*Tetrahedron* Vol. 49, No 44, pp. 10027-10048, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00


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

**Floris P.J.T. Rutjes, Henk Hiemstra*, Frank O.H. Pirrung and W. Nico Speckamp***

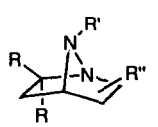
Laboratory of Organic Chemistry, University of Amsterdam
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

(*Received in UK* 9 *July* 1993; *accepted* 20 *August* 1993)

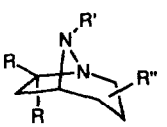
**Abstract**: Bicyclic molecules with the 1,7-diaza-6,6-dimethylbicyclo[2.2.1]heptane and 1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane (1-aza-7,7-dimethyltropane) skeleton are shown to be efficiently synthesized via cyclization reactions of endocyclic *N*-acylhydrazonium intermediates. By using a protected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

## INTRODUCTION

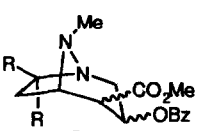
The synthesis of bicyclic hydrazines with a 1,7-diazabicyclo[2.2.1]heptane or a 1,8-diazabicyclo-[3.2.1]octane skeleton (*e.g.* **1** and **2**, respectively) has received only scant attention in the literature. The structures with the heptane skeleton are particularly interesting compounds as both the *N*-chloro and *N*-methyl substituted molecules have been reported to exhibit high nitrogen inversion barriers for the bridge nitrogen atom.[1-3] A noticeable feature of the second types 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.[4] The most distinguished class of tropane alkaloids consists of cocaine and its isomers, of which various analogues have been prepared.[5] The synthesis of azaanalogues **3**, however, has not been reported in the literature.



**1**



**2**

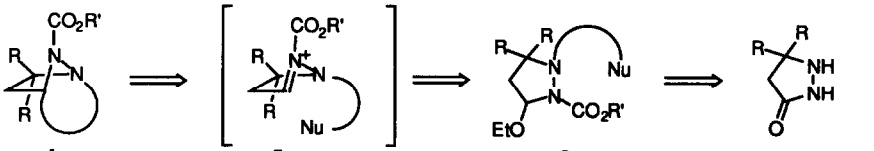


**3**

A method for the preparation of some bridged bicyclic hydrazines **1** and **2** was developed by Oppolzer,[6] 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.[7,8] A serious set-back 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,[9]

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 π-nucleophiles can be used in this cyclization reaction to give the desired functionalized bicyclic products. The use of a (protected) β-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.

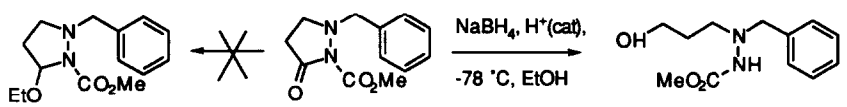



(1)

## RESULTS AND DISCUSSION

*Choice of the pyrazolidinone*

The use of unsubstituted 3-pyrazolidinone (**7**)[10] as starting material will lead to unsubstituted bicyclic hydrazines **4** (R = H). In order to study the sequence of reactions, 1-benzyl-3-pyrazolidinone[10c] 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.[11] 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.



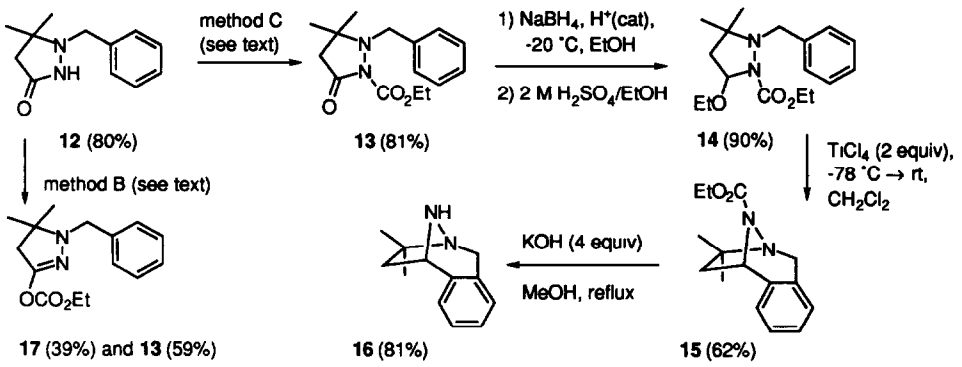

(2)

The undesired ring opening and overreduction are not expected to occur if the pyrazolidinone ring is substituted with a *gem*-dimethyl function (*i.e.* **8**). 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'[12,13] and was observed earlier in similar pyrrolidinone systems.[14] 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.[15] 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 $S_N2$-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;[16] D) deprotonation with LDA (1.1 equiv, -78 °C), followed by methoxycarbonylation with methyl cyanoformate (2 equiv, -78 °C → rt) in THF;[11] 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.[17,18] 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.[17]

**Scheme I**




Reduction of the pyrazolidinone **13** under 'standard conditions'[11] initially afforded the corresponding hydroxypyrazolidine, which was directly converted into the ethoxypyrazolidine **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.[19]

*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 diallylated product was also found. The pyrazolidinone **24** (entry 16) was obtained upon alkylation with 4-iodo-1-(trimethylsilyl)-2-butyne,[20] which was prepared via the corresponding mesylate.[21] The dioxenone substituted pyrazolidinone **25** (entry 19) was obtained after alkylation with the corresponding chloride.[22] 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).[23] 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 $Et_3N$ 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.**

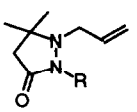
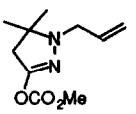
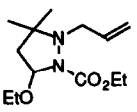
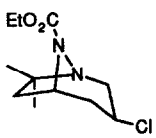
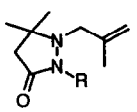
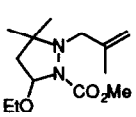
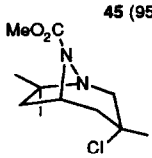
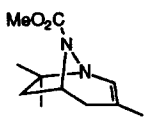
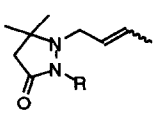
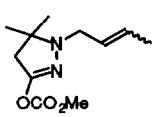
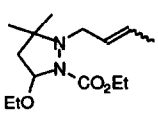
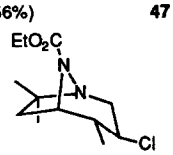
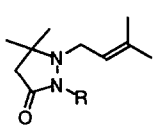
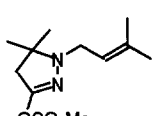
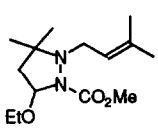
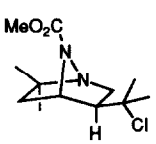
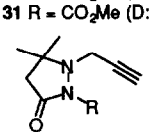
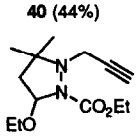
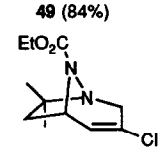
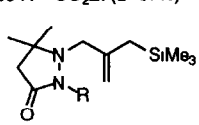
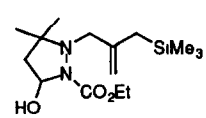
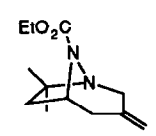
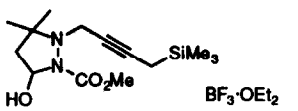
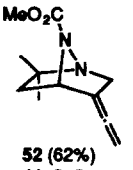
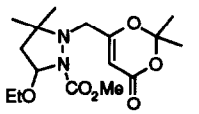
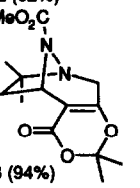
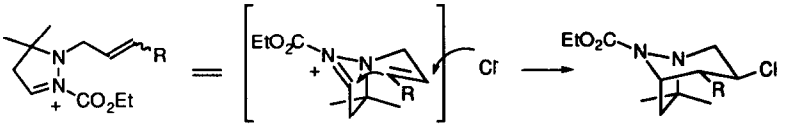
| entry | alkylated product (yield)<br>acylated product(s) (method· yield) | reduction product (yield) | Lewis acid | cyclization products (yield) |
|---|---|---|---|---|
| |   |  | $TiCl_4$ |  |
| 1<br>2 | **18** R = H (66%);<br>**26** (A· 33%) | | | |
| 3 | **27** R = $CO_2Et$ (C· 82%) | **37** (83%) | | **45** (95%) |
| |  |  | $TiCl_4$ |   |
| 4<br>5 | **19** R = H (88%),<br>**28** R = $CO_2Me$ (A: 74%) | **38** (75%) | | **46** (56%) **47** (16%) |
| |   |  | $TiCl_4$ |  |
| 6<br>7<br>8 | **20** R = H (61%),[a]<br>**29** (A· 47%)[a]<br>**30** R = $CO_2Et$ (C: 64%)[a] | **39** (71%)[a] | | **48** (53%) |
| |   |  | $TiCl_4$ |  |
| 9<br>10<br>11 | **21** R = H (82%);<br>**31** R = $CO_2Me$ (A. 24%) **32** (A: 18%)<br>**31** R = $CO_2Me$ (D: 93%) | **40** (44%) | | **49** (84%) |
| |  |  | $TiCl_4$ |  |
| 12<br>13 | **22** R = H (40%),[b]<br>**33** R = $CO_2Et$ (B· 67%) | **41** (65%) | | **50** (24%) |
| |  |  | $BF_3$·$OEt_2$ |  |
| 14<br>15 | **23** R = H (83%),<br>**34** R = $CO_2Et$ (C· 62%) | **42** (96%) | | **51** (61%) |

**Table I. Continued**

| | | | |
|---|---|---|---|
| 16 | **24** R = H (68%); |  |  |
| 17 | **35** R = $CO_2Me$ (A: 62%) | **43** (59%) | **52** (62%) |
| 18 | **35** R = $CO_2Me$ (D: 53%) | | |
| 19 | **25** R = H (61%); |  |  |
| 20 | **36** R = $CO_2Me$ (E: 68%) | **44** (68%) | **53** (94%) |

a) Obtained as a 3 3 1 *E/Z*-mixture b) **22a** R = $CH_2C{\equiv}CH$ was also found in 30% yield

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,[24] 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 ($^3J_{aa}$ = 11.1 Hz) and two axial-equatorial couplings ($^3J_{ae}$ = 6.3 Hz).



**54** **45**, R = H; **48**, R = Me (3)

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 ($^3J_{ae}$ = 6.3 Hz) and two ax-ax couplings ($^3J_{aa}$ = 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

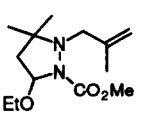
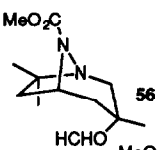
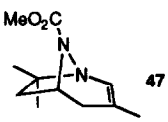
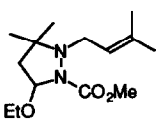
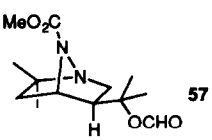
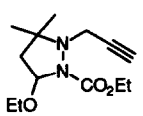
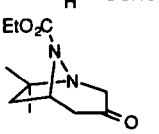
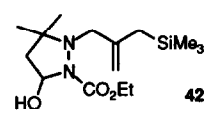
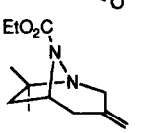
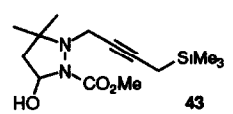
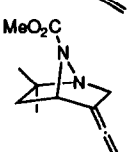
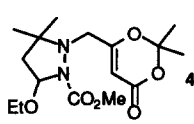
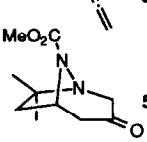
to flatten, a favorable conformation is obtained in which the interaction of the substituents with the carbamate function and the *endo*-methyl group is decreased.

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, $^3J$ = 4.9 Hz).[2] 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.**

| entry | precursor | conditions | cyclization product(s) (yield) |
|---|---|---|---|
| 1 |  **38** | 18 h, 50 °C |  **56** (37%)  **47** (34%) |
| 2 |  **40** | 18 h, 50 °C |  **57** (84%) |
| 3 |  **41** | 18 h, 50 °C[a] |  **58** (47%) |
| 4 |  **42** | 18 h, 25 °C |  **51** (85%) |
| 5 |  **43** | 18 h, 50 °C |  **52** (42%) |
| 6 |  **44** | 5 h, 100 °C |  **59** (42%) |

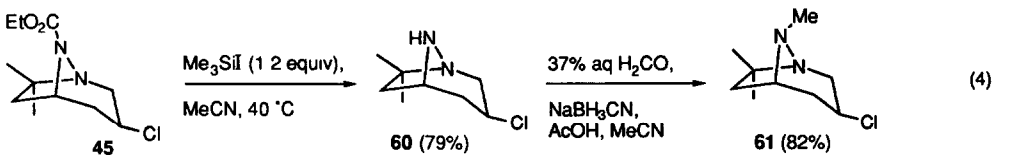
a) After the reaction, water was added and the mixture was stirred for 6 h at 60 °C.

*Formic acid-mediated cyclizations*

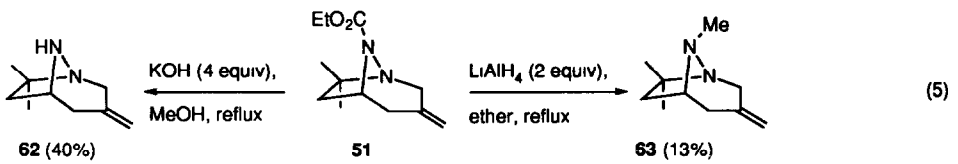
Compared with the yields of the Lewis acid cyclizations, slightly different yields were obtained as is evident from Table II. The stereochemical outcome is similar compared to the Lewis acid cases. In the cases of the precursors **14**, **37** and **39**, cyclization did not take place, but instead the 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)[19] and cleavage with iodotrimethylsilane.[25]




(4)



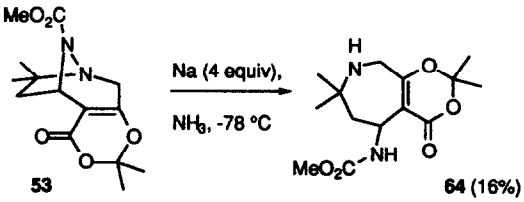

(5)

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.[26]

*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

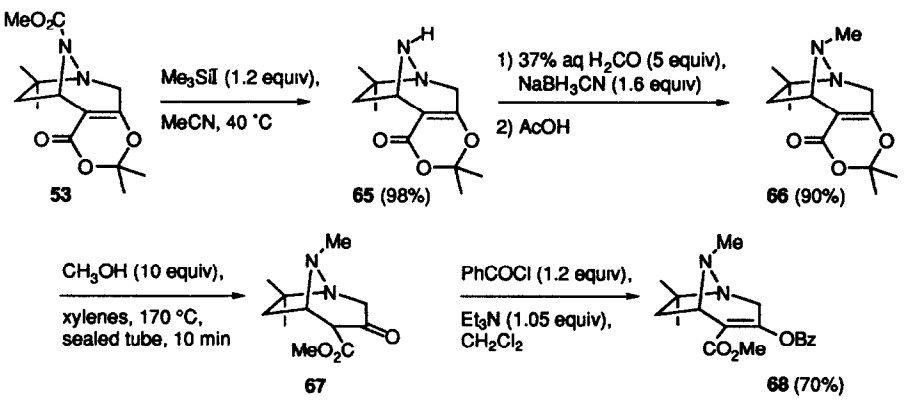
ethylene bridge with the *gem*-dimethyl function and at the top-side the carbamate hinders the approach of a catalyst. If **53** was treated with sodium/ammonia[27] the double bond remained unaffected, but instead the NN bond was cleaved to give the bicyclic system **68** as a single product in poor yield (eq 6).



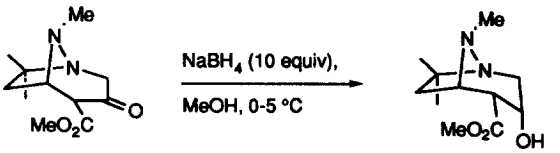

(6)

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).[25] Conversion into the *N*-methyl compound with methyl iodide or dimethyl sulfate did not give satisfactory results. Therefore, a reductive methylation was carried out,[26] using 37% aqueous formaldehyde in acetonitrile to give the intermediate iminium ion which was further reduced with sodium cyanoborohydride to the methylated compound **66**.

**Scheme II**




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 °C in xylenes in the presence of an excess of methanol (Scheme II). The crude β-ketoester **67** was obtained in a quantitative yield but could not be easily purified. Despite the clear $^1$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 β-ketoester **67** was also reduced in the presence of an excess of sodium borohydride at 0 °C to give the ecgonine analog **69** (eq 7). In accordance with the outcome of a similar reduction of 2-(carbomethoxy)-tropanone at -30 °C carried out by Carroll *et al.*,[28] only one isomer was obtained in which both substituents occupy the *endo*-position (allopseudo). They also reported that reduction at 0 °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.




67 69 (73%) (7)

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 hydroxyl 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[28] (in **69**: H3: t, $^3J$ = 4.9 Hz; H4: br t, $^3J$ = 4 Hz; in allopseudococaine: H3: dt, $^3J$ = 1.1, 4.8 Hz; H4: dd, $^3J$ = 3.1, 4.8 Hz).

Attempts to convert this allopseudoecgonine derivative **69** into the benzoyl ester according to literature procedures were not successful.[29] 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

This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

## 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 298 or Perkin-Elmer 1310 spectrophotometer and wavelenghts (ν) 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 Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany. $R_f$ values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 $F_{254}$) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography (fc)[30] using the same solvent 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. $CH_2Cl_2$ was distilled from $P_2O_5$ and stored over MS 4Å under an atmosphere of dry nitrogen. $TiCl_4$ and $SnCl_4$ were distilled and stored under a dry nitrogen atmosphere as a solution in $CH_2Cl_2$. $BF_3$·$OEt_2$ was distilled and stored under a dry nitrogen atmosphere. Dry THF and $Et_2O$ were distilled from sodium benzophenone ketyl prior to use

**1-Benzyl-3-pyrazolidinone-2-carboxylic acid methyl ester (10).** A solution of 1-benzyl-3-pyrazolidinone[10c] (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 $MeO_2CCN$ (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 $CH_2Cl_2$ (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, $R_f$

0.30. IR ν 1780, 1735, 1430, 1210, 690; $^1$H NMR (200 MHz) δ 2.56 (t, $J$ = 7.5 Hz, 2 H, $CH_2$), 3.32 (t, $J$ = 7.6 Hz, 2 H, $NCH_2$), 3.90 ( s, 3 H, $CO_2CH_3$), 4.04 (s, 2 H, $CH_2Ph$), 7.36 (s, 5 H, ArH).

**1-Benzyl-1-(3-hydroxypropyl)-2-hydrazinecarboxylic acid methyl ester (11).** A solution of **10** (44 mg, 0.19 mmol) in EtOH (2 mL) was treated with $NaBH_4$ (22 mg, 0.58 mmol) at -78 °C and every 10 min with one drop of a 2 M $H_2SO_4$/EtOH solution. After 1 h (the reaction was monitored with TLC), the mixture was acidified to pH ≈ 3 at -78 °C, allowed to warm to rt, poured into aq satd $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:1) to give **11** (36.5 mg, 0.15 mmol, 80%) as a colorless oil, $R_f$ 0.20. IR ν 3440, 3340, 1720, 1490, 1450, 1230, 690; $^1$H NMR (200 MHz) δ (1.75 (quintet, $J$ = 5.5 Hz, 2 H, $CH_2$), 2.87 (br s, 2 H, $NCH_2$), 3.64 (s, 3 H, $CO_2CH_3$), 3.74 (t, $J$ = 5.3 Hz, 2 H, $CH_2OH$), 3.93 (s, 2 H, $CH_2Ph$), 5.72 (br s, 1 H, NH); $^{13}$C NMR (50 MHz) δ 28.9 ($CH_2$), 52.1 ($CO_2CH_3$), 55.3 ($NCH_2$), 62.0 ($CH_2Ph$), 127.5, 128.3, 129.2 (ArH), 135.7 (ArC), 157.0 (C(O)).

**General procedure for the alkylation reactions.** The halide (1.1 equiv), $K_2CO_3$ (1.5 equiv) and a catalytic amount of LiI 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*, taken up in water and extracted with $CH_2Cl_2$ (3 ×). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed to afford the pure alkylation 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 was added dropwise a solution of the hydrazide in THF. After being stirred at rt for 30 min, the resulting clear solution was cooled to 0 °C and a solution of $MeO_2CCl$ in THF was added. Stirring was maintained at 0 °C for 30 min and for 2 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was taken up in water and extracted with $CH_2Cl_2$ (3 ×). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by fc to afford the pure product.

**Method B for the ethoxycarbonylation.** See procedure A with $EtO_2CCl$ instead of $MeO_2CCl$.

**Method C for the ethoxycarbonylation.** To a solution of the hydrazide in $CH_2Cl_2$ were added $Et_3N$ (1.1 equiv), diethyl dicarbonate (2.1 equiv) and a solution of DMAP (1.1 equiv) in $CH_2Cl_2$. The light yellow solution was stirred at rt for 18 h, concentrated *in vacuo* and purified by fc.

**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, $MeO_2CCN$ 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 ×). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The pure product was obtained after fc.

**General procedure for the reduction reactions with $NaBH_4$.** A solution of the functionalized pyrazolidinone in ethanol was cooled to -20 °C and $NaBH_4$ (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 $H_2SO_4$/EtOH solution. After being stirred at rt for 4-5 h, the reaction mixture was poured into aq satd $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 ×). The combined organic layers were washed with water, dried ($K_2CO_3$), filtered and concentrated *in vacuo*. The residue was chromatographed to yield the pure pyrazolidine.

**General procedure for the cyclization reactions with $TiCl_4$.** To a 0.1 M solution of the hydrazide in $CH_2Cl_2$ was added $TiCl_4$ (2 equiv, as a solution of $TiCl_4$ in $CH_2Cl_2$) 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 satd $NaHCO_3$ and the resulting suspension was filtered over Celite and extracted with $CH_2Cl_2$ (3 ×). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by fc afforded the pure cyclization product(s).

**1-Benzyl-5,5-dimethyl-3-pyrazolidinone (12).** According to the general procedure, 3-pyrazolidinone **8** (3.02 g, 26.3 mmol) was alkylated by using benzyl chloride (3.03 mL, 26.3 mmol), $K_2CO_3$ (4.00 g, 29.3 mmol) and LiI in 2-butanone (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), $R_f$ 0.42. IR ν 3430, 3400, 1685; $^1$H NMR (200 MHz) δ 1.35 (s, 6 H, $Me_2C$), 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 $C_{12}H_{16}N_2O$· C, 70.56; H, 7.90; N, 13.71. Found: C, 70.52; H, 7.92; N, 13.68.

**1-Benzyl-5,5-dimethyl-3-pyrazolidinone-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 $EtO_2CCl$ (2.86 mL, 30 mmol), while all compounds were dissolved in THF (30 mL). 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, $R_f$ 0.54 and **1-benzyl-5,5-dimethyl-2-[(ethoxycarbonyl)oxy]-2-pyrazoline (17)** (1.07 g, 3.40 mmol, 39%) as a colorless oil, $R_f$ 0.92. **13**: IR ν 1780, 1740; $^1$H NMR (200 MHz) δ 1.17 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.28 (s, 6 H, $Me_2C$), 2.57 (s, 2 H, $CCH_2$), 4.03 (s, 2 H, $NCH_2$), 4.08 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 7.25-7.45 (m, 5 H, ArH). **17**: IR ν 1760, 1635; $^1$H NMR (200 MHz) δ 1.33 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.34 (s, 6 H, $Me_2C$), 2.81 (s, 2 H, $CCH_2$), 3.96 (s, 2 H, $NCH_2$), 4.25 (q, 2 H, $CH_2CH_3$), 7 15-7.45 (m, 5 H, ArH)

**1-Benzyl-5,5-dimethyl-3-pyrazolidinone-2-carboxylic acid ethyl ester (13) via method C.** A solution of **24** (2 00 g, 9.80 mmol) in $CH_2Cl_2$ (40 mL) was treated with $Et_3N$ (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 $CH_2Cl_2$ (4 mL). After being stirred for 66 h, the solution was concentrated *in vacuo* and purified by fc (ethyl acetate/hexane 2:1) to yield **41** (1 36 g, 4.90 mmol, 81% (after correction)) as white crystals.

**1-Benzyl-5,5-dimethyl-3-ethoxy-2-pyrazolidinecarboxylic acid ethyl ester (14).** Following the general procedure, **13** (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 1·4) afforded **14** (2.02 g, 6.53 mmol, 90%) as a colorless oil, $R_f$ 0.43. IR ν 1680; $^1$H NMR (200 MHz) δ 0.97 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.01 (s, 3 H, Me), 1.19 (t, $J$ = 7 1 Hz, 3 H, $CO_2CH_2CH_3$), 1.36 (s, 3 H, Me), 2.21 (dd, $J$ = 5.2, 13.4 Hz, 1 H, CHCHH), 2 32 (dd, $J$ = 7.1, 13.4 Hz, 1 H, CHCHH), 3.59 (q, $J$ = 7.1 Hz, 2 H, $OCH_2CH_3$), 3.89 (d, $J$ = 11.7 Hz, NCHH), 3.92 (q, $J$ = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 4 08 (d, $J$ = 11.7 Hz, 1 H, NCHH), 5.56 (dd, $J$ = 5.3, 7.0 Hz, OCH), 7.15-7.45 (m, 5 H, ArH).

**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 $CH_2Cl_2$ (34 mL) was treated with $TiCl_4$ (5.7 mL of a 1.2 M solution in $CH_2Cl_2$, 6 8 mmol). After being stirred at rt for 18 h, the reaction mixture was worked-up and the residue was chromatographed (ethyl acetate, then ethyl acetate/hexane 1·2) to afford **15** (508 mg, 1.95 mmol, 62% (after correction)) as a colorless oil, $R_f$ 0.28. IR ν 1690; $^1$H NMR (200 MHz) δ (some signals appear as rotamers) 1.17-1.30 (m, 9 H, 3 × Me), 1.89 (d, $J$ = 11.8 Hz, 1 H, $H6_{endo}$), 2.23 (dd, $J$ = 7.0, 11.9 Hz, 1 H, $H6_{exo}$), 4.05-4.25 (m, 3 H, H2 and $CH_2CH_3$), 4.46 (d, $J$ =17.2 Hz, 1 H, H2), 5.02, 5.16 (d, $J$ = 6.0 Hz, 1 H, H5), 6 94-7.15 (m, 4 H, 4 × ArH); $^1$H NMR (250 MHz, $C_6D_6$, 65 °C) δ 0.97 (s, 3 H, Me), 1.06 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.19 (s, 3 H, Me), 1 65 (d, $J$ = 11.8 Hz, 1 H, $H6_{endo}$), 2.06 (dd, $J$ = 7.0, 11.8 Hz, 1 H, $H6_{exo}$), 3.88 (d, $J$ = 17.6 Hz, 1 H, H2), 4.09 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.48 (d, $J$ = 17.6 Hz, 1 H, H2), 5.16 (d, $J$ = 6.7 Hz, 1 H, H5), 6.60-7.00 (m, 4 H, 4 × ArH); $^{13}$C NMR (50 MHz) δ (some signals appear as rotamers) 14.5 ($CH_2CH_3$), 25.4 (Me), 31.9 (Me), 50.9, 51.3 (C6), 52 7 (C2), 56.7, 57 2 (C5), 61.2, 61.5 ($CH_2CH_3$), 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 $C_{15}H_{20}N_2O_4$ 260.1525, found 260.1529.

**3,4-Benzo-1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane (16).** A solution of **15** (187 mg, 0.72 mmol) and KOH (160 mg, 2.88 mmol) in MeOH (7 mL) was heated at reflux temperature for 90 h. The resulting mixture was poured into aq satd $NH_4Cl$ (25 mL) and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* The residue was chromatographed (acetone) to yield **16** (109 mg, 0.58 mmol, 81%) as a yellow oil, $R_f$ 0.13. IR ν 3390, 3060; $^1$H NMR (250 MHz) δ 1.25 (s, 3 H, Me), 1.27 (s, 3 H, Me), 1.95-2.15 (m, 2 H, 2 × H6), 3.90 (br s, 1 H, NH), 4.07 (d, $J$ = 17.3 Hz, 1 H, H2), 4.17 (d, $J$ = 6.0 Hz, 1 H, H5), 4.45 (d, $J$ = 17.3 Hz, 1 H, H2), 6.85-7.15 (m, 4 H, ArH); $^{13}$C NMR (50 MHz) δ 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), 132 (66), 131 (100), 117 (36), 104 (8), 91 (8), 77 (9), 32 (48), 31

(64); HRMS calcd for $C_{12}H_{16}N_2$ 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), $K_2CO_3$ (2.67 g, 19.3 mmol) and LiI in 2-butanone (80 mL). Work-up and fc (ethyl acetate) afforded **18** (1.71 g, 11.5 mmol, 66%) as a white solid, mp 40-42 °C, $R_f$ 0.19. IR ν 3340, 3400, 3080, 1675; $^1$H NMR (200 MHz) δ 1.22 (s, 6 H, $Me_2C$), 2.28 (s, 2 H, $CCH_2$), 3.22 (d, $J$ = 6.4 Hz, 2 H, $NCH_2$), 5.15 (dd, $J$ = 1.8, 8.1 Hz, 1 H, =C*H*H), 5.23 (d, $J$ = 2.8 Hz, 1 H, =CH*H*), 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 3-chloro-2-methyl-1-propene (0.91 mL, 9.21 mmol), $K_2CO_3$ (1.27 g, 9.20 mmol) and LiI in 2-butanone (50 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), $R_f$ 0.45. IR ν 3430, 3400, 3080, 1680; $^1$H NMR (200 MHz) δ 1.25 (s, 6 H, $Me_2C$), 1.75 (s, 3 H, Me), 2.34 (s, 2 H, $CCH_2$), 3.12 (s, 2 H, $NCH_2$), 4.92 (m, 2 H, $=CH_2$), 7.24 (br s, 1 H, NH); Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.27; H, 9.57; N, 16.56.

**1-(2-Butenyl)-5,5-dimethyl-3-pyrazolidinone (20).** Following the general procedure, 3-pyrazolidinone **8** (3.02 g, 26.3 mmol) was alkylated by using 4-bromo-2-butene ((*E*)/(*Z*) 3.3:1) (2.8 mL, 27.6 mmol), $K_2CO_3$ (3.82 g, 27.6 mmol) and LiI in 2-butanone (100 mL). After work-up and fc (ethyl acetate), **20** (2.71 g, 16.0 mmol, 62%) was obtained as white crystals, mp 66.5-68 °C, $R_f$ 0.20, (*E*)/(*Z*) 3.3:1. IR ν 3430, 3190, 1689; (*E*)-isomer: $^1$H NMR (200 MHz) δ 1.29 (s, 6 H, $Me_2C$), 1.69 (dt, $J$ = 6.3, 1.0 Hz, 3 H, Me), 2.35 (s, 2 H, $CCH_2$), 3.21 (d, $J$ = 6.5 Hz, 2 H, $NCH_2$), 5.35-5.55 (m, 1 H, $CH_2CH$=), 5.60-5.80 (dq, $J$ = 15, 6.3 Hz, $CH_3CH$), 7.60 (br s, 1 H, NH). (*Z*)-isomer: $^1$H NMR (200 MHz) δ 1.32 (s, 6 H, $Me_2C$), 1.69 (dt, $J$ = 1.0, 6.3 Hz, 3 H, Me), 2.38 (s, 2 H, $CCH_2$), 3.33 (d, $J$ = 6.9 Hz, 2 H, $NCH_2$), 5.35-5.55 (m, 1 H, $CH_2CH$=), 5.60-5.80 (m, 1 H, $CHCH_3$), 7.60 (br s, 1 H, NH).

**5,5-Dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone (21).** Following the general procedure, 3-pyrazolidinone **8** (7.61 g, 67.0 mmol) was alkylated by using 4-bromo-2-methyl-2-butene (10.5 g, 70.5 mmol), $K_2CO_3$ (13.9 g, 0.10 mol) and LiI in 2-butanone (400 mL). After work-up and fc (ethyl acetate), **21** (9.75 g, 53.6 mmol, 80%) was obtained as white needles, mp 96.5-97 °C ($CH_2Cl_2$/ether 1:10), $R_f$ 0.30. IR ν 3430, 1685; $^1$H NMR (200 MHz), δ 1.30 (s, 6 H, $Me_2C$), 1.74 (s, 3 H, Me), 2.36 (s, 2 H, $CCH_2$), 3.30 (d, $J$ = 7.1 Hz, 2 H, $NCH_2$), 5.20 (tt, $J$ = 1.3, 7.1 Hz, =CH), 6.90 (br s, 1 H, NH).

**5,5-Dimethyl-1-(2-propynyl)-3-pyrazolidinone (22).** Following the general procedure, 3-pyrazolidinone **8** (4.02 g, 35.1 mmol) was alkylated by using 3-bromo-1-propyne (4.11 mL, 36.9 mmol), $K_2CO_3$ (5.11 g, 36.9 mmol) and LiI in 2-butanone (150 mL). Work-up and fc (ethyl acetate/acetone 1:1) afforded **22** (2.11 g, 13.9 mmol, 40%) as yellow crystals, mp 100-105 °C, $R_f$ 0.54 and **5,5-dimethyl-1,2-di(2-propynyl)-3-pyrazolidinone (22a)** (2.01 g, 10.5 mmol, 30%) as a dark oil, $R_f$ 0.89. Data for **22**: IR ν 3430, 3300, 2250, 1690; $^1$H NMR (200 MHz) δ 1.32 (s, 6 H, $Me_2C$), 2.27 (t, $J$ = 2.4 Hz, 1 H, C≡CH), 2.44 (s, 2 H, $CCH_2$), 3.52 (d, $J$ = 2.4 Hz, 2 H, $NCH_2$), 8.07 (br s, 1 H, NH). Data for **22a**: IR ν 3300, 2250, 1690; $^1$H NMR (200 MHz) δ 1.29 (s, 6 H, $Me_2C$), 2.11 (s, 2 H, $CCH_2$), 2.25 (t, $J$ = 2.3 Hz, 2 H, 2 × C≡CH), 3.45-3.75 (m, 4 H, 2 × $NCH_2$).

**5,5-Dimethyl-1-{2-[(trimethylsilyl)methyl]-2-propenyl}-3-pyrazolidinone (23).** According to the general procedure, 3-pyrazolidinone **8** (2.50 g, 21.5 mmol) was alkylated upon use of 2-chloromethyl-3-(trimethylsilyl)-1-propene (2.90 g, 22.8 mmol), $K_2CO_3$ (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, 83%) as white crystals, mp 59-61 °C (ether), $R_f$ 0.60. IR ν 3440, 3400, 3080, 1690, 1250, 850; $^1$H NMR (200 MHz) δ 0.0 (s, 9 H, $Me_3Si$), 1.26 (s, 6 H, $Me_2C$), 1.61 (d, $J$ = 0.7 Hz, 2 H, $CH_2Si$), 2.34 (s, 2 H, $CCH_2$), 3.08 (s, 2 H, $NCH_2$), 4.72 (d, $J$ = 0.6 Hz, 1 H, =C*H*H), 4.85 (d, $J$ = 1.9 Hz, 1 H, =CH*H*), 6.83 (br s, 1 H, NH).

**5,5-Dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone (24).** Following the general procedure, 3-pyrazolidinone **8** (2.60 g, 22.8 mmol) was alkylated with 4-iodo-1-(trimethylsilyl)-2-butyne[20,21] (6.00 g, 23.9 mmol) and $K_2CO_3$ (3.30 g, 23.9 mmol) in 2-butanone (130 mL). After work-up and fc (ethyl acetate), **24** (3.70 g, 15.4 mmol, 68 %) was obtained as yellowish crystals, mp 81.5-83.5 °C (ether), $R_f$ 0.45. IR ν 3420, 3200, 2220, 1690, 1250, 850; $^1$H NMR (200 MHz) δ 0.09 (s, 9

H, $Me_3Si$), 1.33 (s, 6 H, $Me_2C$), 1.46 (t, $J$ = 2.4 Hz, 2 H, $CH_2Si$), 2.42 (s, 2 H, $CCH_2$), 3.52 (t, $J$ = 2.4 Hz, 2 H, $NCH_2$), 7.70 (br s, 1 H, NH).

**5,5-Dimethyl-1-[(3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-3-pyrazolidinone (25).** According to the general procedure, 3-pyrazolidinone **8** (3.55 g, 31.1 mmol) was alkylated with dioxenone[22] (5.50 g, 31.2 mmol), $K_2CO_3$ (4.7 g, 34 mmol) and a catalytic amount of LiI in acetone (130 mL). After being stirred at 45 °C for 48 h, the mixture was worked-up and purified by fc (ethyl acetate) to afford **25** (4.79 g, 18.9 mmol, 61%) as orange crystals, mp 112.5-113 °C (pentane/ether/$CH_2Cl_2$ 10:10:1), $R_f$ 0.28 (ethyl acetate). IR ν 3420, 1720, 1635, 1385, 1370, 1270, 1010; $^1$H NMR (200 MHz) δ 1.30 (s, 6 H, $Me_2CC$), 1.71 (s, 6 H, $Me_2CO$), 2.36 (s, 2 H, $CH_2$), 3.40 (s, 2 H, $NCH_2$), 5.52 (s, 1 H, =CH), 7.70 (br s, 1 H, NH); $^{13}$C NMR (50 MHz) δ 24.9 (4 × Me), 42.7 ($CH_2$), 54.1 ($NCH_2$), 63.0 (NC), 94.6 (=CH), 107.0 (OCO), 160.6, 167.3, 174.9 (2 × C(O) and =C); MS (EI, 70 eV) *m/z* (relative intensity) 196 ($M^+$-58, 100), 127 (100), 83 (62), 43 (74).

**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 $MeO_2CCl$ (3.0 mL, 39 mmol), all compounds dissolved in THF (20 mL). Work-up and fc (ethyl acetate/hexane 1:1) afforded **26** (920 mg, 4.3 mmol, 33%) as a yellow oil, $R_f$ 0.74. IR ν 3080, 1760, 1630; $^1$H NMR (200 MHz) δ 1.26 (s, 6 H, $Me_2C$), 2.73 (s, 2 H, $CCH_2$), 3.40 (dd, $J$ = 1.2, 6.1 Hz, 2 H, $NCH_2$), 3.81 (s, 3 H, $CO_2CH_3$), 5.11 (dd, $J$ = 1.2, 10.7 Hz, 1 H, =C*H*H), 5.22 (dd, $J$ = 1.2, 17.2 Hz, 1 H, =CH*H*), 5.85-6.05 (m, 1 H, =CH).

**5,5-Dimethyl-1-(2-propenyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (27).** According to method C, a solution of **18** (12 6 g, 82.0 mmol) in $CH_2Cl_2$ (300 mL) was treated with $Et_3N$ (11.6 mL, 86 mmol), diethyl dicarbonate (24.1 mL, 164 mmol) and a solution of DMAP (10.0 g, 82.0 mmol) in $CH_2Cl_2$ (30 mL). After concentration *in vacuo* and purification by fc (ethyl acetate), **27** (11.5 g, 50.9 mmol, 82% (after correction)) was obtained as a colorless oil, $R_f$ 0.64. IR ν 3080, 1780, 1730; $^1$H NMR (200 MHz) δ 1.23 (s, 6 H, $Me_2C$), 1.24 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 2.43 (s, 2 H, $CCH_2$), 3.46 (d, $J$ = 6.9 Hz, 2 H, $NCH_2$), 4.22 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 5.05-5.13 (m, 2 H, =$CH_2$), 5.75-5.90 (m, 1 H, =CH).

**5,5-Dimethyl-1-(2-methyl-2-propenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (28).** According to method A, **19** (500 mg, 2.98 mmol) was reacted with NaH (79 mg, 3.28 mmol) and $MeO_2CCl$ (0.69 mL, 8.94 mmol) in THF (5 mL). Work-up and fc (ethyl acetate/hexane 1:1) afforded **28** (497 mg, 2.20 mmol, 74%) as a colorless oil, $R_f$ 0.45. IR ν 3090, 1810, 1760; $^1$H NMR (200 MHz) δ 1.27 (s, 6 H, $Me_2C$), 1.84 (s, 3 H, Me), 2.53 (s, 2 H, $CCH_2$), 3.34 (s, 2 H, $NCH_2$), 3.78 (s, 3 H, $CO_2CH_3$), 4.84, 4 86 (s, 2 H, =$CH_2$).

**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 (630 mg, 14.4 mmol) and $MeO_2CCl$ (3.04 mL, 39.3 mmol), all compounds were dissolved in THF (30 mL). Work-up and fc (ethyl acetate/hexane 1·2) afforded **29** (1.40 g, 6.21 mmol, 47%) as a colorless oil, (*E*)/(*Z*)-ratio 3.3:1, $R_f$ 0.75. IR ν 1760, 1630; (*E*)-isomer: $^1$H NMR (200 MHz) δ 1.26 (s, 6 H, $Me_2C$), 1.67 (d, $J$ = 4.6 Hz, 3 H, Me), 2.74 (s, 2 H, $CCH_2$), 3.33 (dd, $J$ = 1.1, 3.9 Hz, 2 H, $NCH_2$), 3.82 (s, 3 H, $CO_2CH_3$), 5.55-5.70 (m, 2 H, HC=CH); (*Z*)-isomer: $^1$H NMR (200 MHz) δ 1.28 (s, 6 H, $Me_2C$), 1.65 (d, $J$ = 6.1 Hz, 3 H, Me), 2.75 (s, 2 H, $CCH_2$), 3.45 (dd, $J$ = 1.1, 3.9 Hz, 2 H, $NCH_2$), 3.82 (s, 3 H, $CO_2CH_3$), 5.55-5.70 (m, 2 H, HC=CH).

**1-(2-Butenyl)-5,5-dimethyl-3-pyrazolidinone-2-carboxylic acid ethyl ester (30).** Following method C, a solution of **20** (1.13 g, 6.70 mmol) in $CH_2Cl_2$ (25 mL) was treated with $Et_3N$ (0.9 mL, 6.7 mmol), diethyl dicarbonate (1.97 mL, 13.4 mmol) and a solution of DMAP (0.82 g, 6.7 mmol) in $CH_2Cl_2$ (5 mL). Concentration *in vacuo* and fc (ethyl acetate) afforded **30** (1.03 g, 4.3 mmol, 64%) as a yellowish oil, $R_f$ 0.76, (*E*)/(*Z*)-ratio 3.3:1. IR ν 1780, 1730; (*E*)-isomer: $^1$H NMR (200 MHz) δ 1.26 (s, 6 H, $Me_2C$), 1.30 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.60 (d, $J$ = 4.8 Hz, 3 H, Me), 2.50 (s, 2 H, $CCH_2$), 3.57 (d, $J$ = 5.4 Hz, 2 H, $NCH_2$), 4.28 (q, $J$ = 7.1 Hz, $CH_2CH_3$), 5.40-5.70 (m, 2 H, CH=CH); (*Z*)-isomer: $^1$H NMR (200 MHz) δ 1.27 (s, 6 H, $Me_2C$), 1.30 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.56 (d, $J$ = 9.2 Hz, 3 H, Me), 2.46 (s, 2 H, $CCH_2$), 3.43 (d, $J$ = 7.1 Hz, 2 H, $NCH_2$), 4 28 (q, $J$ = 7 1 Hz, $CH_2CH_3$), 5.40-5.70 (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 $MeO_2CCl$ (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, $R_f$ 0.27 and **5,5-dimethyl[(3-methoxycarbonyl)oxy]-1-(3-methyl-2-butenyl)-2-pyrazoline (32)** (486 mg, 2.0 mmol, 18%), as a yellowish oil. **31**: IR ν 3030, 1780, 1730; $^1$H NMR (250 MHz) δ 1.32 (s, 6 H, $Me_2C$), 1.58 (s, 3 H, Me), 1.70 (s, 3 H, Me), 2.51 (s, 2 H, $CCH_2$), 3.55 (d, $J$ = 7.6 Hz, 2 H, $NCH_2$), 3.85 (s, 3 H, $CO_2CH_3$), 5.20-5.35 (m, 1 H, =CH). **32**: IR ν 3030, 1760, 1630; $^1$H NMR (200 MHz) δ 1.28 (s, 6 H, $Me_2C$), 1.65 (s, 3 H, Me), 2.27 (d, $J$ = 0.9 Hz, 3 H, Me), 2.74 (s, 2 H, $CCH_2$), 3.37 (d, $J$ = 6.5 Hz, 2 H, $NCH_2$), 3.83 (s, 3 H, $CO_2CH_3$), 5.30-5.45 (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 *n*-butyllithium (105 mL, 0.17 mmol)) and $MeO_2CCN$ (24 mg, 0.28 mmol), all compounds dissolved in THF (1 mL). After work-up and fc (ethyl acetate/hexane 1:1), **31** (31 mg, 0.13 mmol, 93%) was obtained as a colorless oil, $R_f$ 0.30.

**5,5-Dimethyl-1-(2-propynyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (33).** Following method B, **22** (1.06 g, 7.00 mmol) was treated with NaH (201 mg, 8.36 mmol) and $EtO_2CCl$ (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, 4.70 mmol, 67%) as a light yellow oil, $R_f$ 0.41. IR ν 3300, 2105, 1780, 1725; $^1$H NMR (200 MHz) δ 1.34 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.34 (s, 6 H, $Me_2C$), 2.30 (t, $J$ = 2.4 Hz, 1 H, C≡CH), 2 74 (br s, 2 H, $CCH_2$), 3.81 (d, $J$ = 1.7 Hz, 2 H, $NCH_2$), 4.32 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$).

**5,5-Dimethyl-1-{2-[(trimethylsilyl)methyl]-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 $CH_2Cl_2$ (60 mL) was treated with $Et_3N$ (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 $CH_2Cl_2$ (10 mL). Concentration *in 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, $R_f$ 0.38. IR ν 3080, 1780, 1740, 1250, 850; $^1$H NMR (200 MHz) δ 0.0 (s, 9 H, $Me_3Si$), 1.27 (s, 6 H, $Me_2C$), 1.29 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.70 (d, $J$ = 0.5 Hz, 2 H, $CH_2Si$), 2.52 (s, 2 H, $CCH_2$), 3.23 (s, 2 H, $NCH_2$), 4.23 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.66 (s, 1 H, =CHH), 4.83 (t, $J$ = 0.7 Hz, 1 H, =CHH).

**5,5-Dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone-2-carboxylic acid methyl ester (35) via method A.** **24** (412 mg, 1.73 mmol) was treated with NaH (51 mg, 2.1 mmol) and $MeO_2CCl$ (0.40 mL, 5.2 mmol) in THF (15 mL). Work-up and purification by fc (ethyl acetate/hexane 1:1) afforded **35** (317 mg, 1.07 mmol, 62%) as a colorless oil, $R_f$ 0.60. IR ν 2250, 1780, 1730, 1250, 850; $^1$H NMR (200 MHz) δ 0.03 (s, 9 H, $Me_3Si$), 1.33 (s, 6 H, $Me_2C$), 1.39 (t, $J$ = 2.3 Hz, 2 H, $CH_2Si$), 2.73 (br s, 2 H, $CCH_2$), 3.79 (br s, 2 H, $NCH_2$), 3.87 (s, 3 H, $CO_2CH_3$).

**5,5-Dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone-2-carboxylic acid methyl ester (35) via method D.** **24** (130 mg, 0.55 mmol) was alkylated upon use of LDA (prepared from diisopropylamine (84 μL, 0.60 mmol and *n*-butyllithium (380 μL, 0.61 mmol)) and $MeO_2CCN$ (94 mg, 1.10 mmol). Work-up and fc (ethyl acetate/hexane 1:1) afforded **35** (87 mg, 0.29 mmol, 53%) as a colorless oil, $R_f$ 0.60.

**5,5-Dimethyl-1-[(3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-3-pyrazolidinone-2-carboxylic acid methyl ester (36).** To a suspension of NaH (29 mg, 1.2 mmol) in THF (2 mL) was added dropwise at rt a solution of **25** (303 mg, 1.2 mmol) in THF (4 mL). After being stirred for 15 min, the resulting clear solution was cooled to 0 °C and a solution of $MeO_2CCN$ (306 mg, 3.6 mmol) in THF (1 mL) was added. The mixture was stirred at 0 °C for 15 min and an additional 2 h at rt and poured into aq satd NaCl (20 mL) and extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed (ethyl acetate) to give **36** (255 mg, 0.82 mmol, 68%) as white crystals, mp 116-117 °C (ethyl acetate/hexane), $R_f$ 0.52. IR ν 1790, 1735, 1720, 1635, 1310, 1285, 1015; $^1$H NMR (200 MHz) δ 1.28 (s, 6 H, $Me_2CC$), 1.69 (s, 6 H, $Me_2CO$), 2.79 (s, 2 H, $CH_2$), 3.45 (s, 2 H, $CH_2$), 3.86 (s, 3 H, $CO_2CH_3$), 5.60 (s, 1 H, =CH); $^{13}$C NMR (50 MHz) δ 24.8 (2 × Me), 25.3 (2 × Me), 42.9 ($CH_2$), 53.6 ($NCH_2$), 53.8 ($CO_2CH_3$), 61.6 (NC), 95.2 (=CH), 106.7 (OCO), 150 4, 160.4, 167.5, 171.7 (3 × C(O) and =C), MS (EI, 70 eV) *m/z* (relative intensity) 312 ($M^+$, 7), 254 (48), 185 (100), 103 (20),

83 (41), 69 (27), 43 (27); HRMS calcd for $C_{14}H_{20}N_2O_6$ 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** (10.0 g, 44.2 mmol) was reduced with $NaBH_4$ (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and fc (ethyl acetate/hexane 1:1), **37** (9.36 g, 26.6 mmol, 83%) was obtained as a light yellow oil, $R_f$ 0.50. IR ν 3080, 1720, 1680; $^1$H NMR (200 MHz) δ 0.95 (s, 3 H, Me), 1.08 (t, $J$ = 7.1 Hz, 3 H, $OCH_2CH_3$), 1.19 (t, $J$ = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.26 (s, 3 H, Me), 2.02 (dd, $J$ = 4.7, 13.5 Hz, 1 H, CHC*H*H), 2.22 (dd, $J$ = 6.0, 13.5 Hz, 1 H, CHCH*H*), 3.30-3.70 (m, 4 H, $OCH_2CH_3$ and $NCH_2$), 4.15 (q, $J$ = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 5.01 (s, 1 H, =C*H*H), 5.07 (d, $J$ = 10.0 Hz, 1 H, =CH*H*), 5.49 (dd, $J$ = 5.0, 6.0 Hz, 1 H, OCH), 5.85-6.10 (m, 1 H, =CH).

**5,5-Dimethyl-3-ethoxy-1-(2-methyl-2-propenyl)-2-pyrazolidinecarboxylic acid methyl ester (38).** Following the general procedure, **26** (465 mg, 2.06 mmol) was reduced with $NaBH_4$ (467 mg, 12.3 mmol) in EtOH (25 mL). After work-up and fc (ethyl acetate/hexane 1:1), **38** (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, $R_f$ 0.78. IR ν 3070, 1680; $^1$H NMR (200 MHz) δ 0.99 (s, 3 H, Me), 1.16 (t, $J$ = 7.0 Hz, 3 H, $CH_2CH_3$), 1.28 (s, 3 H, Me), 1.85 (s, 3 H, Me), 2.07 (dd, $J$ = 4.9, 13 5 Hz, 1 H, CHC*H*H), 2.27 (dd, $J$ = 7.3, 13.4 Hz, 1 H, CHCH*H*), 3.38 (s, 2 H, $NCH_2$), 3.59 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_3$), 3 69 (s, 3 H, $CO_2CH_3$), 4.82 (s, 2 H, $=CH_2$), 5.55 (dd, $J$ = 5 0, 7.2 Hz, 1 H, OCH).

**1-(2-Butenyl)-5,5-dimethyl-3-ethoxy-2-pyrazolidinecarboxylic acid ethyl ester (39).** Following the general procedure, **30** (502 mg, 2 1 mmol) was reduced with $NaBH_4$ (473 mg, 12.6 mmol) in EtOH (25 mL). Work-up and fc (ethyl acetate) afforded **39** (404 mg, 1.5 mmol, 71%) as a colorless oil, (*E*)/(*Z*)-ratio 3.3:1, $R_f$ 0.70. IR ν 1690; $^1$H NMR (200 MHz) δ (mixture) 0 98 (s, 3 H, Me), 1.14 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.24 (t, $J$ = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.29 (s, 3 H, Me), 1.55 (m, 3 H, $CHCH_3$), 2.07 (dd, $J$ = 4 7, 13.5 Hz, 1 H, CHC*H*H), 2.24 (dd, $J$ = 7.3, 13.4 Hz, 1 H, CHCH*H*), 3.30-3.45 (m, 2 H, $NCH_2$), 3 45-3 75 (m, 2 H, $OCH_2CH_3$), 4.05-4.40 (m, 2 H, $CO_2CH_2CH_3$), 5.45-5.65 (m, 3 H, CH=CH and OCH).

**5,5-Dimethyl-3-ethoxy-1-(3-methyl-2-butenyl)-2-pyrazolidinecarboxylic acid methyl ester (40).** Following the general procedure, **31** (634 mg, 2.35 mmol) was reduced with $NaBH_4$ (620 mg, 16.5 mmol) in EtOH (60 mL). After work-up and fc (ethyl acetate/hexane 1 1), **40** (318 mg, 1.18 mmol, 44%) was obtained as a colorless oil, $R_f$ 0.55. IR ν 3030, 1685; $^1$H NMR (250 MHz) δ 0.96 (s, 3 H, Me), 1.09 (t, $J$ = 7.0 Hz, 3 H, $CH_2CH_3$), 1.28 (s, 3 H, Me), 1.56 (s, 3 H, Me), 1.64 (s, 3 H, Me), 2.06 (dd, $J$ = 5.0, 13.4 Hz, 1 H, CHC*H*H), 2.23 (dd, $J$ = 7 3, 13.4 Hz, 1 H, CHCH*H*), 3.35-3.40 (m, 1 H, NC*H*H), 3.45-3.65 (m, 3 H, NCH*H* and $CH_2CH_3$), 3.70 (s, 3 H, $CO_2CH_3$), 5.27 (br s, 1 H, =CH), 5.51 (dd, $J$ = 5.4, 6.8 Hz, 1 H, OCH).

**5,5-Dimethyl-3-ethoxy-1-(2-propynyl)-2-pyrazolidinecarboxylic acid ethyl ester (41).** According to the general procedure, **33** (1.00 g, 4.50 mmol) was reduced with $NaBH_4$ (1 02 g, 27.0 mmol) in EtOH (50 mL). After work-up and fc (ethyl acetate/hexane 1:1), **41** (741 mg, 2.92 mmol, 65%) was obtained as a colorless oil, $R_f$ 0 56. IR ν 3310, 1690; $^1$H NMR (200 MHz) δ 0 93 (s, 3 H, Me), 1.07 (t, $J$ = 7.1 Hz, 3 H, $OCH_2CH_3$), 1.18 (t, $J$ = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.22 (s, 3 H, Me), 1.95 (dd, $J$ = 4.4, 14 2 Hz, 1 H, CHC*H*H), 2.07 (t, $J$ = 2.4 Hz, 1 H, C≡CH), 2.20 (dd, $J$ = 7.2, 13.6 Hz, 1 H, CHCH*H*), 3.50-3.70 (m, 2 H, $OCH_2CH_3$), 3 61 (dd, $J$ = 2.4, 9.3 Hz, 2 H, $NCH_2$), 4.05-4.25 (m, 2 H, $CO_2CH_2CH_3$), 5.50 (dd, $J$ = 4.5, 7.0 Hz, 1 H, OCH).

**5,5-Dimethyl-3-hydroxy-1-{2-[(trimethylsilyl)methyl]-2-propenyl}-2-pyrazolidinecarboxylic acid ethyl ester (42).** Following the general procedure, **34** (678 mg, 2.17 mmol) was reduced with $NaBH_4$ (493 mg, 13.0 mmol) in EtOH (25 mL). After being stirred for 2 h at -20 °C, the reaction was quenched with cold aq satd $NaHCO_3$ (30 mL). After work-up according to the general procedure and fc (ethyl acetate/hexane 2.2:1), **42** (653 mg, 2.08 mmol, 96%) was obtained as a white solid, mp 66-68 °C (hexane), $R_f$ 0.68. IR ν 3450, 3080, 1725, 1660, 1240, 850; $^1$H NMR (200 MHz) δ 0.0 (s, 9 H, $Me_3Si$), 1.05 (s, 3 H, Me), 1 25 (t, $J$ = 7 0 Hz, 3 H, $CH_2CH_3$), 1.26 (s, 3 H, Me), 1.63 (d, $J$ = 13.6 Hz, 1 H, C*H*HSi), 1.84 (d, 1 H, $J$ = 13.6 Hz, CH*H*Si), 2.07 (dd, $J$ = 5.4, 13 3 Hz, 1 H, CHC*H*H), 2 22 (dd, $J$ = 7.2, 13.2 Hz, 1 H, CHCH*H*), 3.25 (s, 2 H, $NCH_2$), 4.05-4.20 (m, 2 H, $CH_2CH_3$), 4.62 (s, 1 H, =C*H*H), 4.80 (s, 1 H, =CH*H*), 5.71 (t, $J$ = 5.4 Hz, 1 H, OCH).

**5,5-Dimethyl-3-hydroxy-1-[4-(trimethylsilyl)-2-butynyl]-2-pyrazolidinecarboxylic acid methyl ester (43).** Following the general procedure, **35** (315 mg, 1.06 mmol) was reduced with $NaBH_4$ (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 satd $NaHCO_3$ (50 mL) and worked up following the general procedure. fc (ethyl acetate/hexane 3:2) afforded **43** (185 mg, 0.62 mmol, 59%) as a colorless oil, $R_f$ 0.52. IR ν 3500, 2200, 1679, 1250, 850; $^1$H NMR (200 MHz) δ 0.07 (s, 9 H, $Me_3Si$), 1.15 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1.45 (t, $J$ = 2.3 Hz, 2 H, $CH_2Si$), 2.18 (br s, 1 H, CHC*H*H), 2.41 (dd, $J$ = 7.3, 13.2 Hz, 1 H, CHCH*H*), 3.45 (br s, 1 H, OH), 3.66 (br s, 2 H, $NCH_2$), 3.79 (s, 3 H, $CO_2CH_3$), 5.71 (br s, 1 H, OCH).

**5,5-Dimethyl1-[(3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-3-ethoxypyrazolidine-2-carboxylic acid methyl ester (44).** Following the general procedure, **64** (59 mg, 0.19 mmol) was reduced with $NaBH_4$ (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, 68%) was obtained as white crystals, mp 115-116 °C (ethyl acetate/hexane 1:1), $R_f$ 0.38. IR ν 1720, 1700, 1635, 1445, 1370, 1110, 1080, 1025, 900; $^1$H NMR (200 MHz) δ 1.02 (s, 3 H, Me), 1.17 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.41 (s, 3 H, Me), 1.67 (s, 3 H, Me), 1.69 (s, 3 H, Me), 2.05 (dd, $J$ = 4.7, 13.4 Hz, 1 H, CHC*H*H), 2.31 (dd, $J$ = 7.2, 13.6 Hz, 1 H, CHCH*H*), 3.50-3.75 (m, 4 H, $NCH_2$ and $CH_2CH_3$), 3.73 (s, 3 H, $CO_2CH_3$), 5.55-5.60 (m, 1 H, CHO), 5.60 (s, 1 H, =CH); $^{13}$C NMR (50 MHz) δ 14.8 ($CH_2CH_3$), 23.0 (Me), 24.4 (Me), 25.1 (Me), 28.1 (Me), 45.2 ($CH_2$), 52.9 ($CO_2CH_3$), 54.8 ($NCH_2$), 64.1 ($CH_2CH_3$), 65.8 (NC), 90.9 (OCH), 95.3 (=CH), 106.7 (OCO), 154.0, 161.0, 168.0 ( 2 × C(O) and =C); MS (EI, 70 eV) *m/z* (relative intensity) 342 ($M^+$, 15), 284 (100), 239 (50), 216 (100), 159 (100), 113 (60), 103 (37), 43 (27); HRMS calcd for $C_{16}H_{22}N_2O_6$ 342.1791, found 342.1801; Anal. Calcd. for $C_{16}H_{22}N_2O_6$: C, 56.12; H, 7.65. Found: C, 55.75; H, 7.68.

***rel*-(3*S*,5*S*)-3-Chloro-1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (45).** According to the general procedure, **37** (3.00 g, 11.7 mmol) dissolved in $CH_2Cl_2$ (120 mL) was cyclized with $TiCl_4$ (19.5 mL of a 1.2 M solution, 23.4 mmol). The mixture was worked-up after being stirred at rt for 18 h and the residue was purified by fc (ethyl acetate) to afford **45** (2.72 g, 11.1 mmol, 95%) as a yellow oil, $R_f$ 0.76. IR ν 1670; $^1$H NMR (200 MHz) δ (some signals appear as rotamers) 1.11, 1.16 (s, 3 H, Me), 1.28 (t, $J$ = 7.0 Hz, 3 H, $CH_2CH_3$), 1.41 (s, 3 H, Me), 1.65 (br d, 12.9 Hz, 1 H, $H6_{endo}$), 2.00-2.25 (m, 3 H, $H6_{exo}$ and 2 × H4), 3.05-3.25 (m, 1 H, H2), 3.40-3.50 (m, 1 H, H2), 4.10-4.35 (m, 2 H, $CH_2CH_3$), 4.40-4.45, 4.59-4.62 (m, 1 H, H5); $^1$H NMR (250 MHz, $C_7D_8$, 90 °C) δ 0.94 (s, 3 H, Me), 0.96 (s, 3 H, Me), 1.06 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.17 (d, $J$ = 12.8 Hz, 1 H, $H6_{endo}$), 1.65 (dd, $J$ = 8.0, 12.7 Hz, 1 H, $H6_{exo}$), 1.79 (ddd, $J$ = 2.8, 6.5, 12.7 Hz, 1 H, H4), 2.03 (dt, $J$ = 3.0, 10.7 Hz, 1 H, H4), 3.10-3.20 (m, 2 H, $NCH_2$), 3.90-4.10 (m, 3 H, $CO_2CH_2CH_3$ and H3), 4.08-4.38 (m, 1 H, H5); $^{13}$C NMR (50 MHz) δ (all signals appear as rotamers) 14.5, 14.7 ($CH_2CH_3$), 22.5, 22.6 (Me), 31.1, 31.3 (Me), 40.2, 40.4 (C4), 43.9, 44.5 (C6), 49.5 (C3), 54.7, 55.4 (C5), 56.7, 57.5 (C2), 61.2, 61.6 ($CH_2CH_3$), 64.7, 65.7 (C7), 153.0, 153.7 (C(O)); $^{13}$C NMR (50 MHz, $C_6D_6$, 65 °C) δ 15.5 ($CH_2CH_3$), 22.4 (Me), 32.4 (Me), 41.5 (C4), 45.1 (C6), 51.0 (C3), 56.3 (C5), 58.5 (C2), 61.9 ($CH_2CH_3$), 65.5 (C7), 153.0 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 246 ($M^+$, 40), 211 (100), 142 (32), 128 (36), 70 (18); HRMS calcd for $C_{11}H_{19}N_2O_2Cl$ 246.1135, found 246.1129.

***rel*-(3*R*,5*S*)-3-Chloro-1,8-diaza-3,7,7-trimethylbicyclo[3.2.1]octane-8-carboxylic acid methyl ester (46).** According to the general procedure, **38** (228 mg, 0.89 mmol) dissolved in $CH_2Cl_2$ (9 mL) was cyclized by using $TiCl_4$ (1.48 mL of a 1.2 M solution, 1.78 mmol). After being stirred at rt for 18 h, the reaction was worked-up and the residue was chromatographed (ethyl acetate/hexane 1:1) to give an inseparable mixture (153 mg) of **46** (56%) and **1,8-diaza-3,7,7-trimethylbicyclo[3.2.1]oct-2-ene-8-carboxylic acid methyl ester (47)** (16%) as a colorless oil, $R_f$ 0.37. **46** (mixture): IR ν 1690; $^1$H NMR (200 MHz) δ (some signals appear as rotamers) 1.08-1.62 (m, 9 H, 3 × Me), 1.90-2.12 (m, 2 H, 2 × H6), 2.33-2.36 (m, 1 H, H4), 2.64 (d, $J$ = 12.8 Hz, 1 H, H4), 3.36 (d, $J$ = 16.3 Hz, 1 H, H2), 3.72 (s, 3 H, $CO_2CH_3$), 3.76 (d, $J$ = 16 Hz, 1 H, H2), 4.35-4.55 (m, 1 H, H5); $^{13}$C NMR (50 MHz) δ 25.7 (Me), 31.8 (Me), 37.0 (Me), 40.7 (C6), 41.5 (C4), 52.6 ($CO_2CH_3$), 52.8 (C5), 63.1 (C2), 65.9 (C7), 66.9 (C3), 155.0 (C(O)). **47**: IR ν 1680; $^1$H NMR (200 MHz) δ 1.15 (s, 3 H, Me), 1.33 (s, 3 H, Me), 1.58 (s, 3 H, Me), 1.50-1.70 (m, 2 H, H4 and $H6_{endo}$), 2.08 (dd, $J$ = 11.8, 8.0 Hz, 1 H, $H6_{exo}$), 2.60 (m, 1 H, H4), 3.73 (s, 3 H, $CO_2CH_3$), 4.40-4.50 (m, 1 H, H5), 6.10-6.14 (s, 1 H, H2); $^1$H NMR (250 MHz, $C_6D_6$, 65 °C) δ 1.09 (s, 3 H, Me), 1.14 (s, 3 H, Me), 1.20 (dd, $J$ = 12.3, 5.4 Hz, 1 H, $H6_{endo}$) 1.15-1.25 (m, 1 H, H4), 1.28 (s, 3 H, Me), 1.79 (dd, $J$ = 12.2, 7.9 Hz, 1 H, $H6_{exo}$), 2.56 (d, $J$ = 15.7 Hz, 1 H, H4), 3.54 (s, 3 H, $CO_2CH_3$), 4.46 (br s, 1 H, H5), 6.04 (s, 1 H, H2); $^{13}$C NMR (50 MHz) δ (some signals appear as rotamers) 19.6 (Me), 24.2 (Me), 29.3 (Me), 37.3, 37.6 (C4), 45.5, 46.2 (C6), 52.6

($CO_2CH_3$), 53.6 (C5), 73.2 (C7), 124.7 (C3), 134.8 (C2), 154.6 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 210 ($M^+$, 11), 154 (67), 153 (70), 109 (56), 95 (100); HRMS calcd for $C_{11}H_{18}N_2O_2$ 210.1368, found 210.1322.

***rel*-(3*S*,4*R*,5*S*)-3-Chloro-1,8-diaza-4,7,7-trimethylbicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (48).** Following the general procedure, **39** (145 mg, 0.54 mmol) was cyclized with $TiCl_4$ (0.92 mL of a 1.2 M solution, 1.11 mmol) in $CH_2Cl_2$ (5 mL). Work-up and fc (ethyl acetate/hexane 2:1) afforded **48** (67 mg, 0.26 mmol, 53% (after correction)) as a colorless oil, $R_f$ 0.50. IR ν 1690; $^1$H NMR (200 MHz) δ 1.03 (d, $J$ = 6.7 Hz, 3 H, $CHCH_3$), 1.18 (s, 3 H, Me), 1.30 (t, $J$ = 7.0 Hz, 3 H, $CH_2CH_3$), 1.36 (s, 3 H, Me), 1.63 (d, $J$ = 12.7 Hz, 1 H, $H6_{endo}$), 1.88 (dd, $J$ = 12.7, 8.0 Hz, 1 H, $H6_{exo}$), 2.12 (m, 1 H, H4), 3.10 (dd, $J$ = 14.4, 11.2 Hz, 1 H, $H2_{ax}$), 3.42 (dd, $J$ = 5.9, 11.1 Hz, 1 H, $H2_{eq}$), 3.76 (dt, $J$ = 6.3, 10.8 Hz, 1 H, H3), 4.26 (m, 2 H, $CH_2CH_3$), 4.35 (m, 1 H, H5); $^{13}$C NMR (50 MHz) δ (all signals appear as rotamers) 14.6, 14.8 ($CH_2CH_3$), 14.9, 15.4 ($CHCH_3$), 22.5, 22.6 ($NCCH_3$), 31.2, 31.3 ($NCCH_3$), 39.8, 40.4 (C6), 42.8, 43.1 (C4), 56.7, 57.5 (C2), 57.6, 57.7 (C5), 59.4, 60.1 (C3), 61.2, 61.8 ($CH_2CH_3$), 64.6, 65.6 (C7), 152.8, 153.2 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 260 ($M^+$, 37), 225 (100), 215 (7), 187 (6), 171 (13), 142 (27), 128 (33), 70 (19); HRMS calcd for $C_{12}H_{21}N_2O_2Cl$ 260.1292, found 260.1284.

***rel*-(3*R*,4*S*)-3-(1-Chloro-1-methylethyl)-1,7-diaza-6,6-dimethyl-bicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (49).** To a solution of **40** (141 mg, 0.52 mmol) in $CH_2Cl_2$ (5 mL) was added $TiCl_4$ (0.87 mL of a 1.2 M solution, 1.04 mmol) according to the general procedure F. After being stirred at rt for 18 h, the reaction mixture was worked-up and purified by fc (ethyl acetate) to afford **49** (84 mg, 0.32 mmol, 84% (after correction)) as a light yellow oil, $R_f$ 0.35. IR ν 1690; $^1$H 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, $H5_{endo}$), 1.76 (dd, $J$ = 4.9, 11.5 Hz, 1 H, $H5_{exo}$), 2.02-2.20 (m, 1 H, H3), 2.65-2.80 (m, 1 H, H2), 3.25-3.40 (m, 1 H, H2), 3.70 (s, 3 H, $CO_2CH_3$), 4.53 (d, $J$ = 5.1 Hz, 1 H, H4); $^{13}$C 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 ($CO_2CH_3$), 53.1, 53.8 (C2), 57.4, 57.9 (C4), 61.3, 61.8 (C3), 66.5, 66.7 (C6), 70.5, 70.6 (CCl), 153.4 (C(O)), MS (EI, 70 eV) *m/z* (relative intensity) 260 ($M^+$, 19), 225 (25), 212 (18), 204 (46), 169 (30), 141 (21), 127 (100), 83 (42); HRMS calcd for $C_{12}H_{21}O_2N_2Cl$ 260.1292, found 260.1292.

**3-Chloro-1,8-diaza-7,7-dimethylbicyclo[3.2.1]oct-3-ene-8-carboxylic acid ethyl ester (50).** A solution of **41** (201 mg, 0.79 mmol) in $CH_2Cl_2$ (8 mL) was treated with $TiCl_4$ (1.32 mL of a 1.2 M solution, 1.58 mmol) according to the general procedure F. 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, $R_f$ 0.69. IR ν 1690; $^1$H NMR (200 MHz) δ 1.18 (s, 3 H, Me), 1.28 (t, $J$ = 7.0 Hz, 3 H, $CH_2CH_3$), 1.39 (s, 3 H, Me), 1.95-2.10 (m, 2 H, 2 × H6), 3.49 (d, $J$ = 18.1 Hz, 1 H, H2), 3.95 (d, $J$ =18.2 Hz, 1 H, H2), 4.25 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.50-4.75 (m, 1 H, H5), 6.15 (d, $J$ = 5.5 Hz, H4); $^{13}$C NMR (50 MHz) δ (some signals appear as rotamers) 14.6 ($CH_2CH_3$), 26.1, 26.3 (Me), 32.1 (Me), 49.7, 49.8 (C6), 54.4 (C5), 61.7 ($CH_2CH_3$), 61.8, 61.9 (C2), 67.9 (C7), 128.8 (C4), 150.3 (C3), 153.0 (C(O)); 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 (33); HRMS calcd for $C_{11}H_{17}N_2O_2Cl$ 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 $CH_2Cl_2$ (4 mL) was added $BF_3{\cdot}OEt_2$ (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 $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), 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, $R_f$ 0.32. IR ν 3070, 1690; $^1$H NMR (200 MHz) δ (all signals appear as rotamers) 1.04, 1.09 (s, 3 H, Me), 1.20-1.32 (m, 3 H, $CH_2CH_3$), 1.33 (s, 3 H, Me), 1.64, 1.66 (d, $J$ = 12.3 Hz, 1 H, $H6_{endo}$), 1.75-2.15 (m, 2 H, $H6_{exo}$ 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, $CH_2CH_3$), 4.47-4.65 (m, 2 H, H5), 4.88, 4.93 (s, 2 H, $=CH_2$); $^1$H NMR (250 MHz, $C_7D_8$, 90 °C) δ 1.02 (s, 3 H, Me), 1.10 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.12 (s, 3 H, Me), 1.42 (d, $J$ = 14.3 Hz, 1 H, $H6_{endo}$), 1.71 (dd, $J$ = 7.7, 12.1 Hz, 1 H, $H6_{exo}$), 1.85 (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, $CH_2CH_3$), 4.45-4.60 (m, 1 H, H5), 4.63-4.65 (m, 2 H, $=CH_2$); $^{13}$C NMR (50 MHz) δ (some signals appear as rotamers) 14.8 ($CH_2CH_3$), 22.8 (Me), 31.4, 31.5 (Me), 39.4, 39.6 (C4), 43.7, 44.3 (C6), 54.9, 55.6 (C5), 56.5, 57.3 (C2), 61.2, 61.3 ($CH_2CH_3$), 66.5 (C7), 113.8, 114.0 ($=CH_2$), 140.8, 141.0 (C3), 154.5 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 224 ($M^+$, 93), 209 (24), 168 (38),

151 (100), 137 (42), 109 (32), 95 (25), 81 (17); HRMS calcd for $C_{12}H_{20}N_2O_2$ 224.1525, found 224.1530.

**1,7-Diaza-5,5-dimethyl-3-ethenylidenebicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (52).** To a solution of **43** (109 mg, 0.37 mmol) in $CH_2Cl_2$ (4 mL) was added $BF_3{\cdot}OEt_2$ (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 $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with $H_2O$ (50 mL), dried ($MgSO_4$), 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, $R_f$ 0.36. IR ν 1980, 1960, 1690, 890, 840; $^1$H 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, $H5_{endo}$), 1.94 (dd, $J$ = 4.7, 11.9 Hz, 1 H, $H5_{exo}$), 3.57 (dt, $J$ = 15.1, 4.7 Hz, 1 H, H2), 3.74 (s, 3 H, $CO_2CH_3$), 3.81 (dt, $J$ = 15.1, 3.1 Hz, 1 H, H2), 4.83 (br s, 2 H, $=CH_2$), 4.88 (d, $J$ = 4.7 Hz, 1 H, H4); $^{13}$C NMR (50 MHz) δ 24.9 (Me), 30.6 (Me), 46.3 (C5), 53.0 ($CO_2CH_3$), 54.3 (C2), 64.9 (C6), 65.0 (C4), 79.3 ($=CH_2$), 100.8 ($C{=}C{=}CH_2$), 156.0 (C(O)), 197.1 ($C{=}C{=}CH_2$); MS (EI, 70 eV) *m/z* (relative intensity) 208 ($M^+$, 82), 193 (14), 152 (100), 141 (74), 125 (30), 107 (16), 97 (20), 70 (8); HRMS calcd for $C_{11}H_{16}N_2O_2$ 208.1212, found 208.1205.

**Cyclization product 53.** To a solution of **44** (1.57 g, 4.59 mmol) in $CH_2Cl_2$ (50 mL) was added at 0 °C $BF_3{\cdot}OEt_2$ (2.26 mL, 18.4 mmol). The mixture was stirred at 0 °C for 10 min and for 18 h at rt. The mixture was poured into aq satd NaCl (100 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), 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), $R_f$ 0.36. IR ν 1720, 1645, 1420, 1370, 1290; $^1$H NMR δ 1.22 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.63 (s, 3 H, Me), 1.66 (s, 3 H, Me), 1.98 (d, $J$ = 11.5 Hz, 1 H, $H6_{endo}$), 2.12 (dd, $J$ = 6.0, 12.0 Hz, 1 H, $H6_{exo}$), 3.44 (d, $J$ = 18.9 Hz, 1 H, H2), 3.76 (s, 3 H, $CO_2CH_3$), 3.90 (br d, $J$ = 19 Hz, 1 H, H2), 5.10 (br s, 1 H, H5); $^{13}$C NMR δ (some signals appear as rotamers) 23.2, 25.8, 26.5, 32.1 (Me), 49.7, 50.3, 51.2 (br, C2 and C6), 51.7 (C5), 53.1 ($CO_2CH_3$), 66.8, 67.6 (C7), 107.1, 107.6 (OCO and C4), 155.0, 158.3, 161.7 (C3 and 2 × C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 296 ($M^+$, 15), 238 (100), 210 (30), 155 (66), 109 (25), 80 (12); HRMS calcd for $C_{14}H_{20}N_2O_5$ 296.1372, found 296.1369; Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.76; H, 6.76. Found: C, 56.35; H, 6.76.

***rel*-(3*R*,5*S*)-1,8-Diaza-3-(formyloxy)-3,7,7-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 fc (ethyl acetate/hexane 1:1) afforded **56** (85 mg, 0.33 mmol, 37%) as a colorless oil, $R_f$ 0.20 and **47** (65 mg, 0.31 mmol, 34%) as a colorless oil, $R_f$ 0.34. **56**: IR ν 1720, 1680; $^1$H NMR (200 MHz) δ (some signals appear as rotamers) 1.07 (s, 3 H, Me), 1.43 (s, 3 H, Me), 1.47 (s, 3 H, Me), 1.91-2.13 (m, 3 H, 2 × H6 and H4), 2.51 (d, $J$ = 15.2 Hz, 1 H, H4), 3.16 (d, $J$ = 16.2 Hz, 1 H, H2), 3.74 (s, 3 H, $CO_2CH_3$), 3.79 (d, $J$ = 16.2 Hz, 1 H, H2), 4.35, 4.46 (br s, 1 H, H5); $^1$H NMR (250 MHz, $C_6D_6$, 65 °C) δ 1.05 (s, 3 H, Me), 1.11 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.65 (dd, $J$ = 7.9, 12.3 Hz, 1 H, $H6_{exo}$), 1.82 (d, $J$ = 11.1 Hz, 1 H, $H6_{endo}$), 1.87 (d, $J$ = 16.7 Hz, 1 H, H4), 2.23 (d, $J$ = 15.0 Hz, 1 H, H4), 3.12 (d, $J$ = 16.3, 1 H, H2), 3.55 (s, 3 H, $CO_2CH_3$), 3.59 (d, $J$ = 16.3 Hz, 1 H, H2), 4.20-4.40 (m, 1 H, H5), 7.50 (s, 1 H, CHO); $^{13}$C NMR (63 MHz) δ (some signals appear as rotamers) 23.2 (Me), 27 4 (Me), 31.7 (Me), 40.9 (C6), 41.8, 42.5 (C4), 52.1, 52.4 ($CO_2CH_3$), 52.8, 52.9 (C5), 58.7, 59.4 (C2), 65.3, 65.7 (C7), 78.7 (C3), 155.0, 159.8 (C(O)); MS (EI, 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 $C_{12}H_{20}N_2O_4$ 256.1423, found 256.1407.

***rel*-(3*R*,4*S*)-1,7-Diaza-6,6-dimethyl-3-[dimethyl(formyloxy)methyl]bicyclo[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 fc (ethyl acetate/hexane 1:1) afforded **57** (118 mg, 0.44 mmol, 84%) as a yellow oil, $R_f$ 0.14. IR ν 1715; $^1$H NMR (200 MHz) δ (all signals appear as rotamers) 1.09-1.20 (m, 7 H, 2 × Me and $H5_{endo}$), 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, $H5_{exo}$), 2.05, 2.14 (t, $J$ = 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 ($CO_2CH_3$), 4.45, 4.51 (d, $J$ = 5.0 Hz, 1 H, H4), 7.86, 7.87 (s, 1 H, OCHO); $^1$H NMR (250 MHz, $C_7D_8$, 90 °C) δ 0.88 (d, $J$ = 11.3 Hz, 1 H, $H5_{endo}$), 0.93 (s, 3 H, $NCCH_3$), 1.05 (s, 3 H, $NCCH_3$), 1.25 (s, 3 H, $CHCCH_3$), 1.29 (s, 3 H, $CHCCH_3$), 1.52 (dd, $J$ = 5.0, 11.3 Hz, 1 H, $H5_{exo}$), 1.96 (t, $J$ = 7.3 Hz, 1 H, H3), 2.60 (dd, $J$ = 6.8, 12.6 Hz, 1 H, H2), 2.98 (dd, $J$ = 7.9, 12.6 Hz, 1 H, H2), 3.48 (s, 3 H, $CO_2CH_3$), 4.43 (d, $J$ = 4.9 Hz, 1 H, H4), 7.61 (s, 1 H, OCHO); $^{13}$C NMR (50 MHz) δ (all signals appear as rotamers) 23.1, 23.5 (Me), 23.6, 24.0 (Me), 25.0, 25.1 (Me), 30.4, 30.5 (Me), 46.5,

47.4 (C5), 51.7, 52.1 (C2), 52.4, 52.6 (C3), 53.7, 54.5 (C4), 60.6, 61.4 ($CO_2CH_3$), 65.9, 66.6 (C6), 83.4, 83.5 (CO), 153.7, 159.6, 160.0 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 270 ($M^+$, 15), 225 (16), 168 (100), 153 (47), 141 (72), 127 (81), 123 (41), 109 (32), 83 (38), 59 (45), 41 (89); HRMS calcd for $C_{13}H_{22}N_2O_2$ 270.1580, found 270.1581.

**1,8-Diaza-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 $H_2O$ (5 mL), the reaction mixture was stirred at 60 °C for another 6 h and poured into aq satd $NaHCO_3$ (100 mL). An additional amount of $NaHCO_3$ was added until the water layer reached pH ≈ 9. After extraction with $CH_2Cl_2$ (3 × 100 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. fc (ethyl acetate/hexane 1:1) afforded **58** (56 mg, 0.25 mmol, 47%) as a light yellow oil, $R_f$ 0.28. IR ν 1720, 1690; $^1$H NMR (200 MHz) δ 1.18 (s, 3 H, Me), 1.61 (t, *J* = 6.9 Hz, 3 H, $CH_2CH_3$), 1.61 (s, 3 H, Me), 1.69 (d, *J* = 12.8 Hz, 1 H, $H6_{endo}$), 2.24 (dd, *J* = 7.8, 12.8 Hz, 1 H, $H6_{exo}$), 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, $CH_2CH_3$), 4.75-5.00 (m, 1 H, H5); $^{13}$C NMR (50 MHz) δ 14.8 ($CH_2CH_3$), 24.8 (Me), 31 2 (Me), 45.9 (C6), 48.5 (C4), 54.8 (C5), 62.3 ($CH_2CH_3$), 62.9 (C2), 67.5 (C7), 154.0 (NC(O)), 208.2 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 226 ($M^+$, 12), 198 (84), 157 (31), 143 (100), 71 (26); HRMS calcd for $C_{11}H_{18}N_2O_2$ 226.1305, found 226 1311.

**1,8-Diaza-7,7-dimethyl-3-methylenebicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (51).** A solution of **42** (2.50 g, 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** (1 52 g, 6 8 mmol, 85%) as a yellowish oil, $R_f$ 0.32.

**1,7-Diaza-5,5-dimethyl-3-ethenylidenebicyclo[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, $R_f$ 0.36.

**1,8-Diaza-7,7-dimethylbicyclo[3.2.1]octan-3-one-8-carboxylic acid methyl ester (59).** A solution of **44** (77 mg, 0.23 mmol) was stirred in HCOOH (2 mL) at 100 °C for 5 h. Concentration *in vacuo* and purification by fc (ethyl acetate/hexane 1:1) afforded **59** (15 mg, 0.066 mmol, 29%) as a colorless oil, $R_f$ 0.28. IR ν 1720, 1690; $^1$H NMR (200 MHz) δ 1.18 (s, 3 H, Me), 1.61 (s, 3 H, Me), 1.69 (d, *J* = 12.8 Hz, 1 H, $H6_{endo}$), 2.24 (dd, *J* = 7.8, 12.8 Hz, 1 H, $H6_{exo}$), 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), 3.76 (s, 3 H, $CO_2CH_3$), 4.75-5.00 (m, 1H, H5).

***rel*-(3*S*,5*S*)-3-Chloro-1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane (60).** To a solution of **45** (65 mg, 0.27 mmol) in MeCN (3 mL) was added $Me_3SiI$ (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 aq $NaHSO_3$ and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), 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 °C, $R_f$ 0.35. IR ν 3300; $^1$H NMR (200 MHz) δ 1.13 (s, 3 H, $CH_{3exo}$), 1.42 (s, 3 H, $Me_{endo}$), 1.67 (d, 1 H, *J* = 12 9 Hz, $H6_{endo}$), 1.89 (dd, 1 H, J = 12.9, 7.6 Hz, $H6_{exo}$), 2.12 (m, 2 H, H4), 3.20 (dd, *J* = 11.1, 14.0 Hz, 1 H, $H2_{ax}$), 3 35 (dd, *J* = 6.2, 14.0 Hz, 1 H, $H2_{eq}$), 3 60 (m, 1 H, H5), 3.79 (br s, 1 H, NH), 4.20 (tt, *J* = 11.1, 6.3 Hz, 1 H, H3); $^{13}$C 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 $C_8H_{15}N_2Cl$ 174.0924, found 174.0931.

***rel*-(3*S*,5*S*)-3-Chloro-1,8-diaza-7,7,8-trimethylbicyclo[3.2.1]octane (61).** To a solution of **60** (50 mg, 0.33 mmol) in MeCN (1 mL) were added 37% aq formaldehyde (130 µL, 1 66 mmol) and $NaBH_3CN$ (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 $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with $H_2O$ (10 mL), dried ($K_2CO_3$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:1) to afford **61** (45 mg, 0.27 mmol, 82%) as a colorless oil, $R_f$ 0 40. IR ν 1455, 1260, 900, 635, $^1$H 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, $H6_{endo}$), 1.85-1.90 (m, 1 H, $H6_{exo}$), 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 (s, 3 H,

$NCH_3$), 3.00 (dd, $J$ = 6.4, 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); $^{13}C$ 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 (35), 43 (42); HRMS calcd for $C_9H_{17}N_2Cl$ 188.1081, found 188.1077.

**1,8-Diaza-7,7-dimethyl-3-methylenebicyclo[3.2.1]octane (62).** 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 $NH_4Cl$ (25 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), 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, $R_f$ 0.10. IR ν 3300, 3060, 895; $^1H$ NMR (200 MHz) δ 1.11 (s, 3 H, Me), 1.38 (s, 3 H, Me), 1.66 (d, $J$ = 12.0 Hz, 1 H, $H6_{endo}$), 1.80 (ddd, $J$ = 0.7, 7.1, 12.4 Hz, 1 H, $H6_{exo}$), 2.10 (d, $J$ = 13.9 Hz, 1 H, H4), 2.68 (d, $J$ = 13.3 Hz, 1 H, H4), 3.49 (d, $J$ = 15.4 Hz, 1 H, H2), 3.60-3.80 (m, 2 H, H2 and H5), 3.93 (br s, 1 H, NH), 4.75-4.85 (m, 2 H, $=CH_2$); $^{13}C$ NMR (63 MHz) δ 23.1 (Me), 32.0 (Me), 41.0 (C4), 45.4 (C6), 57.4 (C5), 57.7 (C2), 66.4 (C7), 112.3 ($=CH_2$), 142.7 (C3); MS (EI, 70 eV) *m/z* (relative intensity) 152 ($M^+$, 33), 137 (100), 109 (13), 95 (26), 81 (25), 69 (40), 55 (25), 41 (32); HRMS calcd for $C_9H_{16}N_2$ 152.1313, found 152.1310.

**1,8-Diaza-3-methylene-7,7,8-trimethylbicyclo[3.2.1]octane (63).** To a suspension of $LiAlH_4$ (17 mg, 0.45 mmol) in THF (2 mL) was added dropwise a solution of **51** (51 mg, 0.23 mmol) in THF (2 mL) and the mixture was heated at reflux temperature for 3 h. After cooling to rt, $H_2O$ (53 mL) was added and the resulting suspension was washed with ether (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **63** (9.8 mg, 0.059 mmol, 13%) as a colorless oil, $R_f$ (ethyl acetate) 0.10. IR ν 3060, 890; $^1H$ NMR (200 MHz) δ 1.27 (s, 3 H, Me), 1.32 (s, 3 H, Me), 1.62 (d, $J$ = 12.1 Hz, 1 H, $H6_{endo}$), 1.89 (d, $J$ = 14.9 Hz, 1 H, H4), 2.06 (dd, $J$ = 7.4, 12.1 Hz, 1 H, $H6_{exo}$), 2.73 (s, 3 H, $NCH_3$), 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, $=CH_2$); $^{13}C$ NMR (50 MHz) δ 24.6 (Me), 32.7 (C4), 33.0 (Me), 35.9 ($NCH_3$), 45.9 (C6), 49.1 (C2), 59.8 (C5), 63.9 (C7), 111.3 ($=CH_2$), 142.6 (C3); MS (EI, 70 eV) *m/z* (relative intensity) 166 ($M^+$, 57), 151 (95), 125 (26), 111 (17), 95 (27), 83 (100), 82 (90), 55 (23), 43 (37); HRMS calcd for $C_{10}H_{18}N_2$ 166.1470, found 166.1470.

**Diazepine 64.** A solution of **53** (100 mg, 0.34 mmol) in THF (2 mL) was added to a solution of Na (31 mg, 1.35 mmol) in $NH_3$ (15 mL) at -78 °C. The mixture was stirred at -78 °C for 3 h, quenched by addition of $NH_4Cl$ (182 mg, 3.4 mmol) and the ammonia was allowed to evaporate. The residue was dissolved in $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, 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, $R_f$ 0.20. IR ν 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), 1.65 (s, 3 H, Me), 1.68 (d, $J$ = 14.9 Hz, 1 H, C*H*H), 1.77 (br s, 1 H, NH), 2.22 (dd, $J$ = 7.8, 14.9 Hz, 1 H, CH*H*), 3.44 (d, $J$ = 18.7 Hz, 1 H, NC*H*H), 3.61 (d, $J$ = 18.7 Hz, 1 H, NCH*H*), 3.65 (s, 3 H, $CO_2CH_3$), 4.86 (br t, $J$ = 7.8 Hz, 1 H, NCH), 5.70 (br d, $J$ = 7.8 Hz, 1 H, NH); $^{13}C$ NMR (63 MHz) δ 24.3, 25.5, 27.8, 31.7 (4 × Me), 43.6, 44.5 (NC and $CH_2$), 45.0 (NCH), 52.0 ($CO_2CH_3$), 52.1 ($NCH_2$), 105.3, 107.2 (OCO and C3), 155.9, 161.1, 168.8 (2 × C(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 $Me_3SiI$ (403 μL, 2.83 mmol) and the mixture was stirred at 40 °C for 2 h. It was poured into aq satd $NaHSO_3$ (50 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($K_2CO_3$), filtered, concentrated *in vacuo* and chromatopgraphed (acetone) to afford **65** (550 mg, 2.31 mmol, 98%) as a colorless oil that solidified upon standing, mp 150-160 °C (decomposes before melting), $R_f$ 0.30. IR ν 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), 1.64 (s, 6 H, 2 × Me), 1.91 (dd, $J$ = 5.8, 12.2 Hz, 1 H, $H6_{exo}$), 2.06 (d, $J$ = 12.2 Hz, 1 H, $H6_{endo}$), 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); $^{13}C$ 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 (45), 70 (17), 43 (18). HRMS calcd for $C_{12}H_{18}N_2O_3$ 238.1317, found 238.1313; Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60 49; H, 7.61; N, 11.76. Found· C, 60.36; H, 7.72; H, 11 69.

***N*-Methylhydrazine 66.** To a solution of **65** (600 mg, 2.52 mmol) in MeCN (6 mL) were added 37% aq formaldehyde (1.01 mL, 12.3 mmol) and $NaBH_3CN$ (253 mg, 4.03 mmol). After being stirred for 15 min at rt, glacial acetic acid was 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 (40 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with $H_2O$ (30 mL), dried ($K_2CO_3$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate) to afford **66** (570 mg, 2.26 mmol, 90%) as a white solid, mp 64.5-66.5 °C (ethyl acetate), $R_f$ 0.20. IR ν 1715, 1640, 1415, 1400, 1380, 1370, 1290, 1265, 1100; $^1$H NMR (200 MHz) δ 1.28 (s, 3 H, Me), 1.38 (s, 3 H, Me), 1.69 (s, 6 H, 2 × Me), 1.94 (d, $J$ = 11.9 Hz, 1 H, $H6_{endo}$), 2.33 (dd, $J$ = 6.1, 12.2 Hz, 1 H, $H6_{exo}$), 2.66 (s, 3 H, $NCH_3$), 3.31 (d, $J$ = 19.3 Hz, 1 H, H2), 3.75 (d, $J$ = 19.2 Hz, 1 H, H2), 3.91 (d, $J$ = 6.0 Hz, 1 H, H5); $^{13}$C NMR (50 MHz) δ 23.7, 26.2, 27.4, 33.6 (4 × Me), 38.8 ($NCH_3$), 56.7 (C5), 65.0 (C7), 105.4, 106.4 (OCO and C4), 159.4, 161.9 (C3 and C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 252 ($M^+$, 30), 194 (100), 166 (27), 111 (86), 83 (26), 43 (17); HRMS calcd for $C_{13}H_{20}N_2O_3$ 252.1474, found 252.1479.

**3-Benzoyloxy-7,7,8-trimethyl-1,8-diazabicyclo[3.2.1]oct-3-ene-4-carboxylic acid methyl ester (68).** A solution of **66** (13 mg, 0.052 mmol) and MeOH (18 μL, 0.5 mmol) in xylenes (0.5 mL) was heated at 170 °C for 10 min in a sealed tube. The mixture was concentrated *in vacuo* to afford **3-oxo-7,7,8-trimethyl-1,8-diazabicyclo[3.2.1]octane-4-carboxylic acid methyl ester (67)** (10 mg) as a light yellow oil. $^1$H NMR (200 MHz) δ 1.27 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1.86 (d, $J$ = 11.7 Hz, 1 H, $H6_{endo}$), 2.27 (dd, $J$ = 6.2, 11.9 Hz, 1 H, $H6_{exo}$), 2.64 (s, 3 H, $NCH_3$), 2.82 (d, $J$ = 3.8 Hz, 1 H, H4), 3.34 (d, $J$ = 19.2 Hz, 1 H, H2), 3.76 (s, 3 H, $CO_2CH_3$), 3.82 (d, $J$ = 19.2 Hz, 1 H, H2), 3.83 (dd, $J$ = 6.1, 3.8 Hz, 1 H, H5). The crude residue was dissolved in $CH_2Cl_2$ (1 mL) and treated with benzoyl chloride (6.5 μL, 0.056 mmol) and $Et_3N$ (8 μL, 0.057 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and 5 h at rt and concentrated *in vacuo*. fc (ethyl acetate/hexane 4:1) afforded **68** (12 mg, 0.036 mmol, 70%) as a colorless oil, $R_f$ 0.35. $^1$H 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, H6), 2.30 (dd, $J$ = 6.5, 11.8 Hz, 1 H, H6), 2.74 (s, 3 H, $NCH_3$), 3.45 (d, $J$ = 19.7 Hz, 1 H, H2), 3.59 (s, 3 H, $CO_2CH_3$), 3.82 (d, $J$ = 19.9 Hz, 1 H, H2), 4.04 (d, $J$ = 6.5 Hz, 1 H, H5), 7.40-7.60 (m, 3 H, ArH), 8.06-8.11 (m, 2 H, ArH); $^{13}$C NMR (63 MHz) δ 26 6, 33.1 (2 × Me), 36.5 ($NCH_3$), 45.6 (C6), 51.2 (C2), 51.7 ($CO_2CH_3$), 59.7 (C5), 65.3 (C7), 120.0 (C4), 128.6, 129.8, 133.7 (ArH), 128.9 (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 $C_{18}H_{22}N_2O_4$ 330.1580, found 330.1579.

**(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 xylenes (0.5 mL) was heated at 170 °C for 10 min in a sealed tube and concentrated *in vacuo* to afford **67** (10 mg) as a light yellow oil. The crude residue was dissolved in MeOH (1 mL) and treated at 0 °C with $NaBH_4$ (12 mg, 0.32 mmol). After being stirred at 0 °C for 3 h, the solution was poured into $H_2O$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (acetone) to afford **69** (9 mg, 0 038 mmol, 73%) as a colorless oil, $R_f$ 0.30. IR ν 3600, 1705, 1430, 1290, 1060, 900; $^1$H NMR (200 MHz) δ 1.35 (s, 3 H, $CH_{3exo}$), 1.51 (s, 3 H, $CH_{3endo}$), 1.98 (dd, $J$ = 7.8, 12.5 Hz, 1 H, $H6_{exo}$), 2.26 (d, $J$ = 12.5 Hz, 1 H, $H6_{endo}$), 2.66 (s, 3 H, $NCH_3$), 3.05 (t, $J$ = 4 Hz, 1 H, H4), 3.12 (d, $J$ = 16.2 Hz, H2), 3.43 (dd, $J$ = 5.3, 16.3 Hz, 1 H, H2), 3.47 (dd, $J$ = 7.6, 2.6 Hz, 1 H, H5), 3.73 (s, 3 H, $CO_2CH_3$), 3.79 (br s, 1 H, OH), 4.09 (t, $J$ = 4.9 Hz, 1 H, H3); $^{13}$C NMR (63 MHz) δ 24.4, 33 1, 34.9 (3 × Me), 40.2 (C4), 42.8 (C6), 45.2 (C2), 51.9 ($CO_2CH_3$), 58.5 (C5), 62.6 (C3), 63.2 (C7), 174.3 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 227 ($M^+$-1, 18), 171 ($M^+$-57, 36), 122 (25), 105 (100), 77 (37).

## REFERENCES AND NOTES


1. Shustov, G.V.; Tavakalyan, N.B.; Kostyanovsky, R.G. *Tetrahedron* **1985**, *41*, 1985.
2. Davies, J.W.; Malpass, J.R.; Moss, R.E. *Tetrahedron* **1985**, *37*, 4533.
3. Nelsen, S.F.; Ippoliti, J.T.; Frigo, T.B.; Petillo, P.A. *J. Am. Chem. Soc.* **1989**, *111*, 1776.
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.; Sybirska, E.; Al-Tikriti, M.; Charney, 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,

F.I. *J. Med. Chem.* **1992**, *35*, 135. (c) Abraham, P.A.; Pitner, J.B.; Lewin, A.H.; Boja, J.W.; Kuhar, M.J.; Carroll, F.I. *J. Med Chem.* **1992**, *35*, 141. (d) Carroll, F.I.; Lewin, A.H.; Boja, J.W.; Kuhar, M.J. *J. Med. Chem.* **1992**, *35*, 969.

6. Oppolzer, W. *Tetrahedron Lett.* **1972**, *17*, 1707.
7. Ames, D.E.; Novitt, B. *J. Chem. Soc. (C)* **1969**, 2355.
8. Dennis, N.; Katritzky, A.R.; Ramaiah, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1506.
9. (a) Rutjes, F.P.J.T.; Hiemstra, H.; Mooiweer, H.H.; Speckamp, W.N. *Tetrahedron Lett.* **1988**, *29*, 6975. (b) Pirrung, F.O.H.; Rutjes, F.P.J.T.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron Lett.* **1990**, *37*, 5365. (c) Rutjes, F.P.J.T.; Udding, J.H.; Hiemstra, H.; Speckamp, W.N. *Heterocycles* **1992**, *33*, 81. (d) Rutjes, F.P.J.T.; Teerhuis, N.M.; Hiemstra, H.; Speckamp, W.N. submitted for publication.
10. (a) Dorn, H.; Zubek, A. *Org. Synth.* **1968**, *48*, 8. (b) Dorn, H.; Zubek, A. *Z. Chem.* **1967**, *7*, 150. (c) Dorn, H.; Otto, A *Chem. Ber.* **1968**, *101*, 3287.
11. Esch, P.M.; Hiemstra, H.; Klaver, W.J.; Speckamp, W.N. *Heterocycles* **1987**, *26*, 75.
12. Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. *J. Chem. Soc.* **1915**, *107*, 1080.
13. Allinger, N.L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.
14. Chiron, R.; Graff, Y. *Bull. Soc. Chim. Fr.* **1971**, 2145.
15. Lieser, Th.; Kemmner, K. *Chem. Ber.* **1951**, *84*, 4.
16. Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* **1983**, *48*, 2424.
17. Ternansky, R.J.; Draheim, S.E. *Tetrahedron* **1992**, *48*, 777.
18. Izydore, R.A.; Bernal-Ramirez, J.A. *J. Org. Chem.* **1990**, *55*, 3761.
19. (a) Wenkert, E.; Hudlicky, T.; Showalter, H.D.H. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (b) Natsume, M.; Muratake, H. *Tetrahedron Lett.* **1979**, 3477.
20. (a) Angoh, A.G.; Clive, D.L.J. *J. Chem. Soc., Chem. Commun.* **1984**, 534. (b) Mastalerz, H. *J. Org. Chem.* **1984**, *49*, 4092. (c) Pornet, J.; Damour, D.; Randrianoelina, B.; Miginiac, L. *Tetrahedron* **1986**, *42*, 2501.
21. (a) Hiemstra, H.; Sno, M.H.A.M.; Vijn, R.J.; Speckamp, W.N. *J. Org. Chem.* **1985**, *50*, 4014. (b) Klaver, W.J.; Moolenaar, M.J.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron* **1988**, *44*, 3805.
22. Boeckman, R.K.; Perni, R.B.; Macdonald, J.E.; Thomas, A.J. *Org. Synth.* **1987**, *66*, 194.
23. Mander, L.N.; Sethi, S.P. *Tetrahedron Lett.* **1983**, *24*, 5425.
24. See *e.g.*: (a) Overman, L.E.; Ricca, D.J. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1007. (b) Hiemstra, H.; Speckamp, W.N. *ibid.* p 1047.
25. (a) Jung, M.E.; Lyster, M.A. *J. Chem. Soc., Chem. Commun.* **1978**, 315. (b) Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
26. Borch, R.F.; Hassid, A.I. *J. Org. Chem.* **1972**, *37*, 1673.
27. Denmark, S.E.; Nicaise, O.; Edwards, J.P. *J. Org. Chem.* **1990**, *55*, 6219.
28. Carroll, F.I.; Coleman, M.L.; Lewin, A.H. *J. Org. Chem.* **1982**, *47*, 13.
29. (a) Findlay, S.P. *J. Org. Chem.* **1959**, *24*, 1540. (b) Sinnema, A.; Maat, L.; Van der Gugten, A.J.; Beyerman, H.C. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1027.
30. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.