated according to a previously reported method.[12]

Carboxylic Amide 1:[15] This compound was prepared according to a reported method for the alkylation of amides.[13] Potassium carbonate (1.02 equiv., 5.3 mmol, 0.73 g), tetrabutylammonium hydrogensulfate (0.05 equiv., 0.26 mmol, 89 mg) and ground sodium hydroxide (4.0 equiv., 21 mmol, 0.84 g) were added to a suspension of *N*-phenylacetamide (1.0 equiv., 5.2 mmol, 0.71 g) in toluene (21 mL). The mixture was stirred at 20 °C for 1 h, then at 80 °C for 15 min. But-3-enyl *p*-toluenesulfonate[14] (1.6 equiv., 8.4 mmol, 1.9 g) was added and stirring was continued at 80 °C for 3 h. After cooling to room temperature, 1 N aqueous hydrogen chloride solution (50 mL) was added. The organic layer was separated, and the aqueous extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated to afford a yellow oil (0.96 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 0 to 30%) yielded pure **1** (0.86 g, 4.5 mmol, 87%). Yellow oil. ^{1}H NMR: δ = 1.80 (s, 3 H), 2.28 (qt, *J* = 7, 1 Hz, 2 H), 3.78 (t, *J* = 7 Hz, 2 H), 4.98−5.11 (m, 2 H), 5.76 (ddt, *J* = 17, 10, 7 Hz, 1 H), 7.14−7.20 (m, 2 H), 7.32−7.46 (m, 3 H) ppm. ^{13}C NMR: δ = 22.7, 32.0, 48.0, 116.4, 127.7, 128.0, 130.4, 135.0, 143.3, 170.0 ppm.

Cyclopropylamine 2:[4b] This known compound was prepared according to a slight modification of the reported procedure.[4b] Titanium isopropoxide (1.5 equiv., 6.7 mmol, 2.0 mL) was added to a solution of the amide **1** (1.0 equiv., 4.5 mmol, 0.85 g) in THF (35 mL). Cyclopentylmagnesium chloride (2.0 M in Et_2O, 4.4 equiv., 20 mmol, 10 mL) was then added dropwise over 5 min. After 10 min of stirring at 20 °C, the mixture was diluted in diethyl ether (200 mL) and water (200 mL). The organic layer was separated, and the aqueous layer extracted with diethyl ether (2 × 200 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated to afford a black oil (1.0 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 0 to 2%) yielded pure **2** (0.70 g, 4.0 mmol, 90%). Colourless oil. ^{1}H NMR: δ = 0.73 (t, *J* = 5 Hz, 1 H), 0.82 (dd, *J* = 8, 5 Hz,1 H), 1.36 (dt, *J* = 8, 5 Hz, 1 H), 1.56 (s, 3 H), 1.97 (ddd, *J* = 12, 9, 4 Hz, 1 H), 2.34 (dddd, *J* = 12, 10, 9, 5 Hz, 1 H), 2.87 (dt, *J* = 10, 9 Hz, 1 H), 4.05 (td, *J* = 10, 4 Hz, 1 H), 6.79 (tt, *J* = 7, 1 Hz, 1 H), 6.88−6.94 (m, 2 H), 7.20−7.28 (m, 2 H) ppm. ^{13}C NMR: δ = 17.9, 20.0, 24.8, 26.4, 43.2, 53.5, 117.4, 118.4, 128.8, 150.3 ppm.

Tetrahydroindolone 3. Method 1: A solution of the cyclopropylamine **2** (1.0 equiv., 0.69 mmol, 0.12 g) in acetic anhydride (100 mL) was heated at reflux for 8 h. Most of the acetic anhydride was then removed by distillation, and the remaining solution (about 10 mL) was poured onto chilled 1 N sodium hydroxide aque-

ous solution (225 mL). The mixture was extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated. Flash column chromatography (ethyl acetate/dichloromethane, gradient from 20 to 70%) of the crude product gave pure compound **3** (55 mg, 0.23 mmol, 33%). **Method 2:** Acetic anhydride (10 equiv., 10 mmol, 0.94 mL) was added to a solution of the cyclopropylamine **2** (1.0 equiv., 1.0 mmol, 0.17 g) in chlorobenzene (20 mL). The mixture was heated at reflux for 16 h. The solvent was removed under reduced pressure. The viscous brown oil thus obtained was then dissolved in acetic anhydride (10 mL). The mixture was heated at reflux for 6.5 h, after which the solvent was removed thoroughly. In order to do this, toluene (20 mL) was added and the mixture was concentrated. This process was repeated three times to afford a black viscous oil (0.28 g). Purification by flash column chromatography (ethyl acetate/dichloromethane, gradient from 0 to 100%) gave pure compound **3** (0.16 g, 0.66 mmol, 66%). **Method 3:** A solution of the vinylogous amide **4** (1.0 equiv., 84 μmol, 18 mg) in acetic anhydride (4.0 mL) was heated at reflux for 8 h. After cooling, the solution was poured onto 1 N sodium hydroxide aqueous solution (100 mL). The mixture was stirred at 20 °C for 20 min, then extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated to afford a black oil. Flash column chromatography (ethyl acetate/dichloromethane, gradient from 0 to 100%) of the crude product gave pure compound **3** (13 mg, 54 μmol, 65%). **Method 4:** Compound **3** could also be obtained by dehydrating alcohol **6**. Sulfuric acid (0.50 mL) was added dropwise to alcohol **6** (1.0 equiv., 0.15 mmol, 38 mg) at 0 °C. After 1 h of stirring at 0 °C, the mixture was poured onto a few grams of ice. A 1 N sodium hydroxide aqueous solution (40 mL) was added, and the mixture extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated. Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 100%) of the crude product gave pure compound **3** (28 mg, 0.12 mmol, 78%). Pale yellow crystals. $C_{16}H_{17}NO$ (239.3): calcd. C 80.30, H 7.16; found C 80.03, N 7.04. M.p. 124.4−124.7 °C (Et_2O). MS (CI, NH_3): *m/z* = 240 [MH^+]. IR $\tilde{\nu}$ = 2926, 1651, 1568, 1496, 1406 cm^{-1}. ^1H NMR: δ = 1.47 (s, 3 H), 2.01 (d, *J* = 1 Hz, 3 H), 2.04−2.19 (m, 2 H), 3.85−4.07 (m, 2 H), 5.60 (d, *J* = 1 Hz, 1 H), 5.95 (quint, *J* = 1 Hz, 1 H), 7.16 (tt, *J* = 7, 1 Hz, 1 H), 7.25−7.42 (m, 4 H) ppm. ^{13}C NMR: δ = 18.2, 27.1, 31.4, 49.5, 51.1, 95.3, 122.2, 125.2, 126.6, 129.4, 140.6, 154.8, 171.0, 187.3 ppm.

Vinylogous Amides 4 and 5: Acetic anhydride (10 equiv., 20 mmol, 1.9 mL) was added to a solution of cyclopropylamine **2** (1.0 equiv., 2.0 mmol, 0.35 g) in chlorobenzene (40 mL). The mixture was heated at reflux for 8 h, then hydrolysed with 1 N sodium hydroxide aqueous solution (80 mL). The organic layer was separated, and the aqueous phase extracted with diethyl ether (2 × 80 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated to afford an orange oil (0.50 g). Flash column chromatography (ethyl acetate/dichloromethane, gradient from 0 to 10%) of the crude product gave pure compounds **4** (0.13 g, 0.60 mmol, 30%) and **5** (0.27 g, 1.0 mmol, 52%). **4:** Yellow oil. MS (CI, NH_3): *m/z* = 216 [MH^+]. HRMS (ES^+): calcd. for $C_{14}H_{18}NO$ [MH^+] 216.1388; found 216.1388. IR $\tilde{\nu}$ = 2970, 2870, 1711, 1647, 1599, 1585, 1542, 1494, 1456, 1295, 1203, 1167 cm^{-1}. ^1H NMR: δ = 1.28 (d, *J* = 7 Hz, 3 H), 1.70 (dd, *J* = 12, 7 Hz, 1 H), 1.97 (s, 3 H), 2.17−2.30 (m, 1 H), 3.62 (t, *J* = 10 Hz, 1 H), 3.88 (td, *J* = 10, 7 Hz, 1 H), 4.14 (quint, *J* = 7 Hz, 1 H), 5.25 (s, 1 H), 7.24−7.29 (m, 3 H), 7.41−7.46 (m, 2 H) ppm. ^{13}C NMR: δ = 18.1, 29.6, 31.0, 38.1, 52.7, 91.3, 125.1, 126.5, 129.5, 141.2, 169.8, 194.3 ppm. **5:** Yellow oil. MS (CI, NH_3): *m/z* = 258 [MH^+]. HRMS (ES^+): calcd. for $C_{16}H_{19}NNaO_2$ [MNa^+] 280.1303; found 280.1306. IR $\tilde{\nu}$ = 2976, 1709, 1650, 1534, 1493, 1420 cm^{-1}. ^1H NMR: δ = 1.54 (s, 3 H), 1.87−1.98 (m, 1 H), 1.93 (s, 3 H), 2.20−2.30 (m, 1 H), 2.28 (s, 3 H), 3.72 (td, *J* = 10, 1 Hz, 1 H), 3.88 (td, *J* = 10, 7 Hz, 1 H), 5.29 (s, 1 H), 7.27−7.35 (m, 3 H), 7.44−7.49 (m, 3 H) ppm. ^{13}C NMR: δ = 19.5, 25.5, 30.3, 34.9, 52.4, 59.8, 91.9, 125.2, 127.1, 129.7, 141.1, 166.8, 193.4, 204.5 ppm.

Reaction of 2 in a Mixture of [D_6]Acetic Anhydride and [D_4]Acetic Acid: A solution of cyclopropylamine **2** (1.0 equiv., 0.49 mmol, 85 mg) in a mixture of [D_6]acetic anhydride (4.0 mL) and [D_4]acetic acid (0.75 mL) was heated at reflux for 20 min. After cooling, 1 N sodium hydroxide aqueous solution (130 mL) was added. The mixture was shaken for 10 min at 20 °C, then extracted with dichloromethane (3 × 80 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated. Flash column chromatography (ethyl acetate/dichloromethane, gradient from 0 to 50%) of the crude product gave compounds **5** (69 mg, 0.26 mmol, 53%) and **4** (24 mg, 0.11 mmol, 22%), both obtained as mixtures of deuterated isomers. **Deuterated 4:** ^1H NMR: δ = 1.28 (br. s, 2 H), 1.76 (dd, *J* = 12, 6 Hz, 1 H), 2.22 (dd, *J* = 12, 10 Hz, 1 H), 3.62 (t, *J* = 10 Hz, 1 H), 3.87 (td, *J* = 10, 6 Hz, 1 H), 5.25 (s, 1 H), 7.21−7.31 (m, 3 H), 7.38−7.48 (m, 2 H) ppm. ^{13}C NMR: δ = 17.8 (t, *J* = 19 Hz), 29.5−30.7 (m), 38.0, 52.9, 91.5, 125.2, 126.6, 129.7, 141.4, 169.1, 194.7 ppm. Analysis of the proton or carbon signals of the partially deuterated positions gave the estimated amounts of deuterium incorporation presented in Scheme 6. **Deuterated 5:** ^1H NMR: δ = 1.53 (br. s, 2 H), 1.93 (ddd, *J* = 12, 7, 2 Hz, 1 H), 2.24 (ddd, *J* = 12, 10, 9 Hz, 1 H), 3.72 (ddd, *J* = 10, 9, 2 Hz, 1 H), 3.89 (td, *J* = 10, 7 Hz, 1 H), 5.29 (s, 1 H), 7.25−7.35 (m, 3 H), 7.42−7.51 (m, 3 H) ppm. ^{13}C NMR: δ = 19.0 (t, *J* = 20 Hz), 24.6−25.6 (m), 29.1−30.4 (m), 34.8, 52.4, 59.8, 91.7, 125.2, 125.2, 127.1, 129.8, 141.9, 166.7, 166.8, 193.6, 204.8 ppm. Analysis of the proton or carbon signals of the partially deuterated positions gave the estimated amounts of deuterium incorporation presented in Scheme 6.

Alcohol 6: A solution of diketone **5** (1.0 equiv., 1.0 mmol, 0.26 g) in a 0.1 N solution of potassium hydroxide in methanol (10 mL) was heated at reflux for 5.5 h. After cooling, dichloromethane (100 mL) and water (100 mL) were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic phases were washed with brine (80 mL), dried with sodium sulfate, filtered and concentrated to afford a white solid. Purification by crystallisation (ethyl acetate) yielded pure **6** (0.18 g, 0.70 mmol, 70%) as a single diastereoisomer. Colourless crystals. $C_{16}H_{19}NO_2$ (257.3): calcd. C 74.68, H 7.44; found C 74.55, N 7.62. M.p. 195.4−196.2 °C (ethyl acetate). MS (EI): *m/z* = 170, 184, 198, 242, 257 [$M^{+\cdot}$]. IR $\tilde{\nu}$ = 3368, 3059, 2974, 2918, 2879, 1602, 1563, 1496, 1423, 1288, 1267, 1229 cm^{-1}. ^1H NMR: δ = 1.43 (s, 3 H), 1.45 (s, 3 H), 1.79 (br. s, 1 H, OH), 1.85 (dd, *J* = 12, 6 Hz, 1 H), 2.36 (dt, *J* = 12, 10 Hz, 1 H), 2.65 (AB system, δ_A = 2.43, δ_B = 2.86, J_{AB} = 17 Hz, 2 H), 3.90 (t, *J* = 10 Hz, 1 H), 4.02 (td, *J* = 10, 6 Hz, 1 H), 5.26 (s, 1 H), 7.21−7.27 (m, 3 H), 7.36−7.43 (m, 2 H) ppm. ^{13}C NMR: δ = 19.9, 25.1, 29.2, 49.3, 52.8, 55.5, 73.6, 93.5, 122.9, 126.6, 129.6, 140.4, 171. 9, 196.0 ppm.

Cyclopropylamine 7. a) Alkylation of *N*-(*p*-phenoxyphenyl)acetamide: *N*-(But-3-enyl)-*N*-(*p*-phenoxyphenyl)acetamide was prepared in 78% yield starting from *N*-(*p*-phenoxyphenyl)acetamide[16] (2.2 mmol, 0.50 g) using the same procedure as for the synthesis of the amine **2**. Orange oil. MS (EI): *m/z* = 281 [$M^{+\cdot}$]. HRMS (ES^+): calcd. for $C_{18}H_{19}NNaO_2$ [MNa^+] 304.1313; found 304.1293. IR $\tilde{\nu}$ = 2978, 2931, 1663, 1588, 1506, 1489, 1395, 1238 cm^{-1}. ^1H

NMR: δ = 1.84 (s, 3 H), 2.28 (q, *J* = 7 Hz, 2 H), 3.76 (t, *J* = 7 Hz, 2 H), 4.99−5.11 (m, 2 H), 5.77 (ddt, *J* = 17, 10, 7 Hz, 1 H), 6.99−7.20 (m, 7 H), 7.38 (t, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 23.0, 32.3, 48.3, 116.8, 118.3, 119.6, 124.2, 129.0, 130.1, 135.5, 137.5, 155.5, 157.2, 170.6 ppm. **b) Kulinkovich−de Meijere Reaction:** A similar procedure as for the preparation of **2**, starting from *N*-(but-3-enyl)-*N*-(*p*-phenoxyphenyl)acetamide (1.7 mmol, 0.47 g), yielded pure **7** (0.23 g, 0.87 mmol, 51%). Yellow crystals. $C_{18}H_{19}NO$ (884.8): calcd. C 81.48, H 7.22; found C 81.51, N 7.32. M.p. 76.8−77.3 °C (toluene). MS (ES$^+$): *m*/*z* = 266 [MH$^+$]. IR $\tilde{\nu}$ = 2932, 2870, 1609, 1586, 1506, 1489, 1234 cm^{-1}. ^{1}H NMR: δ = 0.74−0.81 (AB part of an ABX system, δ_A = 0.77, δ_B = 0.79, J_{AB} = 5, J_{AX} = 5, J_{BX} = 7 Hz, 2 H), 1.31 (m, 1 H), 1.51 (s, 3 H), 1.91 (ddd, *J* = 12, 8, 2 Hz, 1 H), 2.28 (m, 1 H), 2.75 (q, *J* = 9 Hz, 1 H), 3.90 (td, *J* = 9, 2 Hz, 1 H), 6.85−7.04 (m, 7 H), 7.28 (t, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 16.8, 20.1, 24.9, 26.4, 43.4, 53.7, 117.7, 118.7, 120.4, 122.3, 129.7, 148.9, 158.9, 159.8 ppm.

Cyclopropylamines 8 and 9: Cyclopropylamine **2** (1.0 equiv., 1.0 mmol, 0.18 g) was added dropwise to concentrated sulfuric acid (0.47 mL) at 0 °C. A mixture (0.13 mL) of 70% nitric acid (0.20 mL) and concentrated sulfuric acid (0.19 mL) was then added at 0 °C. The brown mixture was warmed to 20 °C for 1 h, then poured onto a few grams of ice. A 1 N sodium hydroxide aqueous solution (30 mL) was added, and the mixture extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated to furnish a black oil (0.18 g). Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 20%) of the crude product gave a 30:70 mixture of **2/8** (97 mg), and a 15:85 mixture of **8/9** (42 mg). The yields of the products are thus estimated to be 72 mg for **8** (0.33 mmol, 33%) and 36 mg for **9** (0.16 mmol, 16%). These compounds could be completely separated by further flash column chromatography (dichloromethane/heptane, gradient from 0 to 100%). **8:** Yellow oil. $C_{12}H_{14}N_2O_2$ (218.3): calcd. C 66.04, H 6.47; found C 66.12, N 6.66. MS (ES$^+$): *m*/*z* = 219 [MH$^+$], 241 [MNa$^+$], 273 [M(MeOH)Na$^+$], 459 [M$_2$Na$^+$]. IR $\tilde{\nu}$ = 2957, 2872, 1616, 1569, 1525, 1479, 1346 cm^{-1}. ^{1}H NMR: δ = 0.68 (t, *J* = 5 Hz, 1 H), 0.99 (dd, *J* = 9, 5 Hz, 1 H), 1.43 (m, 1 H), 1.54 (s, 3 H), 1.96 (ddd, *J* = 13, 9, 4 Hz, 1 H), 2.37 (m, 1 H), 2.98 (dt, *J* = 10, 9 Hz, 1 H), 4.03 (td, *J* = 10, 4 Hz, 1 H), 7.08 (m, 1 H), 7.32 (m, 1 H), 7.54−7.65 (m, 2 H) ppm. ^{13}C NMR: δ = 19.6, 20.4, 25.4, 26.5, 43.7, 53.9, 110.4, 112.2, 122.1, 129.4, 149.1, 150.6 ppm. **9:** Yellow solid. M.p. 57.5−59.4 °C. MS (ES$^+$): *m*/*z* = 150, 174, 219 [MH$^+$], 241 [MNa$^+$], 273 [M(MeOH)Na$^+$]. HRMS (ES$^+$): calcd. for $C_{12}H_{15}N_2O_2$ [MH$^+$] 219.1134; found 219.1149. IR $\tilde{\nu}$ = 2931, 2875, 1601, 1579, 1508, 1482, 1435, 1331 cm^{-1}. ^{1}H NMR: δ = 0.70 (t, *J* = 5 Hz, 1 H), 1.13 (dd, *J* = 9, 5 Hz, 1 H), 1.51 (dddd, *J* = 9, 7, 5, 1 Hz, 1 H), 1.54 (s, 3 H), 1.92 (dddd, *J* = 15, 9, 6, 1 Hz, 1 H), 2.39 (dddd, *J* = 15, 10, 7, 5 Hz, 1 H), 3.29 (ddd, *J* = 10, 9, 5 Hz, 1 H), 4.05 (td, *J* = 10, 6 Hz, 1 H), 6.68 (m, 2 H), 8.10 (m, 2 H) ppm. ^{13}C NMR: δ = 19.3, 24.8, 26.0, 27.0, 44.3, 54.5, 113.6, 125.9, 137.6, 153.6 ppm.

Vinylogous Amides 10 and 11: A similar procedure as for the synthesis of **4** and **5** was applied to cyclopropylamine **7** (0.37 mmol, 98 mg), with 14 h of heating at reflux to give pure compounds **10** (21 mg, 68 μmol, 18%) and **11** (79 mg, 0.23 mmol, 61%). **10:** Orange oil. HRMS (ES$^+$): calcd. for $C_{20}H_{22}NO_2$ [MH$^+$] 308.1651; found 308.1636; calcd. for $C_{20}H_{21}NNaO_2$ [MNa$^+$] 330.1470; found 330.1468. IR $\tilde{\nu}$ = 2968, 2869, 1645, 1588, 1546, 1504, 1489, 1295, 1231, 1203, 1165 cm^{-1}. ^{1}H NMR: δ = 1.28 (d, *J* = 7 Hz, 3 H), 1.77 (dd, *J* = 12, 7 Hz, 1 H), 1.99 (s, 3 H), 2.14−2.35 (m, 1 H), 3.60 (t, *J* = 10 Hz, 1 H), 3.86 (td, *J* = 10, 7 Hz, 1 H), 4.13 (quint, *J* = 7 Hz, 1 H), 5.18 (s, 1 H), 7.00−7.23 (m, 7 H), 7.38 (t, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 18.4, 29.8, 31.3, 38.3, 53.3, 91.4, 119.5, 119.7, 124.0, 127.0, 130.2, 136.4, 156.1, 157.0, 169.7, 194.6 ppm. **11:** Orange oil. HRMS (ES$^+$): calcd. for $C_{22}H_{24}NO_3$ [MH$^+$] 350.1756; found 350.1752. IR $\tilde{\nu}$ = 2976, 2932, 2873, 1709, 1642, 1588, 1534, 1503, 1489, 1299, 1239, 1175 cm^{-1}. ^{1}H NMR: δ = 1.55 (s, 3 H), 1.86−2.00 (m, 1 H), 1.95 (s, 3 H), 2.15−2.32 (m, 1 H), 2.29 (s, 3 H), 3.71 (m, 1 H), 3.85 (td, *J* = 10, 7 Hz, 1 H), 5.23 (s, 1 H), 7.02−7.29 (m, 7 H), 7.39 (t, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 19.5, 25.8, 30.5, 35.0, 52.8, 59.8, 91.7, 119.5, 124.1, 126.9, 130.1, 135.8, 156.4, 156.6, 167.3, 193.5, 204.9 ppm.

Vinylogous Amides 12 and 13: A similar procedure as for the synthesis of **4** and **5** was applied to cyclopropylamine **8** (1.0 mmol, 0.22 g), with 57 h of heating at reflux to give pure compounds **12** (21 mg, 81 μmol, 8%) and **13** (18 mg, 60 μmol, 6%), as well as starting material **8** (0.15 g, 0.69 mmol, 69%). **12:** Orange oil. HRMS (ES$^+$): calcd. for $C_{14}H_{17}N_2O_3$ [MH$^+$] 261.1239; found 261.1243; calcd. for $C_{14}H_{16}N_2NaO_3$ [MNa$^+$] 283.1059; found 283.1083. IR $\tilde{\nu}$ = 2961, 1649, 1552, 1528, 1480, 1348, 1164 cm^{-1}. ^{1}H NMR: δ = 1.29 (d, *J* = 7 Hz, 3 H), 1.83 (ddd, *J* = 12, 6, 1 Hz, 1 H), 2.03 (s, 3 H), 2.18−2.34 (m, 1 H), 3.70 (td, *J* = 10, 1 Hz, 1 H), 3.92 (ddd, *J* = 11, 10, 6 Hz, 1 H), 4.14 (quint, *J* = 7 Hz, 1 H), 5.41 (s, 1 H), 7.59−7.69 (m, 2 H), 8.08 (dt, *J* = 8, 2 Hz, 1 H), 8.13 (t, *J* = 2 Hz, 1 H) ppm. ^{13}C NMR: δ = 18.3, 29.5, 31.4, 37.9, 52.3, 92.9, 119.5, 120.6, 130.4, 130.7, 142.8, 149.2, 167.7, 195.1 ppm. **13:** Orange oil. HRMS (ES$^+$): calcd. for $C_{16}H_{19}N_2O_4$ [MH$^+$] 303.1345; found 303.1342; calcd. for $C_{16}H_{18}N_2NaO_4$ [MNa$^+$] 325.1164; found 325.1147. IR $\tilde{\nu}$ = 2929, 1708, 1649, 1528, 1480, 1350, 1303, 1174 cm^{-1}. ^{1}H NMR: δ = 1.57 (s, 3 H), 1.95−2.02 (m, 1 H), 1.99 (s, 3 H), 2.22−2.33 (m, 4 H), 2.32 (s, 3 H), 3.77 (td, *J* = 9, 2 Hz, 1 H), 3.93 (td, *J* = 9, 7 Hz, 1 H), 5.42 (s, 1 H), 7.62−7.73 (m, 2 H), 8.12−8.19 (m, 2 H) ppm. ^{13}C NMR: δ = 19.7, 25.8, 30.6, 35.0, 51.9, 59.6, 92.9, 119.7, 121.3, 130.6, 130.9, 142.2, 149.1, 165.6, 194.1, 204.8 ppm.

Carboxylic Amide 17. a) Alkylation of Tryptamine: Potassium carbonate (1.0 equiv., 26 mmol, 3.6 g) and but-3-enyl *p*-toluenesulfonate[14] (1.0 equiv., 26 mmol, 5.9 g) were added to a solution of tryptamine (1.0 equiv., 26 mmol, 4.2 g) in acetonitrile (200 mL). The mixture was heated at reflux for 7 h. After cooling, it was filtered and concentrated. Dichloromethane (70 mL) and 1 N sodium hydroxide aqueous solution (70 mL) were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 70 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated to give a black oil (6.1 g). The crude product was purified by flash column chromatography (concentrated ammonium hydroxide aqueous solution/ethyl acetate, gradient from 0 to 0.5%) to afford pure *N*-(but-3-enyl)tryptamine (3.1 g, 14 mmol, 56%). Colourless oil. ^{1}H NMR: δ = 2.16 (q, *J* = 7 Hz, 2 H), 2.70 (t, *J* = 7 Hz, 2 H), 2.87−3.07 (m, 5 H), 4.95−5.13 (m, 2 H), 5.74 (ddt, *J* = 17, 10, 7 Hz, 1 H), 7.01 (d, *J* = 2 Hz, 1 H), 7.07−7.22 (m, 2 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.62 (d, *J* = 7 Hz, 1 H), 8.30 (br. s, 1 H) ppm. ^{13}C NMR: δ = 25.9, 34.4, 48.9, 50.0, 111.2, 114.4, 116.3, 119.0, 119.3, 122.0, 122.1, 127.6, 136.5, 136.8 ppm. **b) Acylation:** Acetic anhydride (4.0 equiv., 37 mmol, 3.5 mL) and 1 N sodium hydroxide aqueous solution (100 mL) were added to a solution of *N*-(but-3-enyl)tryptamine (1.0 equiv., 9.3 mmol, 2.0 g) in dichloromethane (100 mL) in a separating funnel. The mixture was shaken for 10 min, then the organic layer was separated, and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic phases were washed with 1 N hydrogen chloride aqueous solution (100 mL), dried with sodium sulfate, filtered and concentrated to afford a

brown oil (2.2 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 50 to 100%) yielded pure **17** (1.5 g, 5.9 mmol, 63%). White solid. $C_{16}H_{20}N_2O$ (256.3): calcd. C 74.87, H 7.86; found C 74.66, N 7.95. M.p. 101.0−101.9 °C. MS (CI, NH_3): *m*/*z* = 177, 191, 199, 257 [MH^+]. IR (mixture of two rotamers): $\tilde{\nu}$ = 3176, 2925, 1614, 1487, 1455, 1368, 1232, 1210 cm^{-1}. ^1H NMR (mixture of two rotamers): δ = 1.91 and 2.12 (2 × s, 3 H), 2.26 and 2.34 (2 × q, *J* = 7 Hz, 2 H), 2.99 and 3.03 (2 × t, *J* = 7 Hz, 2 H), 3.23 and 3.46 (2 × t, *J* = 7 Hz, 2 H), 3.53 and 3.63 (2 × t, *J* = 7 Hz, 2 H), 4.99−5.12 (m, 2 H), 5.65−5.85 (m, 1 H), 6.94 and 6.97 (2 × d, *J* = 2 Hz, 1 H), 7.07−7.23 (m, 2 H), 7.33 and 7.37 (2 × d, *J* = 7 Hz, 1 H), 7.55 and 7.66 (2 × d, *J* = 7 Hz, 1 H), 8.09 and 8.18 (2 × br. s, 1 H) ppm. ^{13}C NMR (mixture of two rotamers): δ = 21.4 and 21.8 ppm, 23.6 and 24.7, 32.3 and 33.3, 45.3 and 47.1, 48.9 and 49.6, 111.3 and 111.6, 111.8 and 113.0, 116.7 and 117.7, 118.1, 118.7, 119.2, 119.4, 121.8, 122.1, 122.2, 122.5, 127.1 and 127.5, 134.3 and 135.5, 136.4 and 136.4, 170.5 and 170.8 ppm.

Cyclopropylamine 18: A similar procedure as for the preparation of **2**, starting from **17** (2.6 mmol, 0.67 g), yielded pure **18** (0.58 g, 2.4 mmol, 93%). Colourless crystals. $C_{16}H_{20}N_2$ (240.3): calcd. C 79.96, H 8.39; found C 79.67, N 8.61. M.p. 112.0−112.9 °C (ethanol). MS (CI, NH_3): *m*/*z* = 241 [MH^+]. IR $\tilde{\nu}$ = 3412, 3257, 3058, 2925, 2852, 1619, 1456 cm^{-1}. ^1H NMR: δ = 0.10 (dd, *J* = 8, 5 Hz, 1 H), 0.80 (t, *J* = 5 Hz, 1 H), 1.19 (dt, *J* = 8, 5 Hz, 1 H), 1.40 (s, 3 H), 1.74−1.88 (m, 1 H), 1.90−2.16 (m, 2 H), 2.41 (ddd, *J* = 11, 9, 7 Hz, 1 H), 3.00 (t, *J* = 8 Hz, 2 H), 3.22 (ddd, *J* = 11, 9, 8 Hz, 1 H), 3.22−3.33 (m, 1 H), 7.00 (d, *J* = 2 Hz, 1 H), 7.12−7.24 (m, 2 H), 7.30 (d, *J* = 8 Hz, 1 H), 7.60 (d, *J* = 8 Hz, 1 H), 8.16 (br. s, 1 H) ppm. ^{13}C NMR: δ = 7.9, 19.7, 22.5, 24.9, 26.2, 46.3, 49.9, 52.7, 111.1, 114.8, 118.8, 119.1, 121.3, 121.9, 127.5, 136.3 ppm.

Diketone 19: A similar procedure as for the synthesis of **4** and **5** was applied to cyclopropylamine **18** (0.42 mmol, 0.10 g), with 2 h of heating at reflux to give pure compound **19** (69 mg, 2.1 mmol, 51%). Colourless crystals. $C_{20}H_{24}N_2O_2$ (324.4): calcd. C 74.04, H 7.46; found C 73.82, N 7.47. M.p. 185.0−187.2 °C (toluene). MS (CI, NH_3): *m*/*z* = 283, 325 [MH^+]. IR $\tilde{\nu}$ = 3225, 3055, 2927, 1705, 1622, 1537, 1481, 1458, 1355, 1300, 1201 cm^{-1}. ^1H NMR: δ = 1.40 (s, 3 H), 1.68 (dd, *J* = 12, 7 Hz, 1 H), 1.92−2.03 (m, 1 H), 1.99 (s, 3 H), 2.20 (s, 3 H), 3.10 (t, *J* = 7 Hz, 2 H), 3.22 (td, *J* = 10, 2 Hz, 1 H), 3.34 (td, *J* = 10, 7 Hz, 1 H), 3.61 (m, 2 H), 5.09 (s, 1 H), 7.03 (d, *J* = 2 Hz, 1 H), 7.10−7.22 (m, 2 H), 7.40 (d, *J* = 8 Hz, 1 H), 7.63 (d, *J* = 8 Hz, 1 H), 8.23 (br. s, 1 H) ppm. ^{13}C NMR: δ = 19.6, 22.0, 25.6, 30.2, 34.4, 47.4, 50.8, 60.4, 88.8, 111.7, 111.8, 118.2, 119.4, 122.1, 122.7, 127.2, 136.6, 167.3, 192.3, 205.3 ppm.

Alcohol 20: This alcohol was prepared in the same way as **6**, starting from diketone **19** (0.15 mmol, 50 mg), with 77 h of heating at reflux. Purification by flash column chromatography (ethyl acetate/heptane, gradient from 50 to 100%) yielded pure **20** (44 mg, 0.14 mmol, 88%) as a single diastereoisomer. Colourless crystals. $C_{20}H_{24}N_2O_2$ (324.4): calcd. C 74.68, H 7.44; found C 74.55, N 7.62. M.p. 201.5−202.7 °C (ethyl acetate). MS (EI): *m*/*z* = 130, 136, 143, 144, 177, 194, 195, 324 ($M^{+\cdot}$). IR $\tilde{\nu}$ = 3250, 3052, 2975, 2923, 2875, 1606, 1552, 1457, 1435, 1361, 1293, 1254, 1215, 1141, 1117, 1086 cm^{-1}. ^1H NMR: δ = 1.22 (s, 3 H), 1.25 (s, 3 H), 1.57 (dd, *J* = 11, 6 Hz, 1 H), 2.02 (br. s, 1 H), 2.05 (q, *J* = 11 Hz, 1 H), 2.57 (AB system, δ_A = 2.29, δ_B = 2.86, J_{AB} = 17 Hz, 2 H), 2.98−3.09 (m, 2 H), 3.30 (m, 1 H), 3.44 (td, *J* = 11, 6 Hz, 1 H), 3.48−3.60 (m, 2 H), 4, 99 (s, 1 H), 6.99 (s, 1 H), 7.10−7.21 (m, 2 H), 7.37 (d, *J* = 8 Hz, 1 H), 7.57 (d, *J* = 8 Hz, 1 H), 8.5 (br. s, 1 H) ppm. ^{13}C NMR: δ = 19.5, 22.4, 24.9, 28.9, 46.9, 49.2, 51.8, 52.6, 73.4, 90.2, 111.2, 111.9, 118.3, 119.5, 122.2, 127.1, 136.3, 173.4, 194.5 ppm.

Vinylogous Amide 21: *n*-Butyric anhydride (16 equiv., 9.2 mmol, 1.5 mL) was added to a solution of the cyclopropylamine **2** (1.0 equiv., 0.58 mmol, 0.10 g) in chlorobenzene (10 mL). The mixture was heated at reflux for 3.5 h, then washed with 1 N sodium hydroxide aqueous solution (2 × 20 mL). The organic layer was dried with sodium sulfate, filtered and concentrated to afford a yellow oil (0.63 g). Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 20%) of the crude product gave pure **21** (71 mg, 0.29 mmol, 50%) and **22** (36 mg, 0.11 mmol, 20%). A 36:64 mixture of both compounds was also isolated (16 mg, 20 and 35 μmol, 3 and 6%).Yellow oil. MS (EI): *m*/*z* = 172, 184, 200, 243 [$M^{+\cdot}$]. IR $\tilde{\nu}$ = 2960, 2871, 1646, 1599, 1584, 1544, 1493, 1459, 1409, 1295, 1136, 1056 cm^{-1}. ^1H NMR: δ = 0.87 (t, *J* = 7 Hz, 3 H), 1.28 (d, *J* = 7 Hz, 3 H), 1.55 (sext, *J* = 7 Hz, 2 H), 1.77 (ddd, *J* = 12, 6, 1 Hz, 1 H), 2.11−2.35 (m, 3 H), 3.62 (ddd, *J* = 10, 9, 1 Hz, 1 H), 3.88 (ddd, *J* = 11, 10, 6 Hz, 1 H), 4.19 (quint, *J* = 7 Hz, 1 H), 5.27 (s, 1 H), 7.21−7.30 (m, 3 H), 7.39−7.47 (m, 2 H) ppm. ^{13}C NMR: δ = 14.1, 18.2, 19.1, 29.6, 38.2, 45.9, 52.7, 91.2, 125.1, 126.4, 129.5, 141.4, 168.9, 197.5 ppm.

Vinylogous Amide 22: When the conditions described above were applied to cyclopropylamine **2** (1.1 mmol, 0.19 g) with 24 h of heating at reflux, the diketone **22** was the major product. Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 30%) of the crude product (yellow oil, 1.5 g) gave pure **21** (42 mg, 0.17 mmol, 16%) and **22** (0.17 g, 0.54 mmol, 49%). Yellow oil. MS (EI): *m*/*z* = 172, 173, 198, 199, 200, 242, 243, 270, 313 [$M^{+\cdot}$]. IR $\tilde{\nu}$ = 2960, 2872, 1709, 1642, 1536, 1493, 1461, 1409, 1297, 1175, 1148, 1126, 1060 cm^{-1}. ^1H NMR: δ = 0.82 (t, *J* = 7 Hz, 3 H), 0.94 (t, *J* = 7 Hz, 3 H), 1.50 (sext, *J* = 7 Hz, 2 H), 1.54 (s, 3 H), 1.67 (sext, *J* = 7 Hz, 2 H), 1.89 (ddd, *J* = 12, 7, 2 Hz, 1 H), 2.12 (t, *J* = 7 Hz, 2 H), 2.21 (dt, *J* = 12, 10 Hz, 1 H), 2.49 (dt, *J* = 17, 7 Hz, 1 H), 2.69 (dt, *J* = 17, 7 Hz, 1 H), 3.71 (td, *J* = 10, 2 Hz, 1 H), 3.88 (td, *J* = 10, 7 Hz, 1 H), 5.32 (s, 1 H), 7.26−7.34 (m, 3 H), 7.44−7.50 (m, 2 H) ppm. ^{13}C NMR: δ = 13.9, 14.0, 17.2, 19.0, 19.2, 34.9, 39.3, 45.3, 52.3, 59.7, 91.9, 125.0, 126.9, 129.7, 141.2, 166.5, 196.3, 206.6 ppm.

Alcohol 23 and Tetrahydroindolone 24: These compounds were obtained when the procedure leading to alcohol **6** was applied to diketone **22** (0.54 mmol, 0.17 g) with 25 h of heating at reflux. Purification by flash column chromatography (ethyl acetate/heptane, gradient from 0 to 50%) yielded pure **23** (76 mg, 0.24 mmol, 45%) as a single diastereoisomer and an 81:19 mixture of starting material **22**/dehydrated product **24** (61 mg). The estimated yields of these compounds are thus 51 mg for **22** (0.16 mmol, 30%) and 10 mg for **24** (34 μmol, 6%). Pure **24** could be obtained by further flash column chromatography. **23:** Colourless crystals. $C_{20}H_{27}NO_2$ (313.4): calcd. C 76.64, H 8.68; found C 76.84, N 8.77. M.p. 188.3−189.1 °C (ethyl acetate). MS (EI): *m*/*z* = 184, 198, 199, 242, 261, 313 [$M^{+\cdot}$]. IR $\tilde{\nu}$ = 3389, 2958, 2872, 1603, 1572, 1495, 1414, 1209 cm^{-1}. ^1H NMR: δ = 0.84 (t, *J* = 7 Hz, 3 H), 1.20 (t, *J* = 7 Hz, 3 H), 1.18−1.29 (m, 2 H), 1.47 (s, 3 H), 1.53−1.75 (m, 4 H), 1.83−1.98 (m, 1 H), 1.84 (dd, *J* = 12, 6 Hz, 1 H), 2.28 (dt, *J* = 12, 10 Hz, 1 H), 2.51 (dd, *J* = 8, 3 Hz, 1 H), 3.89 (t, *J* = 10 Hz, 1 H), 3.96 (td, *J* = 10, 6 Hz, 1 H), 5.29 (s, 1 H), 7.18−7.26 (m, 3 H), 7.38 (m, 2 H) ppm. ^{13}C NMR: δ = 15.2, 16.2, 18.1, 19.3, 20.7, 29.5, 38.3, 52.5, 52.6, 54.3, 78.4, 95.6, 123.6, 126.1, 129.5, 140.8, 169.0, 197.5 ppm. **24:** Orange oil. HRMS (ES^+): calcd. for $C_{20}H_{26}NO$ [MH^+] 296.2014; found 296.2005. IR $\tilde{\nu}$ = 2961, 2871, 1697, 1642, 1587, 1497, 1457, 1405, 1371, 1308, 1254, 1176 cm^{-1}. ^1H NMR: δ = 1.04 (t, *J* = 7 Hz, 6 H), 1.42 (s, 3 H), 1.51−1.65 (m, 2 H), 2.07−2.28 (m, 3 H), 2.29−2.50 (m, 3 H), 3.85 (td, *J* = 10, 6 Hz, 1 H), 3.98 (td, *J* = 10, 1 Hz, 1 H), 5.68 (s, 1 H), 7.14 (m,

1 H), 7.27−7.40 (m, 4 H) ppm. ^{13}C NMR: δ = 14.4, 15.2, 19.5, 23.8, 28.1, 31.8, 32.6, 46.6, 50.9, 95.9, 122.2, 125.0, 129.5, 137.2, 141.1, 151.6, 169.7, 187.0 ppm.

Diketone 25: A solution of **21** (1.0 equiv., 0.41 mmol, 0.10 g) in acetic anhydride (5.0 mL) was heated at reflux for 50 min, and was then hydrolysed with 1 N sodium hydroxide aqueous solution (150 mL). The mixture was shaken vigorously for 10 min, then extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated to afford a black oil (0.11 g). Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 50%) of the crude product gave pure diketone **25** (81 mg, 0.28 mmol, 69%). Yellow oil. MS (EI): *m/z* = 170, 172, 184, 198, 199, 200, 242, 285 [M$^{+\cdot}$]. HRMS (ES$^+$): calcd. for $C_{18}H_{24}NO_2$ [MH$^+$] 286.1807; found 286.1802. IR ṽ = 2960, 2931, 2871, 1710, 1642, 1535, 1494, 1298 cm^{-1}. ^{1}H NMR: δ = 0.83 (t, *J* = 7 Hz, 3 H), 1.51 (sext, *J* = 7 Hz, 2 H), 1.53 (s, 3 H), 1.91 (ddd, *J* = 12, 7, 1 Hz, 1 H), 2.14 (t, *J* = 7 Hz, 2 H), 2.19 (m, 1 H), 2.27 (s, 3 H), 3.71 (td, *J* = 10, 1 Hz, 1 H), 3.87 (td, *J* = 10, 7 Hz, 1 H), 5.33 (s, 1 H), 7.27−7.34 (m, 3 H), 7.44−7.50 (m, 2 H) ppm. ^{13}C NMR: δ = 13.8, 18.8, 19.2, 25.3, 34.6, 45.1, 52.1, 59.7, 91.7, 125.0, 126.8, 129.6, 141.0, 166.3, 196.4, 204.4 ppm.

Alcohol 26: This compound was prepared in an analogous manner to **6**, starting from diketone **25** (0.27 mmol, 77 mg), with 6.5 h of heating at reflux. Purification by crystallisation (ethyl acetate) yielded pure **26** (58 mg, 0.20 mmol, 75%) as a single diastereoisomer. Colourless crystals. $C_{18}H_{23}NO_2$ (285.4): calcd. C 75.76, H 8.12; found C 75.54, N 8.14. M.p. 170.4−171.3 °C (ethyl acetate). MS (ES$^+$): *m/z* = 268, 286 [MH$^+$]. IR ṽ = 3400, 2982, 2873, 1604, 1571, 1497, 1414, 1208 cm^{-1}. ^{1}H NMR: δ = 1.21 (t, *J* = 7 Hz, 3 H), 1.22 (s, 3 H), 1.73 (br. s, 1 H), 1.48 (s, 3 H), 1.56 (dqd, *J* = 13, 7, 3 Hz, 1 H), 1.83 (dd, *J* = 12, 6 Hz, 1 H), 1.89 (dqd, *J* = 13, 8, 7 Hz, 1 H), 2.37 (dt, *J* = 12, 10 Hz, 1 H), 2.53 (dd, *J* = 8, 3 Hz, 1 H), 3.91 (t, *J* = 10 Hz, 1 H), 3.97 (td, *J* = 10, 6 Hz, 1 H), 5.29 (s, 1 H), 7.16−7.27 (m, 3 H), 7.37 (m, 2 H) ppm. ^{13}C NMR: δ = 16.1, 18.3, 19.2, 19.3, 29.6, 52.7, 53.0, 54.5, 77.4, 94.7, 123.6, 126.1, 129.6, 140.7, 169.3, 197.6 ppm.

Tetrahydroindolone 27. Method 1: A solution of the diketone **25** (1.0 equiv., 35 μmol, 10 mg) in acetic anhydride (1.0 mL) was heated at reflux for 13 h. After cooling, dichloromethane (30 mL) and 1 N sodium hydroxide aqueous solution (40 mL) were added. The mixture was vigorously shaken, and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated. Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 50%) of the crude product gave pure compound **27** (6.0 mg, 22 μmol, 64%). **Method 2:** Compound **27** was also obtained by dehydration of alcohol **26** (0.18 mmol, 52 mg), using the same procedure as for the preparation of **3** (Method 4), to give pure compound **27** (42 mg, 0.16 mmol, 86%). Pale yellow oil. MS (EI): *m/z* = 198, 252, 267 [M$^{+\cdot}$]. HRMS (ES$^+$): calcd. for $C_{18}H_{22}NO$ [MH$^+$] 268.1701; found 268.1725. IR ṽ = 2966, 2928, 2867, 1645, 1600, 1587, 1572, 1495, 1406, 1308, 1177 cm^{-1}. ^{1}H NMR: δ = 0.99 (t, *J* = 7 Hz, 3 H), 1.43 (s, 3 H), 2.00 (s, 3 H), 2.07−2.13 (m, 2 H), 2.28−2.58 (m, 2 H), 3.85−4.08 (m, 2 H), 5.71 (s, 1 H), 7.12−7.45 (m, 5 H) ppm. ^{13}C NMR: δ = 13.5, 14.6, 18.8, 27.4, 32.1, 49.2, 50.6, 95.4, 121.9, 124.8, 129.4, 136.5, 140.9, 147.6, 169.4, 186.4 ppm.

Ketone 28: A solution of the vinylogous amide **21** (1.0 equiv., 0.53 mmol, 0.13 g) in acetic anhydride (20 mL) was heated at reflux for 8 h. The solution was then concentrated. Dichloromethane (30 mL) and 1 N sodium hydroxide aqueous solution (30 mL) were added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated to afford a dark green oil (0.17 g). Flash column chromatography (ethyl acetate/heptane, gradient from 0 to 100%) of the crude product gave pure ketone **28** (46 mg, 0.15 mmol, 28%) as a 65:35 mixture of (*E*)/(*Z*) diastereoisomers, and the tetrahydroindolone **27** (44 mg, 0.16 mmol, 31%). Pale yellow oil. MS (ES$^+$) (mixture of the two diastereoisomers): *m/z* = 310 [MH$^+$], 332 [MNa$^+$]. IR (mixture of the two diastereoisomers): ṽ = 2963, 2925, 2870, 1638, 1612, 1592, 1559, 1524, 1496, 1404, 1364, 1315, 1293, 1248 cm^{-1}. ^{1}H NMR (mixture of the two diastereoisomers): δ = 0.92 (t, *J* = 7 Hz, 1.05 H, *Z*), 1.10 (t, *J* = 7 Hz, 1.95 H, *E*), 1.38 (s, 1.95 H, *E*), 1.41 (s, 1.05 H, *Z*), 2.02−2.37 (m, 2 H), 2.16−2.37 (m, 0.70 H, *Z*), 2.48−2.58 (m, 1.30 H, *E*), 2.25 (s, 1.05 H, *Z*), 2.56 (s, 1.95 H, *E*), 3.84−4.03 (m, 2 H), 4.28 (d, *J* = 2 Hz, 0.35 H, *Z*), 4.29 (d, *J* = 2 Hz, 0.65 H, *E*), 4.67 (d, *J* = 2 Hz, 0.65 H, *E*), 4.69 (d, *J* = 2 Hz, 0.35 H, *Z*), 5.64 (s, 0.35 H, *Z*), 7.08 (s, 0.65 H, *E*), 7.06−7.45 (m, 5 H) ppm. ^{13}C NMR (mixture of the two diastereoisomers): δ = 14.6 (*Z*), 15.1 (*E*), 20.3 (*Z*), 21.1 (*E*), 24.9 (*Z*), 25.0 (*E*), 29.7 (*E*), 33.3 (*Z*), 32.9 (*E*), 33.0 (*Z*), 45.2 (*Z*), 45.5 (*E*), 51.2 (*E*), 51.4 (*Z*), 85.6 (*Z*), 86.7 (*E*), 89.8 (*Z*), 90.4 (*E*), 112.4 (*E*), 114.1 (*Z*), 121.0 (*E*), 121.4 (*Z*), 124.3 (*E*), 124.7 (*Z*), 129.5 (*E*), 129.6 (*Z*), 141.4, 153.6 (*Z*), 154.9 (*E*), 158.9 (*Z*), 160.4 (*E*),160.3 (*Z*),160.7 (*E*), 196.8 (*E*), 198.9 (*Z*) ppm.

Cyclopropylamine 29. a) Alkylation of *N*-Phenylbutyramide: *N*-(But-3-enyl)-*N*-phenylbutyramide was prepared in 82% yield starting from *N*-phenylbutyramide[17] (5.6 mmol, 0.91 g) using the same procedure as for the synthesis of amide **2**. Colourless oil. $C_{14}H_{19}NO$ (217.3): calcd. C 77.38, H 8.81; found C 77.21, N 8.97. MS (EI): *m/z* = 106, 176, 217 [M$^{+\cdot}$]. IR ṽ = 2962, 2930, 2873, 1658, 1596, 1495, 1451, 1400 cm^{-1}. ^{1}H NMR: δ = 0.81 (t, *J* = 7 Hz, 3 H), 1.58 (sext, *J* = 7 Hz, 2 H), 1.99 (t, *J* = 7 Hz, 2 H), 2.28 (q, *J* = 7 Hz, 2 H), 3.78 (t, *J* = 7 Hz, 2 H), 4.98−5.10 (m, 2 H), 5.69−5.84 (m, 1 H), 7.12−7.19 (m, 2 H), 7.31−7.50 (m, 3 H) ppm. ^{13}C NMR: δ = 13.7, 18.8, 32.2, 36.3, 48.3, 116.6, 127.8, 128.5, 129.6, 134.4, 142.7, 172.8 ppm. **b) Kulinkovich−de Meijere Reaction:** A similar procedure as for the preparation of **2**, starting from *N*-(but-3-enyl)-*N*-phenylbutyramide (1.3 mmol, 0.28 g), yielded pure **29** (0.17 g, 0.84 mmol, 66%). Colourless oil. $C_{14}H_{19}N$ (201.3): calcd. C 83.53, H 9.51; found C 83.69, N 9.57. MS (ES$^+$): *m/z* = 106, 116, 202 [MH$^+$]. IR ṽ = 2956, 2931, 2870, 1600, 1499, 1455, 1361, 1312 cm^{-1}. ^{1}H NMR: δ = 0.67 (t, *J* = 5 Hz, 1 H), 0.87 (t, *J* = 7 Hz, 3 H), 0.85−0.90 (m, 1 H), 1.21 (m, 1 H), 1.28−1.47 (m, 3 H), 1.91 (ddd, *J* = 12, 9, 4 Hz, 1 H), 2.19−2.35 (m, 2 H), 2.92 (ddd, *J* = 10, 9, 8 Hz, 1 H), 3.94 (td, *J* = 10, 4 Hz, 1 H), 6.75 (tt, *J* = 7, 1 Hz, 1 H), 6.82−6.87 (m, 2 H), 7.18−7.25 (m, 2 H) ppm. ^{13}C NMR: δ = 14.2, 18.7, 20.0, 23.4, 26.8, 34.7, 47.5, 53.9, 116.6, 117.7, 128.8, 150.1 ppm.

Cyclopropylamine 30. a) Acylation: Butyric anhydride (2.4 equiv., 12 mmol, 2.0 mL) and 1 N sodium hydroxide aqueous solution (350 mL) were added to a solution of *N*-(but-3-enyl)tryptamine (see the preparation of **17**) (1.0 equiv., 5.1 mmol, 1.1 g) in dichloromethane (50 mL) in a separating funnel. The mixture was shaken for 15 min, the organic layer was then separated, and the aqueous extracted with dichloromethane (2 × 250 mL). The combined organic phases were washed with 1 N hydrogen chloride aqueous solution (50 mL), dried with sodium sulfate, filtered and concentrated to afford a viscous brown oil (1.7 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 10 to 50%) yielded pure *N*-butyryl-*N*-(but-3-enyl)tryptamine (1.1 g, 3.9 mmol, 75%). Pale yellow crystals. $C_{18}H_{24}N_2O$ (284.4): calcd. C 76.02, H

8.51; found C 75.88, N 8.52. M.p. 71.1−72.6 °C. MS (ES^+): *m/z* = 285 [MH^+], 307 [MNa^+], 323 [MK^+], 569 [M_2H^+], 591 [M_2Na^+], 607 [M_2K^+]. IR (mixture of two rotamers): $\tilde{\nu}$ = 3412, 3272, 2964, 2931, 1652, 1457, 1428 cm^{-1}. ^1H NMR (mixture of two rotamers): δ = 0.82−0.98 (2 × t, *J* = 7 Hz, 3 H), 1.56 and 1.72 (2 × sext, *J* = 7 Hz, 2 H), 2.12 and 2.38 (m, 4 H), 3.00 and 3.02 (2 × t, *J* = 7 Hz, 2 H), 3.26 and 3.45 (2 × t, *J* = 7 Hz, 2 H), 3.56 and 3.63 (2 × t, *J* = 7 Hz, 2 H), 4.97−5.17 (m, 2 H), 5.65−5.88 (m, 1 H), 6.99 and 7.03 (2 × d, *J* = 7 Hz, 1 H), 7.09−7.25 (m, 2 H), 7.37 and 7.38 (2 × d, *J* = 8 Hz, 1 H), 7.57 and 7.69 (2 × d, *J* = 8 Hz, 1 H), 8.04 and 8.13 (2 × br. s, 1 H) ppm. ^{13}C NMR (mixture of two rotamers): δ = 13.4 and 13.8 ppm, 18.8, 23.6 and 25.0, 32.3 and 34.4, 34.9 and 35.1, 45.3 and 47.1, 47.7 and 48.6, 111.1 and 111.4, 112.1 and 113.3, 116.5 and 117.4, 118.1, 118.8, 119.2, 119.5, 121.8, 122.0, 122.1, 122.2, 127.0 and 127.4, 134.2 and 135.6, 136.3 and 136.3, 172.8 and 173.1 ppm. **b) Kulinkovich−de Meijere Reaction:** A similar procedure as for the preparation of **2**, starting from *N*-butyryl-*N*-(but-3-enyl)tryptamine (3.9 mmol, 1.1 g), yielded pure **30** (0.83 g, 3.1 mmol, 80%). Colourless crystals. $C_{18}H_{24}N_2$ (268.4): calcd. C 80.53, H 9.01; found C 80.27, N 9.05. M.p. 101.2−102.7 °C (heptane). MS (ES^+): *m/z* = 269 [MH^+], 291 [MNa^+], 307 [MK^+]. IR $\tilde{\nu}$ = 3419, 3167, 3058, 2930, 2868, 1456, 1353, 1100 cm^{-1}. ^1H NMR: δ = 0.07 (dd, *J* = 8, 5 Hz, 1 H), 0.73 (t, *J* = 8 Hz, 1 H), 0.91 (t, *J* = 7 Hz, 3 H), 1.17−1.50 (m, 4 H), 1.74−1.88 (m, 1 H), 1.91−2.07 (m, 3 H), 2.37 (m, 1 H), 2.84−3.01 (m, 2 H), 3.12−3.30 (m, 2 H), 7.05 (d, *J* = 2 Hz, 1 H), 7.09−7.22 (m, 2 H), 7.35 (d, *J* = 8 Hz, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.98 (br. s, 1 H) ppm. ^{13}C NMR: δ = 7.0, 14.5, 19.6, 21.1, 25.0, 26.5, 34.9, 49.9, 50.2, 52.9, 111.2, 115.2, 119.0, 119.3, 121.4, 122.0, 127.7, 136.4 ppm.

Cyclopropylamine 31: Titanium isopropoxide (1.5 equiv., 3.0 mmol, 0.89 mL) was added to a solution of *N*-acetylmorpholine (1.0 equiv., 2.0 mmol, 0.23 mL) and *p*-allylanisole (1.5 equiv., 3.0 mmol, 0.46 mL) in THF (20 mL). Cyclopentylmagnesium chloride (2.0 M in Et_2O, 8.0 equiv., 16 mmol, 8.0 mL) was then added dropwise over 30 min. Water (100 mL) was added carefully, and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated. Purification by flash column chromatography (dichloromethane/heptane, gradient from 0 to 10%) yielded pure **31** (0.21 g, 0.80 mmol, 40%) as a single diastereoisomer. Colourless oil. MS (CI, NH_3): *m/z* = 262 [MH^+]. IR $\tilde{\nu}$ = 1715, 1611, 1512, 1453, 1246, 1117 cm^{-1}. ^1H NMR: δ = 0.30 (dd, *J* = 5, 4 Hz, 1 H), 0.52 (dd, *J* = 8, 4 Hz, 1 H), 0.90−1.00 (m, 1 H), 1.07 (s, 3 H), 2.52−2.65 (m, 4 H), 2.65−2.84 (AB part of an ABX system: δ_A = 2.69, δ_B = 2.90, J_{AB} = 15, J_{AX} = 8, J_{BX} = 7 Hz, 2 H), 3.65 (t, *J* = 4 Hz, 4 H), 3.79 (s, 3 H), 6.83 (d, *J* = 8 Hz, 2 H), 7.17 (d, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 15.4, 20.4, 28.6, 32.5, 44.0, 49.6, 55.2, 67.5, 113.6, 129.1, 135.0, 157.6 ppm.

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