The Intramolecular Aromatic Electrophilic Substitution of Aminocyclopropanes Prepared by the Kulinkovich–de Meijere Reaction

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Dedicated to Professor Samir Z. Zard on the occasion of his 50th birthday

Keywords: Titanium / Aromatic substitution / Cyclisation / Amides / Cyclopropanes

This article describes new examples of intramolecular Kulinkovich–de Meijere reactions applied to carboxylic amides bearing an olefin moiety and an aromatic ring at a suitable position. Upon heating, the aminocyclopropanes thus obtained undergo intramolecular aromatic electrophilic substitution to afford polycyclic systems. Among the various starting materials prepared, best results are obtained from indole and phenol derivatives. In each case, a benzylic quaternary centre is introduced at the newly-formed ring junction. On one example, the efficiency of the cyclisation has been dramatically improved using a catalytic amount of *para*-toluenesulfonic acid.
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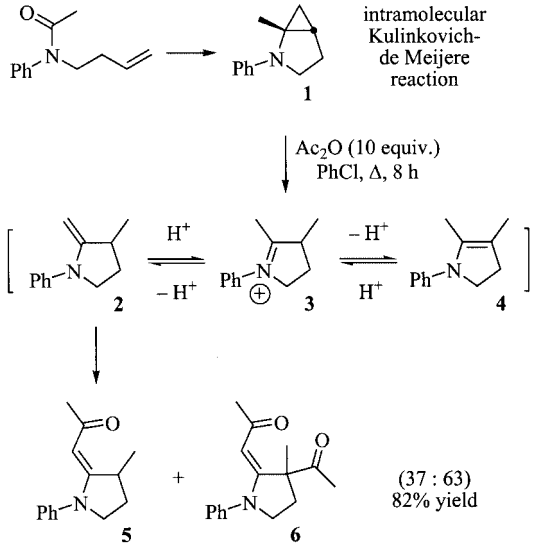
Introduction

The intramolecular version of the de Meijere variation[1] of the Kulinkovich reaction[2,3] provides a straightforward access to bicyclic aminocyclopropanes such as **1**.[4,5] We have recently described the transformation of these interesting compounds into vinylogous amides **5** and **6** under heating in the presence of acetic anhydride (Scheme 1).[6] The mechanism putatively involves the enamine intermediates **2** and **4**, in equilibrium with the corresponding iminium ion **3**.

We envisioned that the intramolecular trapping of cationic species like **3** with nucleophilic moieties would constitute an attractive extension of our method. We became particularly interested in the possibility of carrying out intramolecular aromatic electrophilic substitution reactions. This could provide an access to 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro-2-carboline skeletons, as an hopefully complementary alternative to the Pictet–Spengler,[7] Bischler–Napieralski[7d,8] and Polonovski–Potier[7b,9] reactions.



Scheme 1.

Results and Discussion

Synthesis of the Aminocyclopropane Cyclisation Precursors

Several aminocyclopropanes bearing electron-rich aromatic groups were prepared (Figure 1). We have already reported the synthesis of the indole derivatives **7** and **8** in three steps from tryptamine.[6] As cyclopropane formation by intramolecular Kulinkovich–de Meijere reaction per-

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formed very well in these cases, the same method was applied to make **9**, **10**, and **11** (Scheme 2). Good results were obtained, except in the case of **9**, where the six-membered ring formation proceeded in 37% yield only.[10] Cleavage of the oxygen–methyl bond of **11** by tribromoborane granted access to the free phenol derivative **12**.

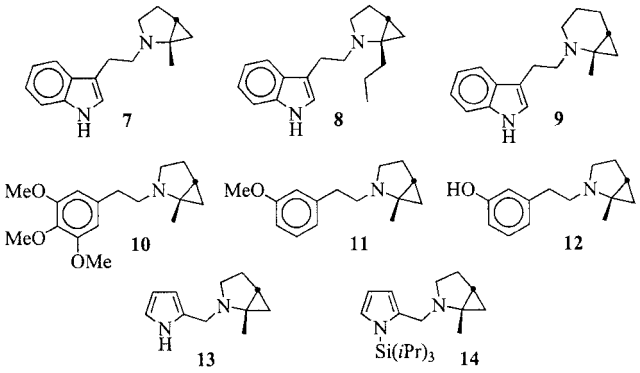
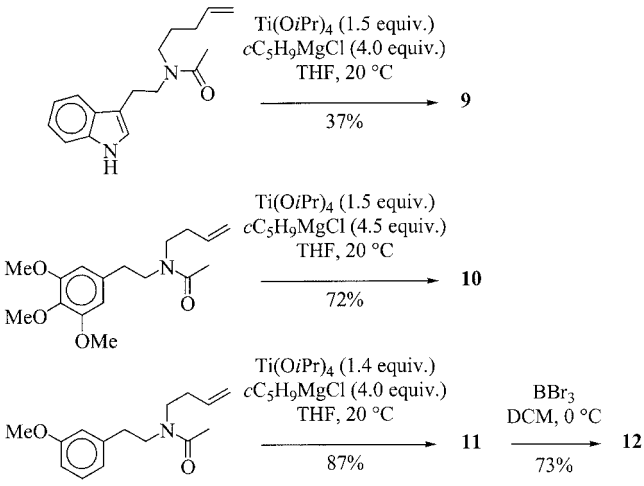


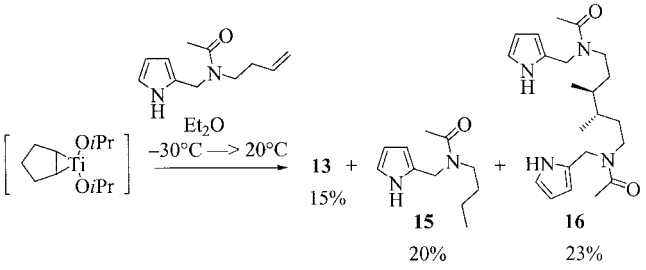
Figure 1. Aminocyclopropanes **7**–**14**.



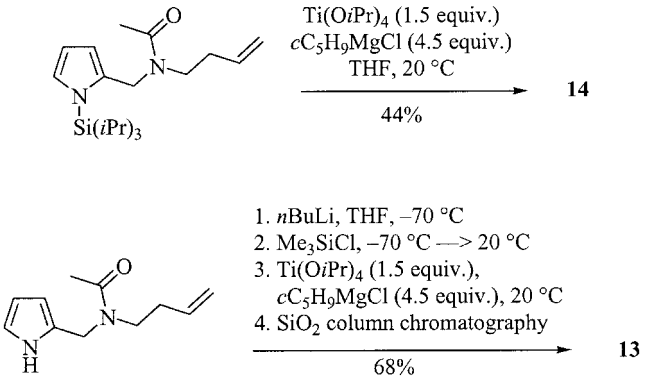
Scheme 2.

Preparing the pyrrole compound **13** in an efficient fashion proved more difficult. This compound was isolated in only 10% yield when our standard conditions were used from the corresponding acetamide. In order to improve this result, we tried to pre-form the intermediate (η^2-cyclopentene)diisopropyloxytitanium complex[11] before adding the acetamide. The reaction was complex. The isolated by-products **15** and **16** indicate that competitive processes become important at low temperature (Scheme 3). Other examples involving these types of reaction pathways can be found in the literature.[12]

Protection of the nitrogen of the pyrrole ring with a triisopropylsilyl group proved beneficial, since the corresponding aminocyclopropane **14** was isolated in 44% yield. On the basis of this result, we next developed a one-pot experimental procedure to synthesise **13** efficiently, with the pyrrole ring being transiently protected by a trimethylsilyl group (Scheme 4).



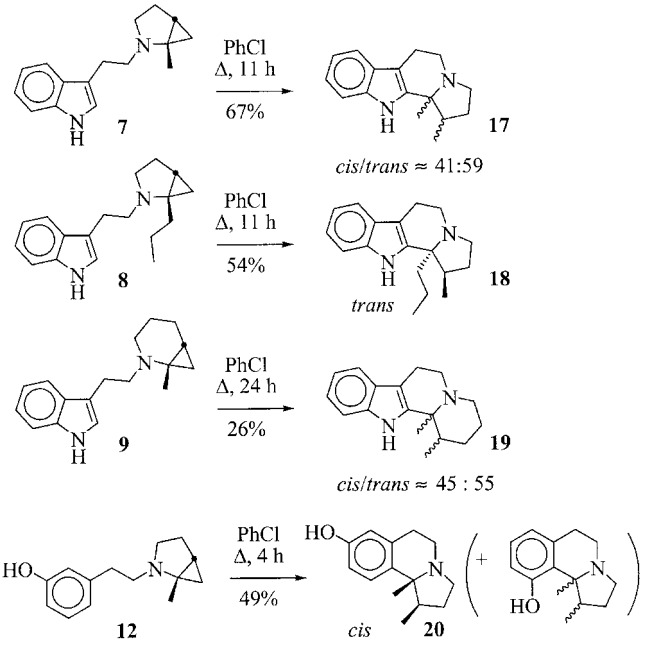
Scheme 3.



Scheme 4.

Cyclisation Studies

With the cyclisation precursors **7**–**14** in hand, the feasibility of the intramolecular aromatic substitution could be investigated. Indeed, upon heating in chlorobenzene at reflux, **7**, **8**, **9**, and **12** cyclised in low to moderate yield to the corresponding 1,2,3,4-tetrahydro-2-carboline or 1,2,3,4-tetrahydroisoquinoline structures **17**–**20** (Scheme 5). In contrast to **12**, the methoxy-substituted derivatives **10** and **11**



Scheme 5.

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did not yield any of the expected adducts. This is not surprising, since phenols are known to be better partners than their *O*-methyl analogues in aromatic electrophilic substitution processes such as the Pictet–Spengler reaction.[7a] The regioselectivity of the cyclisation of **12** was good, 87:13 in favour of the regioisomer **20**. The pyrrole derivatives **13** and **14** decomposed under the same conditions, leading to complex mixtures of products.

Further Studies on the Cyclisation of the Aminocyclopropane 9

As this was a typical case where the cyclisation performed poorly, a more detailed study of the reaction of **9** was undertaken. Beside the expected adduct **19**, two side-products were isolated: Ketone **21** (5%) and the pentacyclic compound **22** (2%), whose relative stereochemistry was determined by X-ray diffraction through a single crystal (Figure 2 and Figure 3). Only 6% of the starting material was recovered. NMR analysis of the crude product revealed that the major compound produced during the reaction had actually not been isolated after purification by chromatography over silica gel, and was tentatively assigned as the enamine structure **23**.[13]

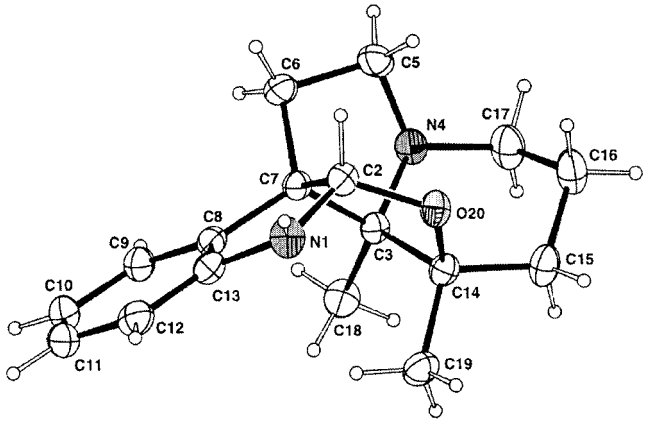


Figure 2. ORTEP drawing of **22**. Displacement ellipsoids are shown at the 30% probability level.

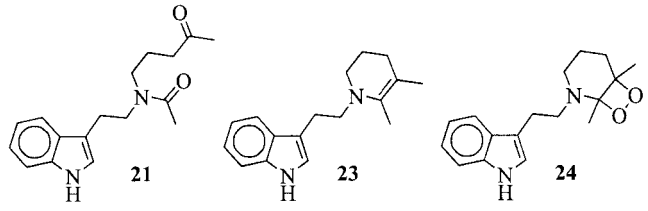
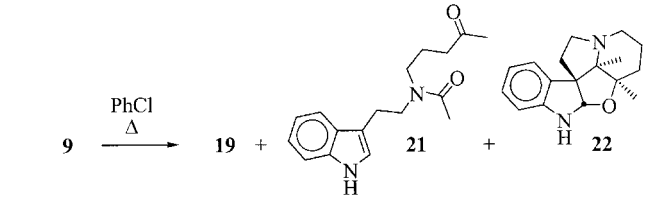


Figure 3. Ketone **21** and putative intermediates **23** and **24**.

The formation of **21** and **22** could be explained by an oxidation of the enamine **23** by traces of oxygen contained in the argon we used,[14] possibly as a dioxacyclobutane **24** (Figure 3),[15] followed by subsequent transformations.[16] There is literature precedent for such processes.[17] This is supported by the fact that when the reaction was maintained at reflux under argon for seven days instead of 24 h, NMR analysis of the crude product showed an increase in the amount of diketone **21**, whereas enamine **23** was no longer observed. Moreover, when the reaction was repeated for 24 h with the reflux condenser deliberately open to the air, the amounts of isolated ketone **21** and aminal **22** increased to 38% and 13%, respectively, with again no enamine **23** being detected by NMR spectroscopy of the crude product.

These facts suggest that the enamine–iminium equilibrium lies more towards the enamine than in the case of the five-membered analogue **7**.[18] In order to favour the iminium reactive intermediate, 0.1 equivalent of *para*-toluenesulfonic acid was added, which indeed increased the yield of the desired tetrahydrocarboline **19** to 68% (Scheme 6).



Scheme 6.

Stereochemical and Mechanistic Issues

In order to assign the relative configurations of both diastereoisomers of tetrahydrocarboline **17** (Scheme 5), one of them was mixed with 2,4,6-trinitrophenol to form the corresponding salt, which was then re-crystallised in acetonitrile. X-ray diffraction through a single crystal revealed that the compound is the *cis* diastereoisomer, "*cis*" referring to the relative configurations of the methyl groups (Figure 4). The proposed structures of both diastereoisomers are also in agreement with NOESY 2D NMR experiments and molecular calculations using the AM1 method,[19] predicting a *cis* ring junction in both cases (Figure 5).

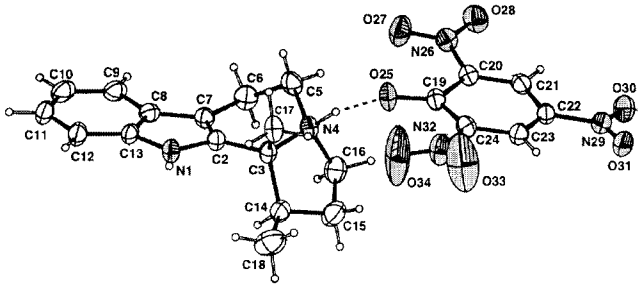


Figure 4. ORTEP drawing of *cis*-**17**•picric acid. Displacement ellipsoids are shown at the 30% probability level.

In contrast to **17**, the homologous compound **18** was isolated as a single diastereoisomer. The relative configuration

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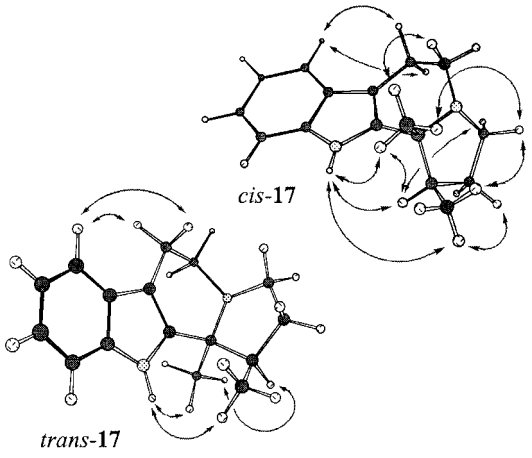

Figure 5. Observed NOE effects on *cis*- and *trans*-**17**.

is *trans*, as shown again by X-ray diffraction through a single crystal of the corresponding 2,4,6-trinitrophenol salt (Figure 6).

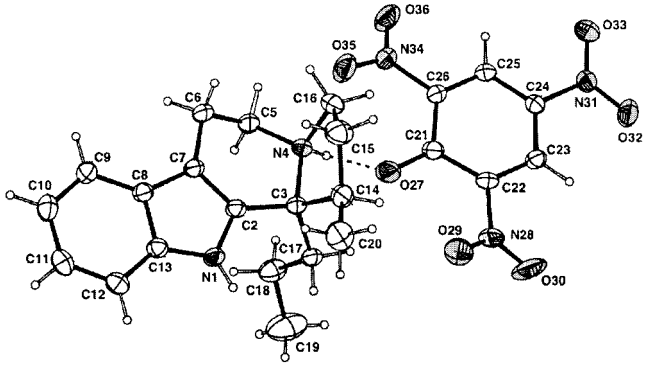

Figure 6. ORTEP drawing of **18**•picric acid. Displacement ellipsoids are shown at the 30% probability level.

In the case of **19**, molecular calculations using the AM1 method[19] predicted a more stable conformation featuring a *cis* ring junction for the *cis* diastereoisomer and a *trans* ring junction for the *trans* diastereoisomer. In the most polar diastereoisomer, the high coupling constant ($^3J_{H,H}$ = 9 Hz) measured at the signal of the proton α to one of the methyl groups is typical for an axial conformation for this proton, and consequently an equatorial conformation for the methyl group, consistent with the proposed structure of *cis*-**19**. NOESY two-dimensional NMR experiments run on both diastereoisomers also fully support this assignment and the calculated conformations (Figure 7).

The tetrahydroisoquinoline **20** was isolated as a single diastereoisomer. Although we failed to obtain crystals that would be suitable for X-ray diffraction analysis, the *cis* relative configuration is tentatively assigned. The ^{1}H NMR signals of the protons borne by the saturated five-membered ring are very similar to those of compound *cis*-**17**,[20] and the proposed structure is in agreement with the observed NOE effects shown in Figure 8.

From a mechanistic point of view, all the results are consistent with a cyclisation by intramolecular aromatic electrophilic substitution onto an iminium ion.[21] The elementary steps leading to this iminium ion from the aminocyclopropane still need to be established. This reactive species could arise from the direct protonation of the cyclopropane or from the prior isomerisation of the aminocyclopropane to an enamine, followed by protonation.[22] In any case, an equilibrium between the iminium and enamine species is expected by loss of proton/reprotonation if the cyclisation step is slow enough. It has been shown in the case of the six-membered aminocyclopropane **9** that the addition of a small amount of acid drives this equilibrium towards the iminium ion and speeds up the reaction. In the case of the phenol derivative **12**, the phenol function might play the same role, which would explain why this compound reacts significantly faster than the corresponding indole derivative **7**.[23]

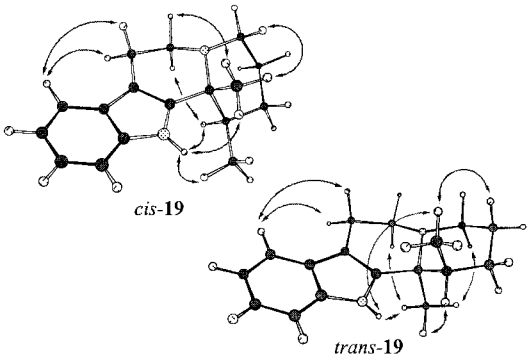

Figure 7. Observed NOE effects on *cis*- and *trans*-**19**.

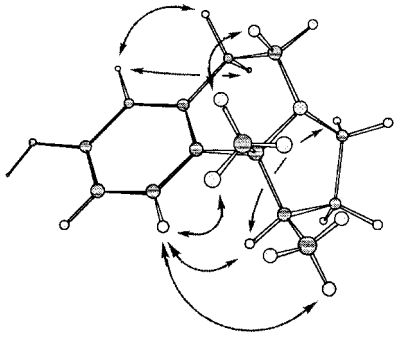

Figure 8. Observed NOE effects on *cis*-**20**.

As far as diastereoselectivity is concerned, the results show some discrepancy, the reaction appearing sometimes highly, and sometimes rather poorly diastereoselective. Moreover, different diastereoselectivities have been observed from the same substrate depending on the reaction conditions (see for instance the case of product **19** in Scheme 6). In all cases, the *cis* diastereoisomers are expected to be the kinetic products. The varying diastereoselectivities could be explained if the cyclisation process was reversible and if the diastereoisomers formed could thus be inter-converted. Indeed, related reversible cyclisations are documented.[24] Further studies are nonetheless needed to get a better understanding and control over these diastereoselectivities.

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Concluding Remarks

Various aminocyclopropanes were used as iminium precursors and cyclised upon heating onto electron-rich aromatic groups by intramolecular Friedel–Crafts alkylation. The new polycyclic structures **17**–**20** thus obtained feature a quaternary carbon at the ring-junction next to the aromatic moiety. This is an interesting feature because creating a quaternary benzylic centre is not easy to achieve using standard methods. Indeed, indirect processes were developed, such as adding an excess of methyllithium to the cyclic iminium ion obtained at the end of the Bischler–Napieralski process.[25] In the Pictet–Spengler reaction, some ketones may actually be used instead of aldehydes,[26] but this is essentially limited to a few types of compounds like pyruvic acid derivatives.[27]

Using our method, it should be noted that the structural diversity of the products synthesised so far is quite restricted. All of them except one feature a ring-junction methyl group and another methyl group in the β position. We are currently devoting our efforts towards the extension to a larger variety of functional groups. The results will be reported in due course.

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 ppm (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at δ = 77.1 ppm (^{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 were not corrected. Unless otherwise stated, 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 dichloromethane and diethyl ether were purchased from SDS and used as such. Chlorobenzene was distilled before use. 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.[11] *n*-Butyllithium solution in hexane was also titrated prior to use.[28]

Aminocyclopropane 9:[29] Titanium isopropoxide (1.5 equiv., 4.5 mmol, 1.3 mL) was added to a solution of *N*-[2-(*1H*-indol-2-yl)-ethyl]-*N*-(pent-4-enyl)acetamide[30] (1.0 equiv., 3.0 mmol, 0.81 g) in THF (30 mL). Cyclopentylmagnesium chloride (1.9 M in Et_2O, 4.0 equiv., 12 mmol, 6.3 mL) was then added dropwise over 30 minutes. After 20 minutes of stirring at 20 °C, the mixture was diluted in dichloromethane (0.10 L) and water (0.10 L). The organic layer was separated, and the aqueous extracted with dichloromethane (2 × 0.10 L). The combined organic phases were dried with sodium sulfate, filtered and concentrated to afford a brown viscous oil (0.94 g). Purification by flash column chromatography on neutral alumina, activity 2 (ethyl acetate/heptane, gradient from 50% to 100%, then methanol/ethyl acetate, gradient from 1% to 4%) yielded pure **9** (0.29 g, 1.1 mmol, 37%), starting amide (0.12 g, 0.43 mmol, 14%), and a reductive dimerisation product[31] (0.17 g, 0.32 mmol, 21%). Analytically pure aminocyclopropane **9** (0.24 g, 0.95 mmol, 32%) was obtained by recrystallisation (ethyl acetate and a few drops of dichloromethane). Colourless crystals. $C_{17}H_{22}N_2$ (254.4): calcd. C 80.27, H 8.72; found C 80.27, H 8.72. M.p. 128.1–128.9 °C. MS (ES^+): *m*/*z* = 293 [MK^+], 294. HRMS (ES^+): calcd. for $C_{17}H_{23}N_2$ [MH^+] 255.1861; found 255.1850. IR $\tilde{\nu}$ = 3415, 2926, 2856, 1454, 1353, 1010 cm^{-1}. ^{1}H NMR δ = 0.35 (dd, *J* = 9, 5 Hz, 1 H), 0.50 (t, *J* = 5 Hz, 1 H), 0.90 (m, 1 H), 1.25 (s, 3 H), 1.29–1.40 (m, 2 H), 1.57 (dddd, *J* = 13, 7, 6, 2 Hz, 1 H), 1.96 (dq, *J* = 13, 7 Hz, 1 H), 2.33 (m, 1 H), 2.66 (m, 1 H), 2.83 (m, 1 H), 2.91–3.10 (m, 3 H), 6.99 (d, *J* = 2 Hz, 1 H), 7.08–7.21 (m, 2 H), 7.31 (d, *J* = 8 Hz, 1 H), 7.63 (d, *J* = 7 Hz, 1 H), 8.18 (br. s, 1 H) ppm. ^{13}C NMR δ = 14.0, 19.5, 19.7, 23.1, 24.6, 26.4, 38.3, 47.9, 54.7, 111.1, 114.9, 118.9, 119.1, 121.5, 121.8, 127.6, 136.2 ppm.

Aminocyclopropane 10:[29] Titanium isopropoxide (1.5 equiv., 1.2 mmol, 0.36 mL) was added to a solution of *N*-but-3-enyl-*N*-[2-(3,4,5-trimethoxyphenyl)ethyl]acetamide[30] (1.0 equiv., 0.81 mmol, 0.25 g) in THF (15 mL). Cyclopentylmagnesium chloride (1.9 M in Et_2O, 4.5 equiv., 3.7 mmol, 1.9 mL) was then added dropwise over 10 minutes. After 10 minutes of stirring at 20 °C, the mixture was diluted in diethyl ether (0.10 L) and water (0.10 L). The organic layer was separated, and the aqueous extracted with diethyl ether (2 × 0.10 L). The combined organic phases were dried with sodium sulfate, filtered, and concentrated to afford a black oil (0.26 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 50% to 100%) yielded pure **10** (0.17 g, 0.58 mmol, 72%). Yellow oil. IR: $\tilde{\nu}$ = 2937, 1589, 1508, 1458, 1420, 1335, 1239, 1129, 1010 cm^{-1}. ^{1}H NMR: δ = 0.11 (dd, *J* = 8, 5 Hz, 1 H), 0.77 (t, *J* = 5 Hz, 1 H), 1.16 (dt, *J* = 8, 5 Hz, 1 H), 1.37 (s, 3 H), 1.79 (m, 1 H), 1.89–2.10 (m, 2 H), 2.29 (dt, *J* = 12, 8 Hz, 1 H), 2.74 (t, *J* = 8 Hz, 2 H), 3.03–3.21 (m, 2 H), 3.82 (s, 3 H), 3.86 (s, 6 H), 6.44 (s, 2 H) ppm. ^{13}C NMR: δ = 7.8, 19.6, 22.4, 26.0, 35.8, 46.2, 49.8, 53.8, 56.0, 60.7, 105.4, 136.1, 136.4, 153.0 ppm.

Aminocyclopropane 11: A similar procedure as for the preparation of **10**, starting from *N*-(but-3-enyl)-*N*-[2-(3-methoxyphenyl)ethyl]-acetamide[30] (2.1 mmol, 0.53 g), yielded pure **11** (0.43 g, 1.9 mmol, 87%). Pale orange oil. MS (CI, NH_3): *m*/*z* = 232 [MH^+], 233, 234. IR: $\tilde{\nu}$ = 2946, 2865, 2832, 2805, 1610, 1602, 1594, 1584, 1488, 1453, 1437, 1259, 1165, 1152, 1054 cm^{-1}. ^{1}H NMR: δ = 0.09 (dd, *J* = 8, 5 Hz, 1 H), 0.75 (t, *J* = 5 Hz, 1 H), 1.14 (dt, *J* = 8, 4 Hz, 1 H), 1.35 (s, 3 H), 1.77 (m, 1 H), 1.88–2.07 (m, 2 H), 2.29 (ddd, *J* = 12, 9, 8 Hz, 1 H), 2.70 (t, *J* = 8 Hz, 2 H), 3.09 (ddd, *J* = 12, 9, 8 Hz, 1 H), 3.16 (t, *J* = 8 Hz, 1 H), 3.80 (s, 3 H), 6.71–6.81 (m, 3 H), 7.20 (t, *J* = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 7.9, 19.8, 22.5, 26.2, 35.7, 46.3, 49.9, 53.9, 55.2, 111.2, 114.5, 121.1, 129.3, 142.4, 159.7 ppm.

Aminocyclopropane 12: Tribromoborane (1.0 M in dichloromethane, 2.0 equiv., 1.4 mmol, 1.4 mL) was added dropwise at 0 °C to a solution of the aminocyclopropane **11** (1.0 equiv., 0.69 mmol, 0.16 g) in dichloromethane (10 mL). The mixture was stirred at room temperature for 4 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was then added. The organic layer was separated, and the aqueous extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried with sodium sulfate, filtered, and concentrated to afford an orange solid (0.15 g). Purification by flash column chromatography (ethyl acetate/dichloromethane, gradient from 0% to 100%) yielded pure **12** (0.11 g, 0.51 mmol, 73%). Brown crystals. $C_{14}H_{19}NO$ (217.3): calcd. C 77.38, H 8.81; found C 77.14, H 9.03. M.p. 112.9–113.2 °C (cyclohexane). MS (CI, NH_3): *m*/*z* = 218

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[MH^+], 219. IR $\tilde{\nu}$ = 3036, 2934, 2865, 2710, 2602, 1592, 1483, 1456, 1388, 1253, 1157 cm^{-1}. ^1H NMR: δ = 0.15 (dd, J = 8, 6 Hz, 1 H), 0.80 (dd, J = 6, 5 Hz, 1 H), 1.27 (dt, J = 8, 5 Hz, 1 H), 1.33 (s, 3 H), 1.80 (m, 1 H), 1.87–2.09 (m, 2 H), 2.29 (ddd, J = 12, 9, 7 Hz, 1 H), 2.76 (t, J = 8 Hz, 2 H), 3.03 –3.20 (m, 2 H), 6.65–6.86 (m, 3 H), 7.14 (t, J = 8 Hz, 1 H), 7.77 (br. s, 1 H, OH) ppm. ^{13}C NMR: δ = 8.3, 18.8, 22.7, 25.9, 35.0, 46.7, 49.4, 54.0, 114.2, 115.5, 119.7, 129.9, 141.4, 157.4 ppm.

Aminocyclopropane 13: *n*-Butyllithium (1.2 M in hexane, 1.1 equiv., 0.57 mmol, 0.47 mL) was added dropwise at –70 °C to a solution of *N*-(but-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl)acetamide[30] (1.0 equiv., 0.52 mmol, 0.10 g) in THF (4.0 mL). After 30 minutes of stirring at –70 °C, chlorotrimethylsilane (1.1 equiv., 0.57 mmol, 73 μL) was added to the yellow mixture, which was then warmed to 20 °C for 50 minutes and became brown. Titanium isopropoxide (1.5 equiv., 0.78 mmol, 0.23 mL) was then added, followed by cyclopentylmagnesium chloride (2.1 M in Et_2O, 4.5 equiv., 2.3 mmol, 1.1 mL) dropwise over 5 minutes. After 10 minutes of stirring at 20 °C, the mixture was diluted in diethyl ether (50 mL) and water (50 mL). The organic layer was separated, and the aqueous extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried with sodium sulfate, filtered, and concentrated to afford a brown oil (0.14 g). Purification by flash column chromatography (methanol/ethyl acetate, 2%) yielded pure **13** (62 mg, 0.35 mmol, 68%). White crystals. $C_{11}H_{16}N_2$ (176.3): calcd. C 74.96, H 9.15; found: C 74.83, H 9.32. M.p. 93.0–94.0 °C (ethyl acetate). HRMS (ES^+): calcd. for $C_{11}H_{17}N_2$ [MH^+] 177.1392; found 177.1389. IR: $\tilde{\nu}$ = 3181, 3094, 2928, 2863, 1447, 1355, 1253, 1241, 1125, 1097, 1025 cm^{-1}. ^1H NMR: δ = 0.14 (dd, J = 8, 6 Hz, 1 H), 0.80 (dd, J = 6, 4 Hz, 1 H), 1.16 (dt, J = 8, 4 Hz, 1 H), 1.34 (s, 3 H), 1.68 (m, 1 H), 1.84–2.00 (m, 2 H), 2.78 (m, 1 H), 3.60 (AB system, δ_A = 3.22, δ_B = 3.98, J_{AB} = 13 Hz, 2 H), 6.00 (m, 1 H), 6.10 (q, J = 3 Hz, 1 H), 6.70 (q, J = 3 Hz, 1 H), 8.89 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 8.0, 19.7, 23.1, 25.8, 46.1, 48.9, 50.3, 106.8, 107.8, 117.3, 129.9 ppm.

Aminocyclopropane 14: A similar procedure as for the preparation of **10**, starting from *N*-(but-3-enyl)-*N*-[1-(triisopropylsilanyl)pyrrol-2-ylmethyl]acetamide[30] (0.23 mmol, 79 mg), yielded pure **14** (34 mg, 0.10 mmol, 44%). Colourless oil. MS (EI) m/z = 115, 194, 235, 236, 237, 332 [$M^{+\cdot}$]. HRMS (ES^+) calcd. for $C_{20}H_{37}N_2Si$ [MH^+] 333.2726, found 333.2739. IR $\tilde{\nu}$ = 2947, 2867, 1467, 1141, 1064, 882 cm^{-1}. ^1H NMR: δ = 0.08 (dd, J = 8, 5 Hz, 1 H), 0.83 (t, J = 5 Hz, 1 H), 0.98–1.17 (m, 19 H), 1.33 (s, 3 H), 1.50 (m, 1 H), 1.59–1.72 (m, 3 H), 1.75–1.90 (m, 2 H), 2.77 (m, 1 H), 3.12 (d, J = 13 Hz, 1 H), 3.98 (d, J = 13 Hz, 1 H), 6.16 (t, J = 3 Hz, 1 H), 6.22 (m, 1 H), 6.78 (dd, J = 3, 2 Hz, 1 H) ppm. ^{13}C NMR δ = 7.7, 13.2, 18.4, 18.6, 19.7, 23.1, 25.8, 46.4, 50.2, 50.5, 108.9, 112.5, 125.8, 136.3 ppm.

Amide 15 and Dimer 16: Cyclopentylmagnesium chloride (2.0 M in Et_2O, 4.0 equiv., 2.1 mmol, 1.0 mL) was added dropwise at –70 °C to a solution of titanium isopropoxide (2.0 equiv., 1.0 mmol, 0.31 mL) in diethyl ether (10 mL). The mixture was warmed to –30 °C in 5 minutes and became black. A solution of *N*-(but-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl)acetamide[30] (1.0 equiv., 0.52 mmol, 0.10 g) in diethyl ether (1.0 mL) was then added. The brown-red mixture was warmed to 20 °C for 1 h20, then diluted in diethyl ether (0.10 L) and water (0.10 L). The organic layer was separated, and the aqueous extracted with diethyl ether (2 × 0.10 L). The combined organic phases were dried with sodium sulfate, filtered, and concentrated to afford a black oil (92 mg). Purification by flash column chromatography (ethyl acetate/dichloromethane, gradient from 0% to 100%) yielded a 74:26 mixture (as determined by ^1H NMR spectroscopy) of **15** and starting material (27 mg, 0.14 mmol, 20% and 7% respectively), and a 53:47 mixture (as determined by ^1H NMR spectroscopy) of the aminocyclopropane **13** and the dimer **16** (50 mg, 0.18 mmol, 19% and 33%, respectively). These two compounds could be obtained in a pure form by performing a second flash chromatography. The isolated yields for **13** and **16** were 14 mg (79 μmol, 15%) and 23 mg (59 μmol, 23%), respectively. **15:** Yellow oil. MS (EI): m/z = 194 [$M^{+\cdot}$]. ^1H NMR: δ = 0.93 (t, J = 7 Hz, 3 H), 1.30 (sext, J = 7 Hz, 2 H), 1.56 (m, 2 H), 2.09 (s, 3 H), 3.23 (dd, J = 8, 6 Hz, 2 H), 4.35 (s, 2 H), 6.00–6.09 (m, 2 H) 6.69 (m, 1 H), 9.22 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.8, 20.1, 21.4, 30.7, 43.0, 49.0, 107.1, 107.2, 118.2, 129.0, 171.7 ppm. **16:** Colourless oil. MS (EI): m/z = 80, 95, 205, 264, 306, 343, 386 [$M^{+\cdot}$]. ^1H NMR: δ = 0.82 (d, J = 6 Hz, 6 H), 1.34 (m, 4 H), 1.56 (m, 2 H), 2.09 (s, 6 H), 3.11–3.33 (m, 4 H), 4.35 (AB system, $\Delta\upsilon$ = 8, J_{AB} = 15 Hz, 4 H), 6.01–6.08 (m, 4 H), 6.70 (br. s, 2 H), 9.23 (br. s, 2 H, NH) ppm. ^{13}C NMR: δ = 14.2, 21.4, 33.6, 34.9, 43.3, 48.1, 107.2, 107.3, 118.3, 129.0, 171.6 ppm.

Tetrahydrocarboline 17: A solution of the aminocyclopropane **7**[6] (1.0 equiv., 4.9 mmol, 1.2 g) in chlorobenzene (100 mL) was heated at reflux for 11 h. After cooling, the solvent was removed under reduced pressure to afford a brown viscous oil (1.2 g). Analysis of this crude product by ^1H and ^{13}C NMR spectroscopy revealed a 41:59 ratio for the *cis* and *trans* products, defined according to the relative configurations of the methyl groups. Purification by flash column chromatography (concentrated ammonium hydroxide aqueous solution/ethyl acetate, gradient from 0% to 1%) yielded pure *cis*-**17** (0.31 g, 1.3 mmol, 26%), a 40:60 mixture (as determined by ^1H NMR spectroscopy) of *cis*- and *trans*-**17** (0.11 g, 0.44 mmol, 4% and 5% respectively), and pure *trans*-**17** (0.38 g, 1.6 mmol, 32%). The total yield was thus 0.80 g (3.3 mmol, 67%). **Less Polar *cis* Isomer:** Oil. MS (CI, NH_3): m/z = 241 [MH^+], 242, 257 [$MH^+ \cdot NH_3$]. HRMS (ES^+): calcd. for $C_{16}H_{21}N_2$ [MH^+] 241.1705; found 241.1677. IR: $\tilde{\nu}$ = 3408, 3271, 2924, 2850, 1619, 1451, 1346, 1294, 1233, 1138 cm^{-1}. ^1H NMR: δ = 1.20 (d, J = 7 Hz, 3 H), 1.36 (s, 3 H), 1.52 (dtd, J = 12, 9, 7 Hz, 1 H), 1.89 (dtd, J = 12, 7, 3 Hz, 1 H), 2.24 (sext, J = 7 Hz, 1 H), 2.52 (ddd, J = 16, 4, 2 Hz, 1 H), 2.83–3.04 (m, 3 H), 3.13–3.34 (m, 2 H), 7.05–7.18 (m, 2 H), 7.31 (m, 1 H), 7.48 (m, 1 H), 7.62 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 16.6, 16.9, 22.7, 32.4, 42.2, 43.4, 48.4, 60.8, 106.6, 110.7, 118.3, 119.4, 121.5, 127.2, 135.7, 141.1 ppm. **More Polar *trans* Isomer:** Oil. MS (CI, NH_3): m/z = 241 [MH^+], 242. HRMS (ES^+): calcd. for $C_{16}H_{21}N_2$ [MH^+] 241.1705; found 241.1711. IR: $\tilde{\nu}$ = 3412, 3283, 2960, 2926, 1597, 1465, 1378, 1347, 1323, 1289, 1267, 1234, 1126, 1099 cm^{-1}. ^1H NMR: δ = 1.23 (d, J = 7 Hz, 3 H), 1.28 (m, 1 H), 1.46 (s, 3 H), 1.92 (dtd, J = 11, 8, 4 Hz, 1 H), 2.22 (dquint, J = 11, 7 Hz, 1 H), 2.50 (dd, J = 15, 4 Hz, 1 H), 2.96–3.25 (m, 5 H), 7.06–7.18 (m, 2 H), 7.32 (d, J = 8 Hz, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.65 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 16.1, 16.1, 26.8, 31.1, 42.8, 44.6, 47.1, 63.2, 110.0, 110.7, 118.2, 119.3, 121.7, 127.1, 135.7, 136.4 ppm.

Tetrahydrocarboline 18: A similar procedure as for the preparation of **17**, starting from aminocyclopropane **8**[6] (1.0 equiv., 0.50 mmol, 0.13 g), gave pure *trans*-**18** (73 mg, 0.27 mmol, 54%) after purification by flash column chromatography (ethyl acetate/dichloromethane, gradient from 0% to 100%). A pyrrole by-product was also isolated in 7% yield.[31] Orange gum. MS (ES^+): m/z = 269 [MH^+], 270. HRMS (ES^+): calcd. for $C_{18}H_{25}N_2$ [MH^+] 269.2018; found 269.1995. IR: $\tilde{\nu}$ = 3413, 3292, 2956, 2930, 2870, 1624, 1460, 1347, 1322, 1295, 1123 cm^{-1}. ^1H NMR: δ = 0.86 (t, J = 7 Hz, 3 H), 1.00 (d, J = 7 Hz, 3 H), 1.10–1.57 (m, 3 H), 1.76 (dd, J = 9, 7 Hz, 2 H), 1.94 (dtd, J = 12, 7, 6 Hz, 1 H), 2.28 (sext, J = 7 Hz, 1 H), 2.52 (ddd, J = 15, 4, 1 Hz, 1 H), 2.85–3.12 (m, 4 H), 3.19 (ddd, J = 4,

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5, 1 Hz, 1 H), 7.06–7.18 (m, 2 H), 7.32 (d, J = 8 Hz, 1 H), 7.51 (d, J = 7 Hz, 1 H), 7.67 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 14.9, 16.7, 16.8, 18.1, 31.7, 42.9, 43.7, 45.6, 49.1, 66.2, 110.7, 111.1, 118.1, 119.2, 121.5, 127.1, 135.7, 136.4 ppm.

Tetrahydrocarboline 19: *para*-Toluenesulfonic acid (0.10 equiv., 95 μmol, 16 mg) was added to a solution of aminocyclopropane **9** (1.0 equiv., 0.95 mmol, 0.24 g) in chlorobenzene (20 mL). The mixture was heated at reflux for 24 h under a static pressure of argon (balloon filled with argon connected to the top of the reflux condenser). After cooling, the solvent was removed under reduced pressure to afford a brown viscous oil (0.29 g). Analysis of this crude product by ^{1}H and ^{13}C NMR spectroscopy revealed a 60:40 ratio for the *cis* and *trans* products, defined according to the relative configurations of the methyl groups. Purification by flash column chromatography (ethyl acetate/heptane, gradient from 40% to 100%) yielded pure *trans*-**19** (66 mg, 0.26 mmol, 27%) and pure *cis*-**19** (0.10 g, 0.39 mmol, 41%). **Less Polar *trans* Isomer:** Yellowish oil. MS (ES$^+$): m/z = 144, 255 [MH$^+$], 256, 323, 325. HRMS (ES$^+$): calcd. for $C_{17}H_{23}N_2$ [MH$^+$] 255.1861; found 255.1849. IR: $\tilde{\nu}$ = 3412, 2925, 2855, 2808, 1460, 1448, 1344, 1296, 1284, 1166, 1128, 1113 cm^{-1}. ^{1}H NMR: δ = 0.91 (d, J = 7 Hz, 3 H), 1.38 (s, 3 H), 1.44–1.52 (m, 2 H), 1.86–2.06 (m, 3 H), 2.60 (dd, J = 14, 4 Hz, 1 H), 2.66 (m, 1 H), 2.75 (dd, J = 11, 6 Hz, 1 H), 2.85 (td, J = 12, 3 Hz, 1 H), 2.91 (ddd, J = 14, 11, 6 Hz, 1 H), 3.00 (td, J = 11, 4 Hz, 1 H), 7.06–7.14 (m, 2 H), 7.30 (d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 7.56 (br. s, 1 H, NH) ppm. ^{13}C NMR δ = 15.4, 17.2, 21.3, 21.8, 26.9, 36.6, 47.8, 48.9, 57.7, 108.3, 110.6, 118.0, 119.1, 121.1, 127.4, 135.9, 140.4 ppm. **More Polar *cis* Isomer:** Yellowish oil. MS (ES$^+$): m/z = 255 [MH$^+$], 256, 271. HRMS (ES$^+$): calcd. for $C_{17}H_{23}N_2$ [MH$^+$] 255.1861; found 255.1842. IR: $\tilde{\nu}$ = 3421, 2923, 2852, 1460, 1297, 1271, 1184, 1101, 1008 cm^{-1}. ^{1}H NMR: δ = 1.16 (d, J = 7 Hz, 3 H), 1.42 (s, 3 H), 1.45–1.62 (m, 3 H), 1.71 (m, 1 H), 2.15 (dqd, J = 9, 7, 4 Hz, 1 H), 2.74 (dt, J = 15, 6 Hz, 1 H), 2.81 (dtd, J = 13, 4, 1 Hz, 1 H), 2.89 (dt, J = 15, 6 Hz, 1 H), 3.06 (ddd, J = 13, 10, 3 Hz, 1 H), 3.10 (dt, J = 12, 6 Hz, 1 H), 3.24 (dt, J = 12, 6 Hz, 1 H), 7.08 (td, J = 8, 1 Hz, 1 H), 7.14 (td, J = 8, 1 Hz, 1 H), 7.31 (d, J = 8 Hz, 1 H), 7.48 (d, J = 8 Hz, 1 H), 7.73 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 17.7, 19.6, 20.7, 21.8, 30.0, 35.1, 46.4, 48.7, 57.8, 107.7, 110.6, 118.1, 119.2, 121.3, 127.3, 135.6, 140.0 ppm.

Tetrahydroisoquinoline 20: A similar procedure as for the preparation of **17**, with 4 h of heating aminocyclopropane **12** (1.0 equiv., 0.50 mmol, 0.11 g) in chlorobenzene at reflux, afforded the crude product (0.10 g). ^{1}H and ^{13}C NMR spectroscopy revealed the ratio of **20** and its regioisomer (with the OH *ortho* to the newly-formed bond) to be about 87:13. Only one diastereoisomer of **20** could be detected. Purification by flash column chromatography (ethyl acetate/dichloromethane, gradient from 0% to 100%) gave somewhat impure regioisomer of **20** (a few milligrams) and the tetrahydroisoquinoline **20** (52 mg, 0.24 mmol, 49%). **20:** Brown crystals.

Table 1. Crystallographic data and parameters for the compounds *cis*-**17**·picric acid, **18**·picric acid, and **22**.

Compound	*cis*-**17**·Picric acid	**18**·Picric acid	**22**
Empirical formula	$(C_{16}H_{21}N_2)^+(C_6H_2N_3O_7)^-\cdot 0.5H_2O$	$(C_{18}H_{25}N_2)^+(C_6H_2N_3O_7)^-$	$C_{17}H_{22}N_2O$
Molecular mass	478.46	497.51	270.37
Temperature [K]	293(2)	293(2)	293(2)
Wavelength [Å]	0.71073	0.71073	0.71073
Crystal system	monoclinic	triclinic	monoclinic
Space group	*P*2/*a*	*P*–1	*P*21/*n*
Unit cell dimensions			
a [Å]	13.604(11)	7.962(4)	10.191(4)
b [Å]	11.742(11)	11.542(5)	12.069(4)
c [Å]	14.467(11)	14.131(7)	11.744(5)
α [°]	90	67.20(3)	90
β [°]	102.87(3)	85.42(3)	95.78(3)
γ [°]	90	87.81(3)	90
Volume [Å^3]	2253(3)	1193.3(10)	1437.1(10)
Z	4	2	4
Density, calculated [Mg/m^3]	1.411	1.385	1.250
Absorption coefficient [mm^{-1}]	0.108	0.104	0.078
F(000)	1004	524	584
Crystal habit	dark orange, prismatic	pale orange	pale yellow, prismatic
Crystal size [mm]	0.35 × 0.30 × 0.20	0.62 × 0.50 × 0.30	0.50 × 0.25 × 0.12
θ range [°]	1.73 to 23.82	1.95 to 30.05	2.43 to 27.86
Index ranges	$-15 \le h \le 15$, $-13 \le k \le 13$, $-16 \le l \le 16$	$-11 \le h \le 11$, $-14 \le k \le 14$, $-19 \le l \le 19$	$-13 \le h \le 13$, $-15 \le k \le 12$, $-15 \le l \le 15$
Reflections collected	15640/6675	13761/11325	17743/5838
Independent reflections [R_{int}]	3448 [0.0335]	5748 [0.0226]	3418 [0.0308]
Reflections observed [$I > 2\sigma(I)$]	2517	4190	2640
Absorption correction	none	none	none
Refinement method	full-matrix least squares on F^2		
Data/restraints/parameters	3444/2/319	5747/0/328	3417/0/187
Goodness-of-fit on F^2	1.081	1.030	1.044
R_1, wR_2 indices [$I > 2\sigma(I)$]	0.0724, 0.1707	0.0609, 0.1589	0.0420, 0.1030
R_1, wR_2 indices (all data)	0.1012, 0.1927	0.0832, 0.1780	0.0587, 0.1136
Extinction coefficient	0.009(2)	0.010(6)	0.049(5)
Largest diff. peak and hole [e·Å^{-3}]	0.316 and –0.331	0.281 and –0.278	0.270 and –0.148

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$C_{14}H_{19}NO$ (217.3): calcd. C 77.38, H 8.81; found C 77.15, H 8.91. M.p. 150.1–152.6 °C (ethyl acetate). MS (EI): *m*/*z* = 147, 175, 186, 202, 203, 217 [$M^{+\cdot}$]. IR: $\tilde{\nu}$ = 2963, 2687, 2596, 1609, 1582, 1497, 1452, 1379, 1355, 1296, 1247, 1157, 1127 cm^{-1}. ^1H NMR: δ = 1.20 (d, *J* = 7 Hz, 3 H), 1.32 (s, 3 H), 1.50 (dq, *J* = 12, 9 Hz, 1 H), 1.91 (dtd, *J* = 12, 7, 3 Hz, 1 H), 2.24 (dquint, *J* = 9, 7 Hz, 1 H), 2.47 (dt, *J* = 16, 4 Hz, 1 H), 2.82 (dt, *J* = 9, 7 Hz, 1 H), 2.92 (ddd, *J* = 16, 11, 5 Hz, 1 H), 3.01 (ddd, *J* = 9, 7, 3 Hz, 1 H), 3.04–3.20 (m, 2 H), 6.47 (d, *J* = 3 Hz, 1 H), 6.64 (dd, *J* = 8, 3 Hz, 1 H), 6.75 (br. s, 1 H, OH), 7.04 (d, *J* = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 16.6, 24.2, 24.5, 32.0, 44.1, 44.2, 49.2, 64.0, 114.4, 115.1, 127.3, 134.7, 136.3, 154.3 ppm. **Regioisomer:** ^1H NMR: δ = 0.80 (d, *J* = 7 Hz, 3 H), 1.26 (m, 1 H), 1.28 (s, 3 H), 1.54 (dddd, *J* = 13, 8, 5, 1 Hz, 1 H), 2.19 (dq, *J* = 13, 8 Hz, 1 H), 2.65 (quint, *J* = 7 Hz, 1 H), 2.75 (m, 1 H), 2.86–3.04 (m, 4 H), 6.53 (d, *J* = 8 Hz, 1 H), 6.70 (d, *J* = 8 Hz, 1 H), 6.99 (t, *J* = 8 Hz, 1 H) ppm. The signal corresponding to the OH group could not be identified clearly on the spectrum we collected.

Ketone 21 and Pentacyclic Aminal 22: A solution of the aminocyclopropane **9** (1.0 equiv., 0.70 mmol, 0.18 g) in chlorobenzene (14 mL) was heated at reflux for 24 h, with the top of the reflux condenser open to the air. After cooling, the solvent was removed under reduced pressure to afford a brown viscous oil (0.20 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 40% to 100%) yielded relatively pure *trans*-**19** (14 mg, 55 μmol, 8%), pure **22** (24 mg, 88 μmol, 13%), and pure **21** (77 mg, 0.27 mmol, 38%). **21:** Colourless crystals. M.p. 124.1–124.8 °C (ethyl acetate and a few drops of dichloromethane). MS (ES^+): *m*/*z* = 287 [MH^+], 309 [MNa^+], 310, 449, 450, 595. HRMS (ES^+): calcd. for $C_{17}H_{22}N_2NaO_2$ [MNa^+] 309.1579; found 309.1533. IR (62:38 mixture of two rotamers): $\tilde{\nu}$ = 3251, 2925, 1710, 1613, 1483, 1455, 1421, 1359, 1229, 1170, 1009 cm^{-1}. ^1H NMR (major rotamer in the 62:38 mixture): δ = 1.85 (quint, *J* = 7 Hz, 2 H), 1.93 (s, 3 H), 2.14 (s, 3 H), 2.47 (t, *J* = 7 Hz, 2 H), 3.02 (t, *J* = 7.5 Hz, 2 H), 3.39 (t, *J* = 7 Hz, 2 H), 3.56 (t, *J* = 7.5 Hz, 2 H), 7.00 (d, *J* = 2 Hz, 1 H), 7.10–7.23 (m, 2 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 7.58 (d, *J* = 8 Hz, 1 H), 8.07 (br. s, 1 H, NH) ppm. ^1H NMR (minor rotamer in the 62:38 mixture): δ = 1.78 (quint, *J* = 7 Hz, 2 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 2.39 (t, *J* = 7 Hz, 2 H), 3.03 (t, *J* = 7.5 Hz, 2 H), 3.16 (t, *J* = 7 Hz, 2 H), 3.62 (t, *J* = 7.5 Hz, 2 H), 7.04 (d, *J* = 2 Hz, 1 H), 7.10–7.23 (m, 2 H), 7.36 (d, *J* = 8.5 Hz, 1 H), 7.69 (d, *J* = 8 Hz, 1 H), 8.00 (br. s, 1 H, NH) ppm. ^{13}C NMR (major rotamer in the 62:38 mixture): δ = 21.3, 21.8, 24.7, 30.0, 40.8, 44.6, 49.1, 111.4, 112.1, 118.2, 119.6, 121.9, 122.2, 127.1, 136.3, 170.8, 208.4 ppm. ^{13}C NMR (minor rotamer in the 62:38 mixture): δ = 21.6, 22.6, 23.6, 30.0, 39.9, 46.9, 48.4, 111.1, 113.3, 118.8, 119.3, 121.9, 122.2, 127.5, 136.3, 170.4, 207.4 ppm. **22:** Pale yellow crystals. M.p. 176.4–176.9 °C (ethyl acetate and a few drops of dichloromethane). MS (ES^+): *m*/*z* = 255, 271 [MH^+], 272. IR: $\tilde{\nu}$ = 2925, 2851, 2359, 1610, 1487, 1469, 1222, 1152, 1041, 953 cm^{-1}. ^1H NMR: δ = 0.95 (s, 3 H), 1.07 (m, 1 H), 1.10 (s, 3 H), 1.42 (td, *J* = 14, 4 Hz, 1 H), 1.83–1.97 (m, 3 H), 2.21 (td, *J* = 12, 6 Hz, 1 H), 2.85–3.05 (m, 3 H), 3.16 (ddd, *J* = 12, 8, 4 Hz, 1 H), 4.66 (br. s, 1 H, NH), 5.46 (d, *J* = 3 Hz, 1 H), 6.56 (d, *J* = 8 Hz, 1 H), 6.73 (t, *J* = 7 Hz, 1 H), 7.05–7.13 (m, 2 H) ppm. ^{13}C NMR: δ = 15.8, 19.7, 27.9, 35.1, 36.4, 45.9, 49.3, 68.0, 70.6, 83.7, 100.3, 108.5, 119.0, 125.0, 128.4, 130.2, 149.3 ppm.

X-ray Crystallographic Study:[32] Crystals suitable for X-ray diffraction studies were grown from acetonitrile for the salts of *cis*-**17** and **18** with picric acid, and ethyl acetate/dichloromethane for **22**. Data were collected at room temperature on a Nonius Kappa CCD aeradetector diffractometer (φ and ω scan mode), using graphite-monochromated Mo-K_α radiation. The structures were solved by the program SHELXS86[33] and were refined with standard methods using SHELXL93[34] with anisotropic parameters for the non-hydrogen atoms. Crystallographic data and parameters of the refinements are listed in Table 1.

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