Synthesis of Bridged Bicyclic Hydrazines via Endocyclic
N-Acylhydrazonium Intermediates:
A Novel Route to the 1-Azatropane Skeleton

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Abstract: Bicyclic molecules with the 1,7-diaza-6,6-dimethylbicyclo[2.2.1]heptane and 1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane (1-aza-7,7-dimethyltropane) skeleton are shown to be efficiently synthesized via cyclization reactions of endocyclic N-acetylhydrazonium intermediates. By using a protected β-ketoester as the internal nucleophile, azacocaine analogues are also accessible via this methodology.

INTRODUCTION

The synthesis of bicyclic hydrazines with a 1,7-diazbicyclo[2.2.1]heptane or a 1,8-diaza[3.2.1]octane skeleton (e.g. 1 and 2, respectively) has received only scant attention in the literature. These structures with the heptane skeleton are particularly interesting compounds as both the N-chloro and N-methyl substituted molecules have been reported to exhibit high nitrogen inversion barriers for the bridge nitrogen atom. A noticeable feature of the second type of compounds is that they possess a 1-azatropane skeleton and therefore might display promising physiological activity. During the last century, tropane alkaloids have been prominent targets in organic synthesis, both for their biological properties and in order to elucidate their mechanism of action. The most distinguished class of tropane alkaloids consists of cocaine and its isomers, of which various analogues have been prepared. The synthesis of azaanalogues 3, however, has not been reported in the literature.

A method for the preparation of some bridged bicyclic hydrazines 1 and 2 was developed by Oppolzer, who obtained such compounds via intramolecular 1,3-dipolar cycloaddition reactions. In addition to this method, intermolecular dipolar reactions have been studied to give a limited number of 1-azatropanes. A serious setback of these methods is the limited possibility to vary ring sizes and substitution patterns. Herein we wish to report a novel pathway for the preparation of such compounds, offering the possibility of synthesizing differently functionalized bridged diazabicycles.

A retrosynthetic outline of the method, which extends our previous work on N-acylhydrazonium ions,
is given in eq 1. The key intermediate is the endocyclic $N$-acylhydrazonium ion 5, which is converted via intramolecular attack of the internal nucleophile into the bicyclic product 4. The precursor 6 of the $N$-acylhydrazonium intermediate 5 is readily obtained in a few steps starting from the corresponding pyrazolidinone 7 or 8. A large variety of $\pi$-nucleophiles can be used in this cyclization reaction to give the desired functionalized bicyclic products. The use of a (protected) $\beta$-ketoester as nucleophile in the cyclization reaction leads to precursors with a substituted tropanone skeleton.

Regarding the ongoing search for new cocaine analogs, it is relevant to note that our method might provide a route to such compounds.

**RESULTS AND DISCUSSION**

**Choice of the pyrazolidinone**

The use of unsubstituted 3-pyrazolidinone (7) as starting material will lead to unsubstituted bicyclic hydrazines 4 (R = H). In order to study the sequence of reactions, 1-benzyl-3-pyrazolidinone was chosen as a model system. Ethoxycarbonylation (1) LDA (1 equiv), -78 °C; 2) methyl cyanoformate (1.3 equiv)) gave the functionalized hydrazine 10, which had to be reduced to obtain the cyclization precursor 9 (eq 2). The reduction was performed under conditions that were also used for the corresponding pyrrolidinones. Treatment of 10 at -20 °C in ethanol with an excess of sodium borohydride (4 equiv) and a catalytic amount of sulfuric acid, however, led to ring opening of the pyrazolidinone and subsequent reduction of the intermediate aldehyde to the alcohol 11. Formation of this undesired product could not be prevented by performing the reaction at lower temperatures. Reduction did not take place at all in the absence of acid.

The undesired ring opening and overreduction are not expected to occur if the pyrazolidinone ring is substituted with a gem-dimethyl function. The effect, that alkyl substitution favors the cyclic structure in cases of ring-chain tautomerism, is an example of the well-known 'gem-dimethyl effect' and was observed earlier in similar pyrrolidinone systems. Therefore, 5,5-dimethyl-3-pyrazolidinone (8) was chosen as starting material and could be efficiently obtained by condensation of hydrazine hydrate with ethyl 3,3-dimethylacrylate in refluxing ethanol. Distillation of the crude residue gave the pure 3-pyrazolidinone 8 as a colorless oil (bp 100-105 °C, 0.1 mbar), which solidified upon standing.

The series of reactions that lead to the desired cyclic molecules is exemplified in Scheme I. The alkylated product 12 is obtained upon $S_{N}2$-alkylation of 8 with benzyl chloride (1.2 equiv), lithium iodide (cat), potassium carbonate (1.5 equiv), 2-butanone, reflux. In this alkylation reaction, the different nature of the two nitrogen atoms was very important. The N1 nitrogen is an amine type nitrogen atom, which is more prone to react with the halide than the less nucleophilic amide type N2 nitrogen. The alkoxycarbonylation at the N2 atom can in principle be achieved by using one of the five different methods A to E: A) deprotonation with a strong base (sodium hydride (1.05 equiv), rt) and alkylation with methyl chloroformate (1.2 equiv, 0 °C → rt) in THF;
B) the same procedure as A with ethyl chloroformate instead of methyl chloroformate; C) treatment with diethyl dicarbonate (2.0 equiv, rt) in the presence of triethylamine (1 equiv) and DMAP (1 equiv) in dichloromethane; D) deprotonation with LDA (1.1 equiv, -78 °C), followed by methoxycarbonylation with methyl cyanoformate (2 equiv, -78 °C → rt) in THF; E) deprotonation with sodium hydride (1.1 equiv, rt), then reaction with methyl cyanoformate (2 equiv, -78 °C → rt) in THF. The disadvantage of the first two alkoxycarbonylation methods is that a mixture of the N- and O-alkylated product (13 and 17, respectively) was obtained. The selectivity of this reaction could not be influenced by changing the temperature of the reaction. The formation of the O-alkylated product was indicated by a strong absorbance in the IR spectrum at 1630 cm⁻¹ as a result of the presence of the C=N bond.

Reduction of the pyrazolidinone 13 under 'standard conditions' initially afforded the corresponding hydroxy(pyrazolidine, which was directly converted into the ethoxypyracilizide 14 by stirring in acidic ethanol. This last step already indicates the intermediacy of the endocyclic N-acylhydrazonium ion. Cyclization to 15 took place upon treatment with titanium tetrachloride. The free hydrazine 16 was obtained through hydrolysis of the carbamate function with potassium hydroxide in refluxing methanol.

**Synthesis of bridged bicyclic hydrazines via Lewis acid-mediated cyclizations**

A summary of this series of reactions applied to differently alkylated pyrazolidinones is presented in Table I. Generally, the aforementioned alkylation conditions were found to give fair yields with several alkylating agents. The low yield in the case of propargyl bromide (entry 12) was explained by the formation of a considerable amount of the dialkylated pyrazolidinone 22a (30%). It was also shown that use of an excess of the alkylating agent led to the formation of the dialkylated product. For example, if 1.5 equivalent of allyl bromide was added, a substantial amount of the dialkylated product was also found. The pyrazolidinone 24 (entry 16) was obtained upon alkylation with 4-iodo-1-(trimethylsilyl)-2-butyne, which was prepared via the corresponding mesylate. The dioxenone substituted pyrazolidinone 25 (entry 19) was obtained after alkylation with the corresponding chloride. The relatively low yield of the alkylated product 25 is explained by the thermal instability of the dioxenone moiety. This result was obtained after stirring in acetone at 40 °C for 40 h. Both higher and lower temperatures showed a decrease of the yield of 25.

As can be seen from Table I, alkoxycarbonylation methods A and B suffer from the formation of O-alkylated products (entries 2, 7 and 10). The lack of regioselectivity could be overcome by using the more selective reagent methyl cyanoformate, instead of methyl or ethyl chloroformate (entries 11, 18 and 20). The alternative method C, in which the use of a strong base is avoided, also gave satisfactory results (entries 3, 8 and 15). Although this reaction does, in principle, not require a base, the best results were obtained by using stoichiometric amounts of Et₃N and DMAP.

Reduction of the pyrazolidinones proceeded without difficulties in reasonable to good yields in all cases.
The hydroxypyrazolidines 42 and 43 were isolated only in the case of the allyl- and propargylsilanes 34 and 35 (entries 15 and 18). This was done in order to prevent protodesilylation under the acidic conditions that are required for the hydroxy/ethoxy exchange.

Table I. Synthesis of bridged hydrazines via Lewis acid-mediated cyclizations.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkylated product (yield)</th>
<th>acylated product(s) (method/ yield)</th>
<th>reduction product (yield)</th>
<th>Lewis acid</th>
<th>cyclization products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 R = H (65%);</td>
<td>26 (A: 33%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27 R = CO2Et (C: 62%)</td>
<td>37 (83%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19 R = H (68%);</td>
<td>38 (75%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20 R = H (61%);*</td>
<td>29 (A: 47%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30 R = CO2Me (C: 64%)*</td>
<td>39 (71%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>21 R = H (62%);</td>
<td>40 (44%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>31 R = CO2Me (A: 24%);</td>
<td>41 (65%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>32 R = CO2Et (C: 18%);</td>
<td>42 (96%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33 R = CO2Et (A: 18%);</td>
<td>43 (62%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>34 R = CO2Et (C: 62%)</td>
<td>44 (95%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>35 R = CO2Et (C: 62%)</td>
<td>45 (88%)</td>
<td></td>
<td>TiCl4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>36 R = H (40%)*</td>
<td>46 (55%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>37 R = CO2Et (B: 67%)</td>
<td>47 (16%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>38 R = H (63%);</td>
<td>48 (50%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>39 R = CO2Et (G: 62%)</td>
<td>49 (16%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates hydroxy/ethoxy exchange.
A novel route to the 1-azatropane skeleton

The cyclization reactions were performed under standard conditions with the Lewis acid titanium tetrachloride (2 equiv, dichloromethane, -78 °C → rt) and in the case of the silanes 42 and 43 with boron trifluoride etherate (2 equiv, dichloromethane, 0 °C → rt). For the cyclization reactions in entries 3, 5, 8 and 11 tin tetrachloride was also tried as the Lewis acid but gave lower yields. Treatment of 37 with titanium tetrachloride afforded the bridged hydrazine 45 in a good yield (entry 3). Its stereochemistry was established by using NOE-difference ¹H NMR techniques on the corresponding free hydrazine 60 (see eq 4). Irradiation of the endo-Me signal of 60 gave a strong enhancement of the signal of the proton adjacent to the chlorine atom. This is only possible if the six-membered ring is in a chair conformation with the chlorine atom in the equatorial position. Such a configuration is in agreement with the expected mechanism for a cationic olefin cyclization, in which the ring closure takes place via a chair-like conformation 54, and chloride comes in from the equatorial side (eq 3, R = H). The assignment was confirmed by the ¹H NMR spectrum of 60, in which the signal of the hydrogen atom adjacent to the chlorine atom (4.20 ppm, tt) showed two axial-axial (Jax = 11.1 Hz) and two axial-equatorial couplings (Jax = 6.3 Hz).

The above reasoning also explains the stereochemical outcome of the cyclization of the crotyl precursor 39 to 48 (entry 8), in which both substituents occupy the equatorial position. In the conformation leading to the transition state of the (E)-precursor, the methyl group is in the equatorial position (54, R = Me), while chloride attacks from the equatorial side, thus giving rise to the formation of the trans-product 48 as the only product. The (Z)-isomer would lead to a transition state with the methyl group in the axial position, so that cyclization to the cis-product would take place. However, this product was not observed in the reaction mixture. The relative configuration of 48 was inferred from the splitting pattern of the ¹H NMR signal of the proton adjacent to the chlorine atom (3.76 ppm, dt) showing one eq-ax (Jeq = 6.3 Hz) and two ax-ax couplings (Jax = 10.8 Hz).

Cyclization of the methallyl precursor 38 (entry 5) afforded an inseparable mixture of 46 and the elimination product 47. The stereochemistry of the product 46 could not be fully ascertained, but it is most likely that the methyl substituent is equatorial in view of the severe steric interaction between the two endo-methyl groups in the alternative stereoisomer. The crowded nature of the product is reflected in the formation of a relatively large amount of the elimination product 47. Because the double bond causes the six-membered ring...
to flatten, a favorable conformation is obtained in which the interaction of the substituents with the carbamate function and the endo-methyl group is decreased.

Upon cyclization of precursor 40, the 1,7-diazabicyclo[2.2.1]-heptane 49 was formed as a single product in high yield (entry 11). The bulky substituent is in the exo-position, which was concluded from the splitting pattern of the signal of the bridgehead hydrogen atom (4.43 ppm, d, \( \beta J = 4.9 \) Hz). The coupling constants of the bridgehead proton with both adjacent endo-protons are zero as a result of dihedral angles of approximately 90°.

The less nucleophilic acetylene 41 cyclized in a rather low yield (entry 13). This can be either a result of the poor nucleophilicity of the acetylene or of the instability of the product 50. Both silanes 42 and 43 cyclized in reasonable yields to give the elimination products 51 and 52.

In addition to these results, the dioxenone precursor 44 led to the expected cyclization product 53 in a high yield. Although many conditions were tried, cyclization took place only after treatment with boron trifluoride etherate (4 equiv). A smaller amount of this milder Lewis acid led to an incomplete conversion of the precursor 44 into the cyclization product 53. The use of tin tetrachloride or titanium tetrachloride led to decomposition of the dioxenone moiety prior to cyclization.

### Table II. Formic acid-mediated cyclization reactions.

<table>
<thead>
<tr>
<th>entry</th>
<th>precursor</th>
<th>conditions</th>
<th>cyclization product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="" /></td>
<td>18 h, 50 °C</td>
<td>55 (37%)&lt;br&gt;47 (34%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="" /></td>
<td>18 h, 50 °C</td>
<td>56 (84%)&lt;br&gt;48 (47%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="" /></td>
<td>18 h, 50 °C</td>
<td>57 (85%)&lt;br&gt;58 (47%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="" /></td>
<td>18 h, 25 °C</td>
<td>59 (42%)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="" /></td>
<td>18 h, 50 °C</td>
<td>60 (42%)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="" /></td>
<td>5 h, 100 °C</td>
<td>61 (42%)</td>
</tr>
</tbody>
</table>

a) After the reaction, water was added and the mixture was stirred for 6 h at 60 °C.
A novel route to the 1-azatropane skeleton

Formic acid-mediated cyclizations

Compared with the yields of the Lewis acid cyclizations, slightly different yields were obtained as is evident from Table II. The stereochemical outcome is similar compared to the Lewis acid cases. In the cases of the precursors 14, 37 and 39, cyclization did not take place, but instead the ethoxypyrazolidines were converted into the corresponding hydroxypyrazolidines (not shown in the Table). This is somewhat remarkable, as during work-up the use of water is avoided. Presumably, the formyloxy group was exchanged during flash chromatography to give the more stable hydroxypyrazolidines. From the formation of the hydroxypyrazolidines it is evident that the N-acylhydrazonium ion was formed, but that cyclization did not take place. These results emphasize that formic acid is less suitable for the cyclization reactions than Lewis acids. For precursor 37, other acidic conditions were also tried e.g. trifluoroacetic acid in dichloromethane, formic acid at 100 °C, hydrogen chloride in methanol, and trimethylsilyl triflate, but none of these conditions proved to be successful. An example that nicely illustrates the usefulness of these formic acid cyclizations is presented in entry 3, in which the propargyl precursor 41 cyclizes to give the 1-azatropanone 58 in one step via hydrolysis of the intermediate enol ester. Surprisingly, a similar ketone was obtained in an attempt to cyclize precursor 44 (entry 6). While at rt and at 50 °C only starting material was recovered, reaction at 100 °C led to cyclization, immediately followed by ring opening of the dioxenone moiety and decarboxylation to give 59.

Deprotection reactions

The cyclization products 45 and 51 were deprotected to give the free hydrazines 60 and 62, respectively (eqs 4 and 5). Two methods were applied i.e. hydrolysis under basic conditions (potassium hydroxide in methanol)\(^1\)\(^9\) and cleavage with iodotrimethylsilane.\(^2\)\(^5\)

\[
\text{EtO}_2C \quad \text{Me}_2Si(1 \text{ equiv}) \quad \text{MeCN, 40 °C} \quad \text{HN} \quad \text{N} \quad \text{Cl} \quad \text{HN} \quad \text{N} \quad \text{Cl} \quad \text{MeOH, reflux} \quad \text{LiAlH}_4(2 \text{ equiv}) \quad \text{MeOH, ether, reflux} \quad \text{HN} \quad \text{N} \quad \text{Me} \quad \text{HN} \quad \text{N} \quad \text{Me} \quad \text{Cl}
\]

Conversion of the carbamate 51 into the corresponding methylated hydrazine 63 took place in a rather poor yield. An alternative route that provided the N-methyl compound is the reductive methylation of the free hydrazine 60, in which the intermediate iminium ion was reduced with sodium cyanoborohydride leading to the desired compound 61 in good yield.\(^2\)\(^6\)

Synthesis of some azatropanone derivatives

In order to convert the cyclization product 53 into azacocaine derivatives 3 two major conversions were to be carried out. The methyl carbamate had to be converted into a methyl function and the dioxenone part had to be deprotected and reduced. It would be advantageous to perform a catalytic hydrogenation of the dioxenone at this stage, as it would immediately give the desired cis-relationship between the two substituents. Various catalysts were tried at different pressures of hydrogen gas, but the double bond could not be reduced. This might be a result of the very hindered nature of this double bond. At the bottom-side, it is shielded by the
ethylene bridge with the gem-dimethyl function and at the top-side the carbamate hinders the approach of a catalyst. If 53 was treated with sodium/ammonia the double bond remained unaffected, but instead the NN bond was cleaved to give the bicyclic system 68 as a single product in poor yield (eq 6).

\[ \text{MeO}_2\text{C} \quad \text{Na (4 equiv),} \quad \text{N₂H}_2 \quad -78 \degree \text{C} \]

\[ 53 \rightarrow \quad 64 (16\%) \]

There are several methods to convert a methyl carbamate into the corresponding N-methyl compound. Direct conversion of 53 into the desired product 66 (see also eq 5) by reduction with lithium aluminum hydride led to decomposition of the dioxenone part. A useful result was obtained if the carbamate 53 was first cleaved with iodotrimethylsilane to give the free hydrazine 65 (Scheme II). Conversion into the N-methyl compound with methyl iodide or dimethyl sulfate did not give satisfactory results. Therefore, a reductive methylation was carried out, using 37% aqueous formaldehyde in acetonitrile to give the intermediate iminium ion which was further reduced with sodium cyanoborohydride to the methylated compound 66.

\[ \text{MeO}_2\text{C} \quad \text{Me}_2\text{Si (1.2 equiv),} \quad \text{MeCN, 40 \degree \text{C}} \]

\[ 53 \rightarrow 1) \text{37\% eq } \text{H}_2\text{CO (5 equiv),} \quad \text{NaBH}_3\text{CN (1.6 equiv)} \quad \quad 2) \text{AcOH} \]

\[ 65 (98\%) \]

\[ \text{MeO}_2\text{C} \quad \text{CH}_3\text{OH (10 equiv),} \quad \text{xylene, 170 \degree \text{C,}} \quad \text{sealed tube, 10 min} \]

\[ 67 \]

\[ \text{MeO}_2\text{C} \quad \text{PhCOCl (1.2 equiv),} \quad \text{Et}_2\text{N (1.05 equiv),} \quad \text{CH}_2\text{Cl}_2 \]

\[ 68 (70\%) \]

Efforts to reduce the double bond of the dioxenone at this stage by using a catalytic hydrogenation also failed. On the other hand, ring opening of the dioxenone proceeded smoothly and was proven to give the best result if the product 66 was heated in a sealed tube for 10 min at 170 \degree \text{C in xylene in the presence of an excess of methanol (Scheme II). The crude } \beta\text{-ketoester 67 was obtained in a quantitative yield but could not be easily purified. Despite the clear } ^1\text{H NMR spectrum of the crude product, flash chromatography led to a very low yield. Therefore, crude 67 was treated with benzoyl chloride to afford the azatropane derivative 68 in a reasonable overall yield. Unfortunately, this product could not be reduced to the desired cocaine derivative. The crude } \beta\text{-ketoester 67 was also reduced in the presence of an excess of sodium borohydride at 0 \degree \text{C to give the ecgonine analog 69 (eq 7). In accordance with the outcome of a similar reduction of 2-(carbomethoxy)-tropanone at -30 \degree \text{C carried out by Carroll et al. only one isomer was obtained in which both substituents occupy the endo-position (allopseudo). They also reported that reduction at 0 \degree \text{C gave a mixture of the pseudo- and the allopseudoisomer. The high stereoselectivity of the reduction of 67 is probably a result of the presence of the endo-methyl substituent, which shields the bottom side of the molecule, thus preventing an endo-attack.} \]
A novel route to the 1-azatropene skeleton

The stereochemistry of 69 was proven by using $^1$H NMR NOE-difference techniques. Irradiation of the proton adjacent to the hydroxy function (H3) showed an enhancement of the signals of all of the H2 and H4 protons, thus confirming its equatorial position. Irradiation of the hydroxy proton showed a slight enhancement of the signal of the H2 eq proton, but not of the H4 proton, indicating its axial position. The assigned stereochemistry of 69 was confirmed by comparison of the coupling constants of H3 and H4 with the corresponding data of allopseudococaine (in 69: H3: $\delta J = 4.9$ Hz; H4: br $\delta J = 4$ Hz; in allopseudococaine: H3: dt, $\delta J = 1.1, 4.8$ Hz; H4: dd, $\delta J = 3.1, 4.8$ Hz).

Attempts to convert this allopseudococgonine derivative 69 into the benzoyl ester according to literature procedures were not successful. A possible explanation might be that the reactivity of the hydroxy function is strongly decreased as a result of the presence of the endo-methyl group. Present work in our group is aimed at achieving the methodology described here by using 3-pyrazolidinones lacking the geminal methyl groups, so as to produce 1-azatropanes with more resemblance to natural products.

ACKNOWLEDGEMENT

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EXPERIMENTAL

General information. All reactions were carried out under an inert atmosphere of dry nitrogen, unless otherwise described. Standard syringe techniques were applied for transfer of Lewis acids and dry solvents. Infrared (IR) spectra were obtained from CHCl$_3$ solutions, unless indicated otherwise, using a Perkin-Elmer 239 or Perkin-Elmer 1310 spectrophotometer and wavelengths (v) are reported in cm$^{-1}$. Proton nuclear magnetic resonance ($^1$H NMR) spectra were determined in CDCl$_3$ (unless indicated otherwise) using a JEOL PMX 60 (60 MHz), a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or a Bruker AMX 300 (300 MHz) spectrometer. The latter three machines were also used for $^{13}$C NMR (APT) spectra (50, 63 and 75 MHz respectively) in CDCl$_3$ (unless indicated otherwise). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. Elemental analyses were performed by Doms u. Kolb Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany. $R_f$ values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plates (Merck silica gel 60 F$_{254}$) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography (fcp) using the same solvents as for TLC and Merck silica gel 60 (230-400 mesh) or Janssen Chimica silica gel (0.030-0.075 mm). Melting and boiling points are uncorrected. CH$_3$Cl$_2$ was distilled from P$_2$O$_5$ and stored over MS 4A under an atmosphere of dry nitrogen. TiCl$_4$ and SnCl$_4$ were distilled and stored under a dry nitrogen atmosphere as a solution in CH$_2$Cl$_2$. BF$_3$-Et$_2$O was distilled and stored under a dry nitrogen atmosphere. Dry THF and Et$_2$O were distilled from sodium benzophenone knoxl prior to use.

1-Benzyl-3-pyrazolidinone-2-carboxylic acid methyl ester (10). A solution of 1-benzyl-3-pyrazolidinone (500 mg, 2.84 mmol) in THF (5 mL) was deprotonated with LDA (prepared from diisopropylamine (0.44 mL, 3.13 mmol) and n-butyllithium (2.0 mL of a 1.6 M solution in hexane, 3.2 mmol) in THF (10 mL) at 0 °C) at -78 °C and treated at that temperature with a solution of MeO$_2$CCN (483 mg, 5.68 mmol) in THF (5 mL). The mixture was stirred at -78 °C for 1 h, allowed to warm to rt, poured into water (50 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to give 10 (263 mg, 1.12 mmol, 40%) as a colorless oil, $R_f$...
butyllithium (1.1 equiv) at 0°C for 1 h. The reaction mixture was monitored by TLC. After complete reduction, the reaction mixture was poured into aq. satd NaHCO₃ and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo to afford the pure cyclization product (11).

General procedure for the alkylation reactions. The halide (1.1 equiv), K₂CO₃ (1.5 equiv) and a catalytic amount of LiTMS were added to a solution of 3-pyrazolidinone 8 in 2-butanone. The solution was heated at reflux temperature for 18 h, concentrated in vacuo, and the residue was taken up in water and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo to afford the pure product.

Method A for the methoxycarbonylation. To a suspension of NaH (obtained from a 55% dispersion in oil by washing with dry pentane) in THF (2 mL) was added a solution of the hydrazide (1 equiv) in THF. After being stirred at -78 °C for 10 min, 1 drop of a 2 M H₂SO₄/THF solution was added. After being stirred at -78 °C for 1 h, MeC(O)CN dissolved in THF, was added and the mixture was allowed to warm to rt. After being stirred for 30 min, the mixture was poured into an ice/water mixture and extracted with ether (3 x). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. The residue was chromatographed to afford the pure alkylation product.

Method B for the ethoxycarbonylation. See procedure A with EtO₂CCl instead of MeO₂CCl.

Method C for the ethoxycarbonylation. To a solution of the functionalized pyrazolidinone in CH₂Cl₂ (2.1 equiv) and a solution of DMAP (1.1 equiv) in CCl₄ were added Et₂N (1.1 equiv), diethyl dicarbonate (2.1 equiv) and a catalytic amount of UiO (1.5 equiv) and a catalytic amount of UiO was added Et₂N (1.1 equiv), diethyl dicarbonate (2.1 equiv) and a catalytic amount of UiO was added. The solution was heated at reflux temperature for 18 h, concentrated in vacuo, and purified by fc to afford the pure product.

Method D for the methoxycarbonylation. To a solution of LDA (prepared from diisopropylamine (1.1 equiv) and n-butyllithium (1.1 equiv) at 0°C) in THF was added at -78 °C a solution of the hydrazide (1 equiv) in THF. After being stirred at -78 °C for 1 h, MeO₂CCl dissolved in THF, was added and the mixture was allowed to warm to rt. After being stirred for 30 min, the mixture was poured into an ice/water mixture and extracted with ether (3 x). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo to afford the pure product.

General procedure for the reduction reactions with NaBH₄. A solution of the functionalized pyrazolidinone in ethanol was cooled to -20 °C and NaBH₄ (6 equiv) was added in one portion. The solution was stirred at -20 °C while each 10 min 1 drop of a 2 M solution of sulfuric acid in ethanol was added to the mixture. The reaction was monitored by TLC. After complete reduction (2-3 h), the solution was cooled to -78 °C and acidified to pH = 3 with a 2 M H₂SO₄/THF solution. After being stirred at rt for 5 h, the mixture was poured into aq. NaHCO₃ and extracted with CH₂Cl₂ (3 x). The combined organic layers were washed with water, dried (K₂CO₃), filtered, and concentrated in vacuo. The residue was chromatographed to yield the pure pyrazolidone.

General procedure for the cyclization reactions with TiCl₄. To a 0.1 M solution of the hydrazide in CH₂Cl₂ was added TiCl₄ (2 equiv, as a solution of TiCl₄ in CH₂Cl₂) at -78 °C by a syringe. The mixture was stirred at -78 °C for 15 min and for 5-18 h at rt. The reaction mixture was poured into cold aq. NaHCO₃ and the resulting suspension was filtered over Celite and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by fc afforded the pure cyclization product(s).
1-Benzy 1.5,5-dimethyl-3-pyrrolidinone (12). According to the general procedure, 3-pyrrolidinone 8 (3.02 g, 26.3 mmol) was alkylated by using benzyl chloride (3.03 mL, 26.3 mmol), K$_2$CO$_3$ (4.00 g, 29.3 mmol) and Ll in 2-butaneone (130 mL). Work-up and fc (ethyl acetate) afforded 12 (4.30 g, 22.1 mmol, 80%) as white needles, mp 107.5-108.5°C (hexane). IR v 3430, 3400, 1685; $^1$H NMR (200 MHz) 8 1.35 (s, 6 H, Me$_2$C), 2.39 (s, 2 H, CCH$_2$), 3.77 (s, 2 H, NCH$_2$), 6.77 (br s, 1 H, NH), 7.31 (s, 5 H, ArH); Anal. Calcd. for C$_{12}$H$_{16}$O$_4$N: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.52; H, 7.92; N, 13.68.

1-Benzy 1.5,5-dimethyl-3-pyrrolidinone-2-carboxylic acid ethyl ester (13) via the method B. 12 (2.03 g, 10.0 mmol) was treated with NaH (550 mg, 12.7 mmol) and EtO$_2$CCl$_2$ (2.86 mL, 30 mmol), while all compounds were dissolved in vacuo 200 g. Work-up and fc (ethyl acetate/hexane 2:1) afforded 13 (1.64 g, 5.94 mmol, 59%) as white crystals, mp 89-92°C. $^1$H NMR (200 MHz) 8 1.33 (t, $J$ = 7.1 Hz, 3 H, CH$_2$), 1.34 (s, 3 H, Me), 2.34 (s, 2 H, CCH$_2$), 4.03 (s, 2 H, CH$_2$), 4.08 (q, $J$ = 7.1 Hz, 2 H, CH$_2$CH$_2$), 7.25-7.45 (m, 5 H, ArH), 17: IR v 1760, 1635; $^1$H NMR (200 MHz) 8 1.13 (t, $J$ = 7.1 Hz, 3 H, CH$_2$CH$_2$), 1.34 (s, 6 H, Me$_2$C), 2.81 (s, 2 H, CCH$_2$), 3.96 (s, 2 H, NCH$_2$), 4.25 (q, 2 H, CH$_2$CH$_2$). 7.15-7.45 (m, 5 H, ArH)

1-Benzy 1.5,5-dimethyl-3-pyrrolidinone-2-carboxylic acid ethyl ester (13) via method C. A solution of 12 (2.00 g, 7.24 mmol) was reduced with NaBH$_4$ (1.64 g, 43.4 mmol) in EtOH (100 mL). Work-up and fc (ethyl acetate/hexane 2:1) afforded 14 (2.02 g, 6.53 mmol, 90%) as a colorless oil, Ay 0.43. IR v 1680; $^1$H NMR (200 MHz) 8 (some signals appear as rotamers) 1.17-1.30 (m, 9 H, 3 x Me), 1.89 (d, $J$ = 11.8 Hz, 1 H, H$_2$), 4.09 (q, $J$ = 7.1 Hz, 2 H, NCH$_2$), 5.56 (dd, $J$ = 6.0 Hz, 1 H, H$_5$), 6.94-7.15 (m, 4 H, 4 x ArH); $^1$H NMR (250 MHz, CD$_3$OD, 65°C) 8 0.97 (s, 3 H, Me), 1.06 (t, $J$ = 7.1 Hz, 3 H, CH$_2$C), 1.19 (s, 3 H, Me), 1.65 (d, $J$ = 11.8 Hz, 1 H, H$_2$), 4.08 (q, $J$ = 7.1 Hz, 2 H, CH$_2$), 4.48 (d, $J$ = 6.0 Hz, 1 H, H$_2$), 5.16 (d, $J$ = 6.7 Hz, 1 H, H$_5$), 6.60-7.00 (m, 4 H, 4 x ArH); $^{13}$C NMR (50 MHz) 8 (some signals appear as rotamers) 14.5 (CH$_2$CH$_2$), 25.4 (Me), 31.9 (Me$_2$), 50.9, 51.3 (C6), 52.7 (C2), 56.7, 57.2 (C5), 61.2, 61.5 (CH$_2$), 66.0, 66.5 (C7), 124.1, 125.4, 126.2, 127.1 (ArH), 131.0, 140.0 (ArC), 154.0, 154.5 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 260 (M$^+$, 81), 245 (11), 204 (62), 187 (37), 159 (370, 131 (100), 117 (72), 91 (36), 77 (17); HRMS calcd for C$_{12}$H$_{18}$N$_2$O$_2$ 260.1525, found 260.1539.

3,4-Benzo[1,8]-diaza-7,7-dimethylbicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (15). According to the general procedure, a solution of 14 (1.04 g, 3.4 mmol) in CH$_2$Cl$_2$ (40 mL) was treated with EiBr (1.47 mL, 10.9 mmol), diethyl dicarbonate (2.9 mL, 19.6 mmol) and a solution of DMAP (1.20 g, 9.80 mmol) in CH$_2$Cl$_2$ (200 g, 30 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was chromatographed (acetone) to yield 15 (109 mg, 0.58 mmol, 81%) as a yellow oil, IR v 3390, 3060; $^1$H NMR (250 MHz) 8 1.25 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.95-2.15 (m, 2 H, 2 x H$_2$), 3.90 (br s, 1 H, NH), 4.07 (d, $J$ = 17.3 Hz, 1 H, H$_2$), 4.17 (d, $J$ = 6.0 Hz, 1 H, H$_2$), 4.45 (d, $J$ = 17.3 Hz, 1 H, H$_5$), 6.85-7.15 (m, 4 H, ArH); $^{13}$C NMR (50 MHz) 8 26.1 (Me), 32.7 (Me), 53.1, 53.3 (C2 and C6), 65.6 (C7), 124.4, 125.4, 125.8, 126.9 (ArH), 132.1, 141.7 (ArC); MS (EI, 70 eV) m/z (relative intensity) 188 (M$^+$, 64), 173 (23), 145 (8), 122 (66), 131 (100), 117 (36), 104 (8), 91 (8), 77 (9), 32 (48), 31
(54); HRMS calc'd for C_{12}H_{10}N_2O 188.1313, found 188.1320.

5,5-Dimethyl-1-(2-propenyl)-3-pyrazolidinone (18). According to the general procedure, 3-pyrazolidinone (8; 2.0 g, 17.5 mmol) was alkylated with allyl bromide (1.51 mL, 17.5 mmol) and LiI in 2-butanone (80 mL). Work-up and fc (ethyl acetate) afforded 18 (2.71 g, 16.0 mmol, 62%) as white crystals, mp 66.5-68.5 °C (ether), 98.5 °C (CH2Cl2/ether 1:10). IR v 3430, 3400, 3080, 1680; 1H NMR (200 MHz) δ 1.29 (s, 6 H, Me2), 2.28 (s, 2 H, CCH2), 3.22 (d, J = 6.4 Hz, 2 H, NCH2), 5.15 (dd, J = 1.8, 8.1 Hz, 1 H, =CH), 5.23 (d, J = 2.8 Hz, 1 H, =CH2), 5.65-5.90 (m, 1 H, =CH), 8.27 (br s, 1 H, NH).

5,5-Dimethyl-1-(2-methyl-2-propenyl)-3-pyrazolidinone (19). 3-Pyrazolidinone (8; 1.00 g, 8.80 mmol) was alkylated (according to the general procedure) with chloro-2-methyl-1-propene (0.91 mL, 9.21 mmol) and LiI in 2-butanone (100 mL). After work-up and fc (ethyl acetate), 19 (1.29 g, 7.69 mmol, 88%) was obtained as a white solid, mp 97.5-98.5 °C (ether), IR v 3430, 3300, 1675; 1H NMR (200 MHz) δ 1.29 (s, 6 H, Me2), 1.75 (s, 3 H, Me), 2.34 (s, 2 H, CH2), 3.12 (s, 2 H, NCH2), 4.92 (m, 2 H, =CH2), 7.24 (br s, 1 H, NH). Anal. Calcd. for C6H10N2O: C, 64.25; H, 9.59; N, 15.06; Found: C, 64.27; H, 9.57; N, 16.56.

1-(2-Butenyl)-5,5-dimethyl-1,2-dil(2-propynyl)-3-pyrazolidinone (21). Following the general procedure, 3-pyrazolidinone (8; 3.02 g, 26.3 mmol) was alkylated by using 4-bromo-2-methyl-2-butene (0.15 mL, 27.6 mmol), K2CO3 (2.12 g, 15.2 mmol) and LiI in 2-butanone (400 mL). After work-up and fc (ethyl acetate), 21 (8.75 g, 26.0 mmol, 88%) was obtained as white crystals, mp 66.5-68 °C, IR v 3430, 3190, 1669; 1H NMR (200 MHz) δ 1.29 (s, 6 H, Me2), 1.69 (dt, J = 6.3, 1.0 Hz, 3 H, Me), 2.35 (s, 2 H, CCH2), 3.21 (d, J = 6.5 Hz, 2 H, NCH2), 5.35-5.55 (m, 1 H, =CH2CH=), 5.60-5.80 (eq, J = 15, 6.3 Hz, =CH2CH=), 7.60 (br s, 1 H, NH). (Z)-isomer. 1H NMR (200 MHz) δ 1.29 (s, 6 H, Me2), 1.69 (dt, J = 1.0, 6.3 Hz, 3 H, Me), 2.38 (s, 2 H, CH2), 3.33 (d, J = 6.9 Hz, 2 H, NCH2), 5.35-5.55 (m, 1 H, =CH2CH=), 5.60-5.80 (m, 1 H, =CH2CH=), 7.60 (br s, 1 H, NH).

5,5-Dimethyl-1-(3-methyl-2-butyl)-3-pyrazolidinone (22). Following the general procedure, 3-pyrazolidinone (8; 2.01 g, 10.5 mmol, 30%) as a dark oil, Rf 0.30. IR v 3430, 3300, 2250, 1690; 1H NMR (200 MHz) δ 1.26 (s, 9 H, Me3), 1.32 (s, 3 H, Me), 2.44 (s, 2 H, CCH2), 3.45-3.75 (m, 4 H, 2 x NCH2), 5.36-5.60 (m, 1 H, =CH2CH=), 6.90 (br s, 1 H, NH). Data for 22a: IR v 3300, 2250, 1690; 1H NMR (200 MHz) δ 1.29 (s, 6 H, Me2), 2.11 (s, 2 H, CH2), 2.25 (s, J = 2.3 Hz, 2 H, =CH2), 3.45-3.75 (m, 4 H, 2 x NCH2).

5,5-Dimethyl-1-(2-propynyl)-3-pyrazolidinone (23). According to the general procedure, 3-pyrazolidinone (8; 2.50 g, 21.5 mmol) was alkylated upon use of 2-chloroethyl-3-(trimethylsilyl)-1-propene (2.90 g, 22.8 mmole, K2CO3 (2.73 g, 19.7 mmol) and LiI in 2-butanone (70 mL). Work-up and fc (ethyl acetate) afforded 23 (3.61 g, 14.8 mmol, 89%) as white crystals, mp 59-61 °C (ether), IR v 3440, 3400, 3080, 1690, 1250, 850; 1H NMR (200 MHz) δ 0.0 (s, 9 H, Me3Si), 1.26 (s, 6 H, Me2), 1.61 (d, J = 0.7 Hz, 2 H, CH2Si), 2.34 (2 H, 2 x CCH2), 3.08 (s, 2 H, NCH2), 4.72 (d, J = 0.6 Hz, 1 H, =CH), 4.83 (d, J = 1.9 Hz, 1 H, =CH2), 6.83 (br s, 1 H, NH).
A novel route to the 1-azatropine skeleton

5,5-Dimethyl-1-{[3,3-dimethyl-5-oxo-2,4-dioxo-6-ethyl-5-ethylmethyl]-3-pyrazolidinone (25). According to the general procedure, 3-pyrazolidinone 3 (3.55 g, 31.1 mmol) was alkylated with dioxenone 24 (5.50 g, 32 mmol) and a catalytic amount of Lil in acetone (130 mL). After being stirred at 45 °C for 48 h, the mixture was worked-up and purified by fct (ethyl acetate) to afford 25 (4.79 g, 18.9 mmol, 61%) as orange crystals, mp 112.5-113 °C (pentane/ether/CH2Cl2). IR (KBr): v 3420, 1720, 1635, 1385, 1370, 1270, 1010; 'H NMR (200 MHz, CDCl3): δ 1.33 (s, 6 H, Me2C), 1.46 (t, J = 2.4 Hz, 2 H, CH2Si), 2.42 (s, 2 H, CCH2), 3.52 (t, J = 2.4 Hz, 2 H, NCH2), 7.70 (br s, 1 H, NH).

5,5-Dimethyl-3-{[methoxycarbonyl]oxy}-1-{(2-propenyl)-2-pyrazoline (26). According to method A, 18 (2.00 g, 13.0 mmol) was treated with NaH (680 mg, 15.6 mmol) and MeO2CCl (3.0 mL, 39 mmol), all compounds dissolved in THF (20 mL). Work-up and fct (ethyl acetate/hexane 1:1) afforded 26 (920 mg, 4.3 mmol, 33%) as a yellow oil, δ 0.28 (ethyl acetate). IR: v 3420, 1720, 1635, 1385, 1370, 1270, 1010; 'H NMR (200 MHz, CDCl3): δ 1.30 (s, 6 H, Me2C), 1.71 (s, 3 H, Me2CO), 2.36 (s, 2 H, CH2), 3.40 (s, 2 H, NCH2), 5.52 (s, 1 H, =CH), 7.70 (br s, 1 H, NH); 13C NMR (50 MHz): δ 24.9 (4 × Me), 42.7 (CH2), 54.1 (NCH2), 63.0 (NC), 94.6 (CH2), 107.0 (CHO) and =C); MS (EI, 70 eV) m/z (relative intensity): 196 (M+ - 58, 50), 127 (100), 83 (62), 43 (74).

5,5-Dimethyl-1-{(2-propenyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (27). According to method A, 19 (500 mg, 2.98 mmol) was treated with NaH (79 mg, 3.28 mmol) and MeO2CCl (0.69 mL, 8.94 mmol) in THF (5 mL). Concentration in vacuo and fct (ethyl acetate) afforded 27 (497 mg, 2.20 mmol, 74%) as a colorless oil, δ 0.45. IR: v 3090, 1760, 1630; 'H NMR (200 MHz, CDCl3): δ 1.27 (s, 6 H, Me2C), 1.84 (s, 3 H, Me), 2.53 (s, 2 H, CCH2), 3.34 (d, J = 6.7 Hz, 2 H, NCH2), 3.78 (s, 3 H, CO2CH3), 4.84 (4 × 86, s, 2 H, =CH2).

1-(2-Butenyl)-5,5-dimethyl-3-{[(methoxycarbonyl)oxy]-2-pyrazoline (28). Following method A, 20 (2.20 g, 13.1 mmol) was treated with NaH (680 mg, 15.6 mmol) and MeO2CCl (3.0 mL, 39 mmol), all compounds dissolved in THF (20 mL). Work-up and fct (ethyl acetate/hexane 1:1) afforded 28 (497 mg, 2.20 mmol, 74%) as a colorless oil, δ 0.45. IR: v 3080, 1760, 1630; 'H NMR (200 MHz, CDCl3): δ 0.75. IR v 3080, 1760, 1630; (E)-isomer: 1H NMR (200 MHz): δ 1.26 (s, 6 H, Me2C), 1.67 (d, J = 4.6 Hz, 3 H, Me), 2.74 (s, 2 H, CCH2), 3.35 (d, J = 1.1, 3.9 Hz, 2 H, NCH2), 3.82 (s, 3 H, CO2CH3), 5.55-5.70 (m, 2 H, =CH=CH); (Z)-isomer: 1H NMR (200 MHz): δ 1.28 (s, 6 H, Me2C), 1.65 (d, J = 6.1 Hz, 3 H, Me), 2.75 (s, 2 H, CCH2), 3.45 (d, J = 1.1, 3.9 Hz, 2 H, NCH2), 3.83 (s, 3 H, CO2CH3), 5.55-5.70 (m, 2 H, =CH=CH).

1-(2-Butenyl)-5,5-dimethyl-3-{[(methoxycarbonyl)oxy]-2-pyrazoline (29). Following method A, 20 (2.20 g, 13.1 mmol) was treated with NaH (680 mg, 15.6 mmol) and MeO2CCl (3.0 mL, 39 mmol), all compounds dissolved in THF (20 mL). Work-up and fct (ethyl acetate/hexane 1:1) afforded 29 (140 g, 6.21 mmol, 47%) as a colorless oil, δ 0.75. IR v 3080, 1760, 1630; (E)-isomer: 1H NMR (200 MHz): δ 1.26 (s, 6 H, Me2C), 1.67 (d, J = 4.6 Hz, 3 H, Me), 2.74 (s, 2 H, CCH2), 3.35 (d, J = 1.1, 3.9 Hz, 2 H, NCH2), 3.82 (s, 3 H, CO2CH3), 5.55-5.70 (m, 2 H, =CH=CH); (Z)-isomer: 1H NMR (200 MHz): δ 1.28 (s, 6 H, Me2C), 1.65 (d, J = 6.1 Hz, 3 H, Me), 2.75 (s, 2 H, CCH2), 3.45 (d, J = 1.1, 3.9 Hz, 2 H, NCH2), 3.83 (s, 3 H, CO2CH3), 5.55-5.70 (m, 2 H, =CH=CH).
5.5-Dimethyl-1-((3-methyl-2-butenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (31) via method A. 21 (2.02 g, 11.0 mmol) was treated with NaH (380 mg, 15.8 mmol) and MeO2CCl (2.56 mL, 33.0 mmol) in THF (20 mL). Work-up and fc (ethyl acetate/hexane 1:1) afforded 31 (635 mg, 2.65 mmol, 24%) as a light yellow oil, Rf 0.27 and 5.5-Dimethyl-1-((3-methoxy carbonyl)oxy)-1-((3-methyl-2-butenyl)-3-pyrazolidinone (32) (486 mg, 2.0 mmol, 18%), as a yellowish oil. 31: IR v 3080, 1780, 1740, 1250, 850; 1H NMR (200 MHz) 6 7.1 Hz, 2 H, CCH2), 3.55 (d, 2 H, CCH2), 3.81 (s, 3 H, COjCH2), 3.50-5.45 (t, J = 2.4 Hz, 1 H, =CH), 4.32 (q, J = 7 Hz, 2 H, NCH2), 4.66 (s, 1 H, =CWH), 4.83 (t, J = 6.5 Hz, 2 H, Me), 2.74 (s, 3 H, CO2CH3). 32: IR v 3030, 1780, 1730; 1H NMR (200 MHz) 6 7.1 Hz, 2 H, CCH2), 3.85 (s, 3 H, COjCH2), 2.52 (s, 2 H, CCH2), 3.83 (s, 3 H, CO2CH3). 3.50-5.45 (t, J = 6.5 Hz, 1 H, =CH).

5.5-Dimethyl-1-((3-methyl-2-butenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (31) via method D. 21 (25 mg, 0.14 mmol) was alkylated by using LDA (prepared from diisopropylamine (24 mL, 0.17 mmol) and s-butyllithium (105 mL, 0.17 mmol)) and MeO2CCN (24 mg, 0.28 mmol), all compounds dissolved in THF (1 mL). After work-up and fc (ethyl acetate/hexane 1:1) afforded 31 (31 mg, 0.13 mmol, 93%) as a colorless oil, Rf 0.30.

5.5-Dimethyl-1-((2-propyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (33). Following method B, 22 (1.06 g, 7.00 mmol) was treated with NaH (201 mg, 5.90 mmol) and Bu2OCCl (2.0 mL, 21 mmol) in THF (50 mL). Work-up and purification by fc (ethyl acetate/hexane 1:1) afforded 33 (1.05 g, 2.80 mmol, 67%) as a light yellow oil, Rf 0.41. IR v 3300, 2105, 1780, 1725; 1H NMR (200 MHz) 6 7.1 Hz, 3 H, CH2CH2), 1.34 (s, 6 H, Me2C), 2.30 (t, J = 2.4 Hz, 1 H, =CH), 2.74 (br, s, 2 H, CCH2), 3.81 (d, J = 1.7 Hz, 2 H, NCH2), 4.32 (q, J = 7 Hz, 2 H, CH2CH3).

5.5-Dimethyl-1-((2-(trimethylsilyl)ethyl)-2-propenyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (34). Following the general procedure C, a solution of 23 (3.50 g, 14.6 mmol) in CH2Cl2 (60 mL) was treated with Et3N (2.06 mL, 15.3 mmol), diethyl dicarbonate (8.6 mL, 58 mmol) and a solution of DMAP (1.78 g, 14.6 mmol) in CH2Cl2 (10 mL). Concentration as vacuo and purification by fc (ethyl acetate/hexane 1:2) afforded 34 (2.11 g, 6.76 mmol, 62%) (after correction) as a colorless oil, Rf 0.38. IR v 3080, 1780, 1740, 1250, 850; 1H NMR (200 MHz) 6 7.0 Hz, 3 H, Me2C), 0.03 (s, 9 H, Me3Si), 1.27 (s, 6 H, Me2C), 1.29 (s, 6 H, Me2C), 1.58 (s, 3 H, Me), 3.60-5.35 (m, 1 H, =CH). 32: IR v 3030, 1760, 1730; 1H NMR (200 MHz) 6 7.1 Hz, 2 H, C(CH3)2), 3.85 (s, 3 H, COjCH2), 2.90-5.60 (m, 1 H, =CH). 32: IR v 3030, 1760, 1730; 1H NMR (200 MHz) 6 7.1 Hz, 2 H, C(CH3)2), 3.85 (s, 3 H, COjCH2), 2.90-5.60 (m, 1 H, =CH).
A novel route to the 1-azatropine skeleton

5,5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid ethyl ester (37). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.

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\text{5.5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid methyl ester (41). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.}
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5,5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid methyl ester (41). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.

5,5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid ethyl ester (37). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.

5,5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid methyl ester (41). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.

5,5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid ethyl ester (37). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.

5,5-Dimethyl-3-ethoxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid methyl ester (41). According to the general procedure, 27 (100.0 g, 44.2 mmol) was reduced with NaBH₄ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), 37 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, mp 70-71 °C (mixture) 83 (41), 69 (27), 43 (27); HRMS calcd for C₁₄H₂₀N₂O₂ 312.1321, found 312.1306.
5,5-Dimethyl-3-hydroxy-1-(4-(trimethylsilyl)-2-butynyl)-2-pyrrolidinidinecarboxylic acid methyl ester (43).

Following the general procedure, 35 (315 mg, 1.06 mmol) was reduced with NaBH₄ (241 mg, 6.39 mmol) in EtOH (10 mL). After being stirred at -20°C for 2 h, the reaction was quenched with cold aq 10% Na₂CO₃ (50 mL) and worked up following the general procedure. The crude product was purified by flash chromatography (ethyl acetate/hexane 1:1) to afford 43 (185 mg, 0.62 mmol, 59%) as a colorless oil, R_f 0.52, IR ν 3500, 2900, 1679, 1250, 850. ᵃ¹H NMR (200 MHz) δ 0.07 (3 H, Me₂Si), 1.15 (3 H, Me), 1.35 (3 H, Me), 1.45 (3 H, Me), 2.35 (2 H, CH₂), 2.18 (br s, 1 H, CH₂OH), 2.31 (dd, J = 7.3, 13.2 Hz, 1 H, CH₂OH), 3.43 (br s, 1 H, CH₂), 3.66 (br s, 2 H, NCH₂), 3.79 (3 H, 2 × CO₂CH₃), 5.71 (br s, 1 H, OCH) ppm.

5,5-Dimethyl-1-(3,4-dimethyl-5-oxo-2,4-dioxo-6-aryl)methyl-3-ethoxyprrolididine-2-carboxylic acid methyl ester (44). Following the general procedure, 64 (59 mg, 0.19 mmol) was reduced with NaBH₄ (29 mg, 0.76 mmol) in EtOH (2 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 64 (44 mg, 0.13 mmol) was obtained as a white crystal, m.p 115-116°C (ethyl acetate/hexane 1:1), R_f 0.38, IR ν 1720, 1700, 1635, 1445, 1370, 1110, 1080, 1025, 900. ᵃ¹H NMR (200 MHz) δ 0.82 (3 H, Me), 1.17 (3 H, Me), 1.41 (3 H, Me), 1.67 (3 H, Me), 1.69 (3 H, Me), 2.05 (dd, J = 4.7, 13.4 Hz, 1 H, CH₂), 1.31 (dd, J = 7.2, 13.6 Hz, 1 H, CH₂), 3.30-3.75 (m, 4 H, NCH₂ and CH₂CH₂), 3.73 (3 H, CO₂CH₃), 5.55-5.60 (m, 1 H, CHO), 5.60 (1 H, CHO); ᵃ¹C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂); 13C NMR (50 MHz) δ 14.8 (CH₂CH₂), 23.0 (Me), 25.1 (Me), 28.1 (Me), 45.2 (CH₂), 52.9 (CO₂CH₃), 54.8 (NCH₂), 61.4 (CH₂CH₂), 65.8 (NC), 90.9 (OCH); 1H NMR (200 MHz, CDCl₃) δ 0.45 (s, 3 H, CH₂), 1.45, 1.47 (CH₂), 2.31 (dd, J = 7.1, 13.2 Hz, 1 H, CH₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₂).
A novel route to the 1-azatropine skeleton

1H,17H-1H21N2O2Cl 206.1292, found 260.1284.

rel-(3S,4R,5S)-3-Chloro-1,8-diaza-4,7,7-trimethylbicyclo[3.2.1]octane-7-carboxylic acid ethyl ester (48). Following the general procedure, 39 (145 mg, 0.54 mmol) was cyclized with TiCl4 (0.92 mL of a 1.2 M solution, 1.11 mmol) in CH2Cl2 (5 mL). Work-up and purification by fc (ethyl acetate/hexane 2:1) afforded 48 (67 mg, 0.26 mmol, 55% yield) as a colorless oil. IR ν 1690; 1H NMR (200 MHz) δ 1.03 (d, J = 6.7 Hz, 3 H, CH(C2H5)), 1.18 (t, J = 7.0 Hz, 3 H, CH2CH3), 1.57 (δ, 3 H, Me), 1.63 (δ, J = 12.7 Hz, 1 H, H3), 2.12 (m, 1 H, H4), 3.08 (m, J = 5.9, 11.1 Hz, 1 H, H2, 5.1 Hz, 1 H, H2, 6.3 Hz, 1 H, H3), 3.76 (d, J = 8.8 Hz, 1 H, H4, 153.0 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 260 (M+, 37), 225 (100), 215 (7), 187 (15), 142 (27), 128 (33), 70 (19); HRMS calculated for C17H21N2O2Cl 260.1292, found 260.1284.

rel-(3R,4S)-3-(1-Chloro-1-methylpropyl)-1,8-diaza-4,6,6-dimethylbicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (49). To a solution of 40 (141 mg, 0.52 mmol) in CH2Cl2 (5 mL) was added TiCl4 (0.87 mL of a 1.2 M solution, 1.04 mmol) according to the general procedure P. After being stirred at rt for 18 h, the reaction mixture was worked-up and purified by fc (ethyl acetate/hexane 1:1) to afford 46 (44 mg, 0.19 mmol, 24%) as a yellow oil, Rf 0.69. IR ν 1690; 1H NMR (200 MHz) δ 1.23 (s, 3 H, Me), 1.24 (s, 3 H, Me), 1.43 (s, 3 H, Me), 1.54 (s, 3 H, Me), 1.69 (d, J = 9.3 Hz, 1 H, H3), 1.76 (dd, J = 4.9, 11.5 Hz, 1 H, H5), 2.02-2.20 (m, 1 H, H2), 6.25-6.80 (m, 1 H, H2), 3.70 (s, 3 H, CO2Et), 4.53 (d, J = 5.1 Hz, 1 H, H4); 13C NMR (50 MHz) δ (all signals appear as rotamers) 25.1, 25.2 (Me), 28.6, 29.0 (Me), 30.1, 30.2 (Me), 30.4, 30.5 (Me), 46.3, 47.1 (C5), 52.6, 53.0 (CO2Et), 53.1, 53.8 (C2), 57.4, 57.9 (C4), 61.3, 61.8 (C3), 66.5, 66.7 (C6), 70.5, 70.6 (CC1), 153.4 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 260 (M+, 19), 225 (21), 215 (18), 204 (46), 169 (30), 141 (21), 127 (100), 83 (42); HRMS calculated for C17H21N2O2Cl 260.1292, found 260.1292.

3-Chloro-1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (50). A solution of 41 (201 mg, 0.79 mmol) in CH2Cl2 (8 mL) was treated with TiCl4 (1.32 mL of a 1.2 M solution, 1.58 mmol) according to the general procedure P. After being stirred at rt for 18 h, the reaction was worked-up and purified by fc (ethyl acetate/hexane 1:1) to afford 50 (46 mg, 0.19 mmol, 24%) as a yellow oil, Rf 0.69. IR ν 1690; 1H NMR (200 MHz) δ 1.18 (s, 3 H, Me), 1.28 (t, J = 7.0 Hz, 3 H, CH2CH3), 1.56-2.10 (m, 2 H, 2 × H6), 3.48 (d, J = 8.1 Hz, 1 H, H2), 3.56 (d, J = 18.2 Hz, 1 H, H2), 4.25 (q, J = 7.1 Hz, 2 H, CH2CH3), 4.50-4.75 (m, 1 H, H5), 6.15 (d, J = 5.5 Hz, H4); 13C NMR (50 MHz) δ (all signals appear as rotamers) 14.6 (CH2CH3), 26.1, 26.3 (Me), 32.1 (Me), 49.7, 49.8 (C6), 54.4 (C5), 61.7 (CH2CH3), 61.8, 61.9 (C2), 67.9 (C7), 128.8 (C4), 150.3 (C3), 153.0 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 244 (M+, 90), 208 (61), 187 (39), 152 (37), 143 (38), 121 (57), 115 (100), 80 (44), 65 (22), 58 (33), 41 (31); HRMS calculated for C17H17N2O2Cl 244.0979, found 244.0981.

1,8-Diaza-7,7-dimethyl-3-methylenebicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (51). To a solution of 42 (101 mg, 0.32 mmol) in CH2Cl2 (4 mL) was added BF3·OEt2 (79 µL, 0.64 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and 2 h at rt, poured into aq satd NaCl (40 mL) and extracted with CH2Cl2 (3 × 40 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. Purification of the residue by fc (ethyl acetate/hexane 1:1) afforded 51 (43 mg, 0.19 mmol, 61%) as a colorless oil, Rf 0.32. IR ν 3070, 1690; 1H NMR (200 MHz) δ (all signals appear as rotamers) 0.04, 1.09 (s, 3 H, Me), 2.07-3.12 (m, 3 H, CH2CH3), 1.33 (δ, 3 H, Me), 1.64, 1.66 (d, J = 12.3 Hz, 1 H, H6,exd), 1.75-2.15 (m, 2 H, H6,exd and H4), 2.50-2.70 (m, 1 H, H4), 3.45-3.70 (m, 2 H, 2 × H2), 4.11-4.23 (m, 2 H, CH2CH3), 4.47-4.65 (m, 2 H, H5), 4.15 (s, 2 H, =CH2); 1H NMR (250 MHz, CD2D2, 90 °C) δ 1.02 (s, 3 H, Me), 1.10 (t, J = 7.1 Hz, 3 H, CH2CH3), 1.12 (s, 3 H, Me), 1.42 (d, J = 14.3 Hz, 1 H, H6,exd), 1.71 (d, J = 7.7, 12.1 Hz, 1 H, H6,exd), 1.83 (d, J = 14.3 Hz, 1 H, H4), 2.58 (d, J = 14.1 Hz, 1 H, H4), 3.31 (d, J = 7.7, 12.1 Hz, H2), 3.61 (d, J = 15.6 Hz, 1 H, H2), 4.03-4.15 (m, 2 H, CH2CH3), 4.45-4.60 (m, 1 H, H5), 4.63-4.65 (m, 2 H, =CH2); 13C NMR (50 MHz) δ (some signals appear as rotamers) 14.8 (CH2CH3), 22.8 (Me), 31.4, 31.5 (Me), 39.4, 39.6 (C6), 43.7, 44.3 (C6), 54.9, 55.6 (C5), 56.5, 57.3 (C2), 61.2, 613 (CH2CH3), 66.5 (C7), 113.8, 114.0 (=CH2), 140.8, 141.0 (C3), 154.5 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 224 (M+, 93), 209 (24), 168 (38),
1,7-Diaza-5,5-dimethyl-3-ethenylidene bicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (52). To a solution of 43 (109 mg, 0.37 mmol) in CH₂Cl₂ (4 mL) was added BF₃·OEt₂ (91 µL, 0.74 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and for 18 h at rt. The resulting orange solution was poured into aq satd NaCl (50 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with H₂O (50 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed (ethyl acetate/hexane 1:1) to give 52 (48 mg, 0.23 mmol, 62%) as a colorless oil, Rf 0.36. IR ν 1980, 1960, 1690, 890, 840; ¹H NMR (200 MHz) δ 1.23 (s, 3 H, Me), 1.24 (s, 3 H, Me), 1.51 (d, J = 11.3 Hz, 1 H, H₅exoo), 1.94 (dd, J = 4.7, 11.9 Hz, 1 H, H₅exoo), 3.57 (dt, J = 15.1, 4.7 Hz, 1 H, H₂), 3.74 (s, 3 H, CO₂CH₃), 3.81 (dt, J = 15.1, 3.1 Hz, 1 H, H₂), 4.83 (br s, 2 H, =C=CH₂), 4.88 (d, J = 4.7 Hz, 1 H, H₄); ¹³C NMR (50 MHz) δ 24.8 (C₃), 34.0, 34.6 (Cα), 155.0, 159.8 (C(0)); MS (El, 70 eV) m/z (relative intensity) 256 (M⁺, 25). 13C NMR (50 MHz)δ (all signals appear as rotamers) 23.2, 23.5, 24.0 (Me), 25.1 (Me), 30.4, 30.5 (Me), 46.5, 47.0 (C₂ and C₃), 66.6, 67.6 (C7), 78.7 (C3), 155.0, 159.8 (C(O)); MS (El, 70 eV) m/z (relative intensity) 256 (M⁺, 15), 238 (100), 210 (30), 155 (66), 109 (25), 80 (12); HRMS calcd for C₁₂H₂₀N₂O₂ 226.1372, found 226.1369; Anal. Calc'd for C₁₂H₂₀N₂O₂: C, 56.76; H, 6.76. Found: C, 56.73; H, 6.76.

Cyclization product 53. To a solution of 44 (1.57 g, 4.59 mmol) in CH₂Cl₂ (50 mL) was added at 0 °C BF₃·OEt₂ (2.26 mL, 18.4 mmol). The mixture was stirred at 0 °C for 15 min and for 18 h at rt. The mixture was poured into aq satd NaCl (100 mL) and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with H₂O (50 mL), dried (MgSO₄), filtered and concentrated in vacuo. The resulting orange solution was poured into aq satd NaCl (50 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed (ethyl acetate/hexane 1:1) to give 53 (1.44 g, 4.86 mmol, 94%) as a colorless oil that solidified upon standing, mp 106-107 °C (ethyl acetate/hexane).

rel-(3R,5S)-1,8-Diaza-3-(formyloxy)-7,7-trimethylbicyclo[3.2.1]octane-8-carboxylic acid methyl ester (56). A solution of 38 (232 mg, 0.91 mmol) in HCOOH (9 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and 56 (some signals appear as rotamers) 23.2, 23.5, 24.0 (Me), 25.1 (Me), 30.4, 30.5 (Me), 46.5, 47.0 (C₂ and C₃), 66.6, 67.6 (C7), 78.7 (C3), 155.0, 159.8 (C(O)); MS (El, 70 eV) m/z (relative intensity) 256 (M⁺, 15), 238 (100), 210 (30), 155 (66), 109 (25), 80 (12); HRMS calcd for C₁₂H₂₀N₂O₂ 226.1372, found 226.1369; Anal. Calc'd for C₁₂H₂₀N₂O₂: C, 56.76; H, 6.76. Found: C, 56.73; H, 6.76.

rel-(3R,4S)-1,7-Diaza-6,6-dimethyl-3-(formyloxy)methylbicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (57). A solution of 40 (142 mg, 0.52 mmol) in HCOOH (5 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and 57 (all signals appear as rotamers) 1.09-1.20 (m, 7 H, 2 x Me and H₅exoo), 1.39 (s, 3 H, Me), 1.42 (s, 3 H, Me), 1.72, 1.70 (dd, J = 4.9, 11.5 Hz, 1 H, H₅exoo), 2.05, 2.14 (s, J = 7.4 Hz, 1 H, H₃), 2.70, 2.73 (dd, J = 6.5, 13.0 Hz, 1 H, H₂), 3.22, 3.24 (dd, J = 8.0, 12.6 Hz, 1 H, H₂), 3.62, 3.67 (CO₂CH₃), 4.45, 4.51 (d, J = 5.0 Hz, 1 H, H₁), 7.86, 7.87 (s, 1 H, OCHO); ¹H NMR (200 MHz) δ 0.34, 56: IR ν 1720, 1680; ¹H NMR (200 MHz) δ 1.30-1.66 (m, 7 H, 2 x Me and H₅exoo), 1.94 (dd, J = 11.5 Hz, 1 H, H₅exoo), 2.05, 2.14 (s, J = 7.4 Hz, 1 H, H₃), 2.70, 2.73 (dd, J = 6.5, 13.0 Hz, 1 H, H₂), 3.22, 3.24 (dd, J = 8.0, 12.6 Hz, 1 H, H₂), 3.62, 3.67 (CO₂CH₃), 4.45, 4.51 (d, J = 5.0 Hz, 1 H, H₁), 7.86, 7.87 (s, 1 H, OCHO); ¹³C NMR (50 MHz) δ (all signals appear as rotamers) 22.1, 22.3 (Me), 23.6, 24.0 (Me), 25.0, 25.1 (Me), 30.4, 30.5 (Me), 46.5, 47.0 (C₂ and C₃), 66.6, 67.6 (C7), 78.7 (C3), 155.0, 159.8 (C(O)); MS (El, 70 eV) m/z (relative intensity) 256 (M⁺, 25), 227 (59), 154 (31), 143 (29), 129 (60), 128 (100), 95 (43), 70 (64); HRMS calcd for C₁₂H₂₀N₂O₂ 236.1423, found 236.1407.
A novel route to the 1-azatropene skeleton

1,8-Diaz-7,7-dimethylbicyclo[3.2.1]octan-3-one-8-carboxylic acid ethyl ester (58). A solution of 41 (134 mg, 0.53 mmol) in HCOOH (5 mL) was stirred at 50 °C for 20 h. After addition of H2O (5 mL), the reaction mixture was stirred at 60 °C for another 6 h and poured into aqueous NaHCO3 (100 mL). An additional amount of NaHCO3 was added until the water layer reached pH = 9. After extraction with CH2Cl2 (3 × 100 mL), the combined organic layers were dried (MgSO4), filtered, and concentrated in vacuo. A solution of 58 (56 mg, 0.25 mmol, 47%) as a light yellow oil, Rf 0.28. IR ν 1720, 1690; 1H NMR (200 MHz) δ 1.18 (s, 3 H, Me), 1.61 (t, J = 6.9 Hz, 3 H, CH2CH3), 1.61 (s, 3 H, Me), 1.69 (d, J = 12.8 Hz, 1 H, H6exo), 2.24 (dd, J = 7.8, 12.8 Hz, 1 H, H6exo), 2.42 (d, J = 16.6 Hz, 1 H, H4), 2.78 (dd, J = 3.2, 16.3 Hz, 1 H, H4), 3.63 (s, 2 H, 2 × H2), 4.28 (q, J = 6.9 Hz, 2 H, CH2CH3), 4.75-5.00 (m, 1 H, H3), 13C NMR (50 MHz) δ 14.8 (CH2CH3), 24.8 (Me), 31.2 (Me), 45.9 (C6), 48.5 (C4), 54.8 (C5), 62.9 (C2), 67.5 (C7), 154.0 (CO), 208.2 (CO); MS (EI) 270.1580 (M+, 15), 226 (M+, 12), 198 (84), 157 (31), 143 (100), 71 (26); HRMS calcd for C11H18N2O2 270.1580, found 270.1581.

1,8-Diaz-7,7-dimethylbicyclo[3.2.1]octane-3-one-8-carboxylic acid methyl ester (51). A solution of 42 (250 mg, 7.97 mmol) in HCOOH (80 mL) was stirred for 18 h at rt. Concentration in vacuo and fc (ethyl acetate/hexane 1:1) afforded 51 (152 g, 6.8 mmol, 85%) as a yellowish oil, Rf 0.32.

1,7-Diaz-5,5-dimethyl-3-ethylenedibicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (52). A solution of 43 (96 mg, 0.45 mmol) in HCOOH (5 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and fc (ethyl acetate/hexane 1:1) afforded 52 (28 mg, 0.13 mmol, 42%) as a colorless oil, Rf 0.36.

rel-(3S,5S)-3-Chloro-1,8-diaz-7,7-dimethylbicyclo[3.2.1]octane (60). To a solution of 45 (65 mg, 0.27 mmol) in MeCN (3 mL) was added Me3SiI (0.11 mL, 0.80 mmol) and the reaction mixture was stirred at 40 °C for 2 h. The resulting dark brown solution was poured into aqueous NaHCO3 and extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated in vacuo. The residue was chromatographed (acetone) to yield 60 (37 mg, 0.21 mmol, 79%) as white crystals, mp 44.5-45.0 °C, Rf 0.33. IR ν 3300; 1H NMR (200 MHz) δ 1.13 (s, 3 H, Me), 1.69 (d, J = 12.9 Hz, 1 H, H6exo), 1.89 (dd, J = 7.6 Hz, 1 H, H6exo), 2.12 (m, 2 H, H4), 3.20 (dd, J = 11.1, 14.0 Hz, 1 H, H2exo), 3.35 (dd, J = 6.2, 14.0 Hz, 1 H, H2exo), 3.60 (m, 1 H, H3), 3.79 (br s, 1 H, NH), 4.20 (a, J = 11.1, 6.3 Hz, 1 H, H3), 13C NMR (50 MHz) δ 22.9 (Me), 31.9 (Me), 42.2 (C4), 45.3 (C6), 50.9 (C3), 57.7 (C5), 58.1 (C2), 65.6 (C7); MS (EI, 70 eV) m/z (relative intensity) 174 (M+, 52), 143 (5), 139 (100), 118 (24), 111 (76), 70 (75), 67 (35), 56 (32), 41 (31); HRMS calcd for C12H19ClN2O2 245.1393, found 245.1392.

rel-(3S,5S)-3-Chloro-1,8-diaz-7,7,8-trimethylbicyclo[3.2.1]octane (61). To a solution of 46 (50 mg, 0.33 mmol) in MeCN (1 mL) were added 37%aq formaldehyde (130 μL, 1.66 mmol) and NaBH4CN (33 mg, 0.53 mmol). After being stirred for 15 min at rt, a few drops of glacial acetic acid were added carefully until the pH was neutral. Stirring was continued for 45 min, while the pH was kept neutral by dropwise addition of glacial acetic acid. The solution was poured into 1 N KOH (10 mL) and extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with H2O (10 mL), dried (K2CO3), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to afford 61 (45 mg, 0.27 mmol, 82%) as a colorless oil, Rf 0.40. IR ν 1455, 1260, 900, 635; 1H NMR (200 MHz) δ 1.28 (s, 3 H, Me), 1.33 (s, 3 H, Me), 1.56 (d, J = 13.1 Hz, 1 H, H6exo), 1.85-1.90 (m, 1 H, H6exo), 2.10 (dd, J = 12.6, 7.7 Hz, 1 H, H4), 2.23 (dd, J = 13.1, 2.4 Hz, 1 H, H4), 2.68 (a, 3 H, Me), 2.78 (dd, J = 7.2, 12.8 Hz, 1 H, H4), 3.20 (dd, J = 11.1, 14.0 Hz, 1 H, H2exo), 3.35 (dd, J = 6.2, 14.0 Hz, 1 H, H2exo), 3.60 (m, 1 H, H3), 3.79 (br s, 1 H, NH), 4.20 (a, J = 11.1, 6.3 Hz, 1 H, H3), 13C NMR (50 MHz) δ 22.9 (Me), 31.9 (Me), 42.2 (C4), 45.3 (C6), 50.9 (C3), 57.7 (C5), 58.1 (C2), 65.6 (C7); MS (EI, 70 eV) m/z (relative intensity) 174 (M+, 52), 143 (5), 139 (100), 118 (24), 111 (76), 70 (75), 67 (35), 56 (32), 41 (31); HRMS calcd for C13H22ClN2O2 260.1568, found 260.1568.
F. P. J. T. Rutjes et al.

NCH3), 3.00 (dd, J = 11.3, 14.9 Hz, 1 H, H2), 3.25 (dd, J = 11.3, 14.9 Hz, 1 H, H2), 3.30-3.40 (m, 1 H, H5), 4.28 (tt, J = 11.1, 6.8 Hz, 1 H, H3); 13C NMR (63 MHz) δ 22.8 (Me), 29.5 (C6), 31.0 (Me), 32.7 (Me), 42.9 (C4), 47.8 (C3), 52.4 (C2), 58.1 (C5), 73.9 (C7); MS (EI, 70 eV) m/z (relative intensity) 188 (M+*, 18), 153 (100), 97 (33), 43 (42); HRMS calc for C12H17N2Cl 188.1081, found 188.1077.

1,8-Diaza-7,7-dimethyl-3-methylenecyclo[3.2.1]octane (63). A solution of 51 (78 mg, 0.35 mmol) and KOH (78 mg, 1.4 mmol) in MeOH (4 mL) was heated at reflux temperature for 90 h. The resulting solution was poured into aq satd NH4Cl solution (25 mL) and extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. Purification of the residue by fc (acetone) afforded 62 (21.5 mg, 0.14 mmol, 40%) as a colorless oil that solidified upon standing, mp 150-160 °C (decomposes before melting), Rf 0.30. IR v 3060, 890; 1H NMR (200 MHz) δ 1.17 (s, 3 H, Me), 1.21 (s, 3 H, Me), 1.61 (s, 3 H, Me), 1.63 (d, J = 14.9 Hz, 1 H, H6exo), 1.89 (d, J = 14.9 Hz, 1 H, H4), 2.06 (dd, J = 7.4, 12.1 Hz, 1 H, H6exo), 2.73 (s, 3 H, NCCH3), 2.78 (d, J = 14.9 Hz, 1 H, H4), 3.25 (d, J = 16.2 Hz, 1 H, H2), 3.36-3.46 (m, 1 H, H5), 3.80 (dd, J = 1.0, 16.2 Hz, 1 H, H2), 4.71-4.84 (m, 2 H, -CH2); 13C NMR (50 MHz) δ 24.6 (Me), 32.7 (C4), 33.0 (Me), 35.9 (NCCH3), 45.9 (C6), 49.1 (C2), 59.8 (C5), 63.9 (C7), 111.3 (−CH2), 142.6 (C3); MS (EI, 70 eV) m/z (relative intensity) 166 (M+, 57), 151 (95), 127 (26), 111 (17), 95 (27), 83 (100), 82 (90), 55 (23), 43 (37); HRMS calc for C12H18N2O2 166.1470, found 166.1470.

Diazepine 64. A solution of 53 (100 mg, 0.34 mmol) in THF (2 mL) was added dropwise to a solution of Na (31 mg, 1.35 mmol) in NH3 (15 mL) at -78 °C. The mixture was stirred at -78 °C for 3 h, quenched by addition of aq NH4Cl solution (182 mg, 3.4 mmol) and the ammonia was allowed to evaporate. The residue was dissolved in H2O (20 mL) and extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo and chromatographed (ethyl acetate/hexane 4:1) to afford 53 (12 mg) and 64 (12 mg, 0.040 mmol, 16% (after correction)) as a white solid, mp 157-159 °C, Rf 0.20. IR v 3440, 1720, 1640, 1500, 1270; 1H NMR (250 MHz) δ 1.17 (s, 3 H, Me), 1.21 (s, 3 H, Me), 1.61 (s, 3 H, Me), 1.63 (d, J = 14.9 Hz, 1 H, CH2); 11C NMR (63 MHz) δ 24.3, 25.5, 27.8, 31.7 (4 × Me), 43.6, 44.5 (NC and CH2), 45.0 (NC), 52.0 (CO2CH2), 52.1 (NCH2), 105.3, 107.2 (OCO and C2), 155.9, 161.1, 168.8 (2 × CO (O and C4)); MS (EI, 70 eV) m/z (relative intensity) 298 (M+, 7), 223 (50), 183 (17), 165 (100), 150 (25), 71 (30), 58 (85).

Hydrazine 65. To a solution of 53 (700 mg, 2.36 mmol) in MeCN (3 mL) was added Me3SiI (403 µL, 2.83 mmol) and the mixture was stirred at 40 °C for 2 h. It was poured into aq NaH2SO4 solution (50 mL) and extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were dried (K2CO3), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 65 (550 mg, 2.31 mmol, 98%) as a colorless oil that solidified upon standing, mp 150-160 °C (decomposes before melting), Rf 0.30. IR v 3295, 1710, 1640, 1420, 1295, 1110, 1030, 890; 1H NMR (200 MHz) δ 1.21 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.46 (s, 6 H, 2 × Me), 1.91 (dd, J = 5.8, 12.2 Hz, 1 H, H6exo), 2.06 (dd, J = 12.2 Hz, 1 H, H6exo), 3.41 (d, J = 18.8 Hz, 1 H, H2), 3.81 (d, J = 18.7 Hz, 1 H, H2), 4.16 (d, J = 5.7 Hz, 1 H, H5), 4.20 (br s, 1 H, NH); 13C NMR (50 MHz) δ 23.3, 26.2, 26.5, 32.6 (Me), 51.5, 51.6 (C2 and C6), 53.2 (C5), 66.2 (C7), 106.5 (OCO), 107.9 (C4), 159.0, 162.6 (C3 and C(O)); MS (EI, 70 eV) m/z (relative intensity) 238 (M+, 7), 180 (67), 152 (20), 97 (43), 70 (17), 43 (18); HRMS calc for C12H17N2O3 238.1317, found 238.1313; Anal. Calcd for C12H17N2O3: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.36; H, 7.72; N, 11.69.
(3-Hydroxy-7,7,8-trimethyl-1,8-diazabicyclo[3.2.1]octane-4-carboxylic acid methyl ester (69). A solution of 66 (13 mg, 0.052 mmol) and MeOH (18 μL, 0.5 mmol) in xylene (0.5 mL) was heated at 170°C for 10 min in a sealed tube. The mixture was concentrated in vacuo to afford 67 (10 mg) as a light yellow oil. The crude residue was dissolved in CH2Cl2 (1 mL) and treated with benzoyl chloride (0.5 μL, 0.0056 mmol) and Et3N (8 μL, 0.057 mmol) at 0°C for 10 min and 5 h at rt and concentrated in vacuo. LC (ethyl acetate:hexane 4:1) afforded 68 (12 mg, 0.036 mmol, 70%) as a colorless oil, Rf 0.35. 1H NMR (200 MHz) δ 1.39 (s, 3 H, Me), 1.45 (s, 3 H, Me), 2.01 (d, J = 11.8 Hz, 1 H, H6exo), 2.30 (dd, J = 6.5, 11.8 Hz, 1 H, H6exo), 2.74 (s, 3 H, NCH3), 3.45 (d, J = 19.7 Hz, 1 H, H2), 3.59 (s, 3 H, CO2CH3), 3.82 (d, J = 19.9 Hz, 1 H, H5), 7.40-7.60 (m, 3 H, ArH), 8.06-8.11 (m, 2 H, ArH); 13C NMR (63 MHz) δ 26.6, 33.1, 34.6 (2 x Me), 36.5 (NCH3), 45.6 (C6), 51.2 (C2), 51.7 (CO2CH3), 59.7 (C5), 63.5 (C7), 120.0 (C4), 128.6, 129.8, 133.7 (ArH), 129.3 (ArC), 152.0 (C3), 164.0, 164.2 (C=O); MS (EI, 70 eV) m/z (relative intensity) 330 (M+, 20), 169 (20), 105 (100), 77 (21); HRMS calcd for C15H22N2O2 350.1580, found 350.1579.

REFERENCES AND NOTES


4. See e.g.: (a) Lounasmaa, M. Alkaloids 1988, 33, 1. (b) Fodor, G.; Dharanipragada, R. Nat. Prod. Reports 1991, 603.

5. For some examples, see e.g.: (a) Neumeyer, J.L.; Wang, S.; Milius, R.A.; Baldwin, R.M.; Zea-Ponce, Y.; Hoffer, P.B.; Sybraska, E.; Al-Tikriti, M.; Charnney, D.S.; Malison, R.T.; Laruelle, M.; Innis, R.B. J. Med. Chem. 1991, 34, 3144. (b) Lewin, A.H.; Gao, Y.; Abraham, P.; Boja, J.W.; Kuhar, M.J.; Carroll,