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Synthesis of Cyclic α-Hydrazino Acid Derivatives via *N*-Acylhydrazonium Ions

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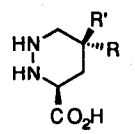
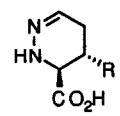
Abstract: The synthesis of various cyclic α-hydrazino esters is described. The key-step involves an intramolecular reaction of a highly reactive *N*-acylhydrazonium ion, leading to a cyclic cationic intermediate which either rearranges via an aziridinium ion, or leads to the unrearranged piperazic ester. A deprotection sequence that furnishes the free α-hydrazino acids is detailed.

INTRODUCTION

Since the first discovery three decades ago,[1] various tetra- and hexahydro-3-pyridazinecarboxylic acids, or piperazic acids (Piz) have been isolated. As constituents of several biologically active peptides such as the cyclic peptides monamycin,[2] L-156,602[3] and luzopeptin A,[4] the acyclic antrimycins,[5] cirratiomycins,[6] azinothricin antitumor antibiotics[7] and the recently discovered antibiotic mathlystatin B,[8] these compounds constitute a novel subclass of cyclic amino acids. Some of the piperazic acids present in these peptides are shown below.



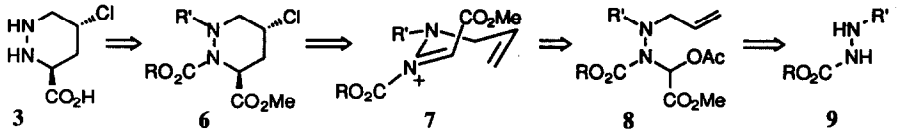
1 R = R' = H
2 R = H, R' = OH
3 R = Cl, R' = H



4 R = H
5 R = OH

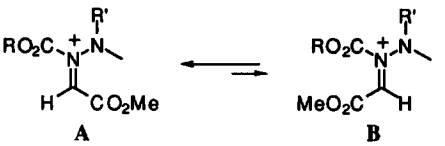
The resemblance of these types of molecules with the corresponding α-amino acids suggests a promising potential as pharmacologically important compounds.[9,10] Recently, several syntheses of cyclic hydrazino acids were reported among which piperazic acid **2** was synthesized via a hetero Diels-Alder reaction of a dienophile with an azo compound.[11] Furthermore, the acids **1**, **4** and **5** were obtained via intramolecular condensations of enantiopure 2-hydrazino-5-oxo-pentanoic esters,[12-15] the latter being prepared by enantioselective α-amination of enolates with an azodicarboxylate.[16]

Herein, we wish to report a novel approach to the synthesis of (racemic) cyclic α-hydrazino acids, which extends our previously reported work on *N*-acylhydrazonium ion cyclizations.[17] For example, a sequence that is expected to lead to the chlorine substituted α-hydrazino acid **3** involves ring closure of **8** via the *N*-acylhydrazonium ion **7** to the protected α-hydrazino acid **6** (eq 1).



(eq 1)

Comparison with well-investigated *N*-acyliminium ion cyclizations[18] leads to the expectation that the cationic intermediate **7** will adopt a chair-like conformation, in which the *N*-acyliminium part has a (*Z*)-geometry. The preference for this geometry can be understood by considering the two possible conformations **A** and **B** of the hydrazonium ion. The (*E*)-isomer **B** is likely to be less stable as a result of *pseudo*-allylic 1,3-strain[19] between the two carbonyl functions, which is absent in the (*Z*)-isomer **A**.

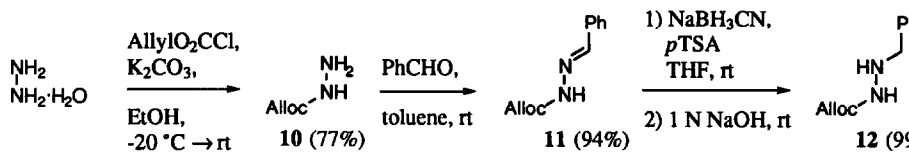


Attack of a nucleophile (*e.g.* chloride) on the intermediate π-complex of the olefin with the iminium ion will result in an overall *trans*-addition to the double bond, leading to the desired *trans*-relationship between the substituents in compound **6**. The free hydrazine **3** might be obtained by deprotection of **6**, in which R and R' are appropriate functional groups. The cyclization precursor **8** will be prepared from the suitably functionalized hydrazine **9** by alkylation with allyl bromide and methyl glyoxylate, respectively.

Moreover, introduction of various nucleophilic side chains will be shown to lead to the synthesis of numerous functionalized cyclic α-hydrazino acids of different ring sizes.

RESULTS AND DISCUSSION

The benzyl and allyloxycarbonyl (Alloc)[20] function were considered to be proper groups to functionalize both nitrogen atoms. In order to obtain the desired starting material **12**, an excess of hydrazine hydrate was treated at -20 °C with allyl chloroformate to give allyl carbazate **10** (eq 2),[21] which was readily purified by distillation. At lower temperatures, the reaction did not proceed whereas at higher temperatures the diacylated product was obtained. Because straightforward alkylation of **10** with benzyl chloride mainly led to dibenzylation of allyl carbazate (**10**), an alternative route was chosen for the synthesis of the monobenzylated carbazate **12**.



(eq 2)

Thus, allyl carbazate (**10**) was condensed with benzaldehyde to give the hydrazone **11**, which was reduced with $NaBH_3CN$ to give **12** as its cyanoborane complex.[22] Hydrolysis of the complex with NaOH afforded the monobenzylated carbazate **12**. Distillation of **12** led to a dramatic decrease of the yield, so that crude **12** (virtually pure according to ^1H NMR data) was used for further reactions.

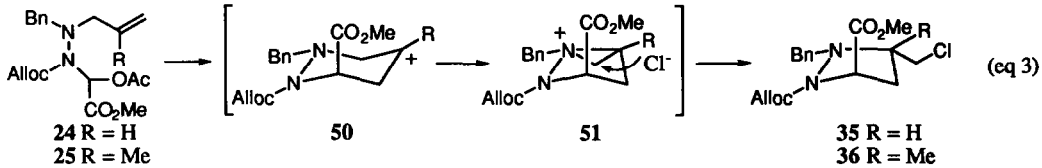
The functionalized hydrazine **12** was alkylated at the nucleophilic benzylic nitrogen atom with various halides as summarized in Table I {halide (1.1 equiv), K_2CO_3 (1.2 equiv), LiI (cat), butanone, acetone or ethanol, reflux}. In general, reasonable to good yields were obtained for the activated halides. The less reactive butenyl bromide gave a lower yield (entry 8). Surprisingly, reaction of **12** with 4-iodo-1-(trimethylsilyl)-2-butyne[23,24] under refluxing conditions led to desilylation of the propargylsilane moiety so that the allene **17** was

formed in a rather low yield (entry 7). At room temperature, however, the desired propargylsilane **21** was formed (entry 12). The (*E*)-vinylsilane **22** (entry 13) was obtained upon alkylation of **12** with (*E*)-3-bromo-1-(trimethylsilyl)-1-propene[25,26] while the 1:1.9 (*E*)/(*Z*) mixture of vinylsilanes **23** (entry 13) was obtained by alkylation of **12** with a 1:2.5 (*E*)/(*Z*)-mixture of 3-bromo-1-(trimethylsilyl)-1-propene.[26-28]

Introduction of the glyoxylate moiety was performed by stirring the alkylation product in the presence of anhydrous methyl glyoxylate.[29] The reaction rate of this condensation with glyoxylate proved to be strongly dependent on the steric bulk of the alkyl group. For example, the allyl precursor **13** (entry 1) reacted within 2 h to give the desired product, while for the benzyl precursor **19** (entry 9) a longer reaction time was required (up to 40 h). Because polymerization of unreacted methyl glyoxylate was a major side reaction, freshly distilled methyl glyoxylate had to be added after 18 h if the reaction was not completed. In some cases, large amounts (ca. 20 equiv) of methyl glyoxylate were used, so that purification by flash chromatography of the intermediate hydroxy compound was necessary. Acetylation (acetic anhydride (5 equiv), DMAP (cat), pyridine, rt) led to the cyclization precursors **24-34** in good yields as shown in Table I.

The cyclization reactions were carried out with the Lewis acids titanium tetrachloride (2 equiv, -78 °C → rt), tin tetrachloride (2 equiv, -78 °C → rt), diethylaluminum chloride (2-4 equiv, -78 °C → rt), and boron trifluoride etherate (2-6 equiv, 0 °C → rt) and the protic acid formic acid (neat). The results are shown in Table I.

Cyclization of the allyl precursor **24** (entry 1) led to the unexpected formation of the five-membered rings **35** with the *trans*-isomer as the main product. These products cannot arise from a 'normal' 5-*exo*-type cyclization, because the chloromethyl substituent would then be at the 4-position. A possible explanation for the formation of **35** is detailed in eq 3. Presumably, cyclization initially gives rise to the formation of the secondary carbocation **50** (R = H), which is then trapped by the relatively nucleophilic N1 atom to give the aziridinium intermediate **51** (R = H). Attack of chloride gives ring opening of the aziridinium moiety, thus leading to the *trans*-azaproline derivative **35**. Similar types of ring contractions via aziridinium intermediates have been described in the literature.[30]



24 R = H
25 R = Me

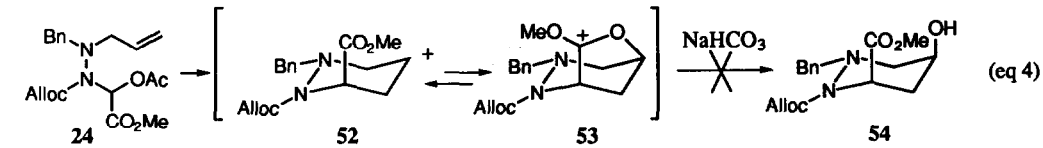
50

51

35 R = H
36 R = Me

(eq 3)

It has been shown that in corresponding *N*-acyliminium cyclizations,[18] the cationic intermediate is already formed at -78 °C and stabilized as a dioxycarbenium ion by the carbamate function (compare **53**, eq 4). Quenching with saturated aqueous sodium bicarbonate at -78 °C then gives the corresponding hydroxy compound. In the case of these hydrazonium ions, such a sequence might block the rearrangement and directly give the precursor **54** for the piperazic acid **2**. However, when the cyclization reaction of **24** was quenched with saturated aqueous sodium bicarbonate at -78 or at -30 °C, only starting material was recovered. Apparently, formation of the *N*-acylhydrazonium ion is more difficult than of its iminium analog. Reaction only took place at -20 °C (according to TLC), but quenching after stirring for 30 min at this temperature afforded a mixture of starting material and the rearranged products **35**. This probably means that as soon as the intermediate cationic six-membered ring **50** (R = H) is formed, stabilization via the aziridinium intermediate **51** (R = H) takes place so that stabilization via the dioxycarbenium ion **53** does not occur.



24

52

53

54

(eq 4)

Table I. Synthesis of cyclic α-hydrazino acid derivatives.

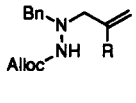
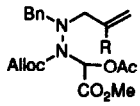
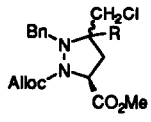
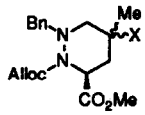
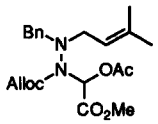
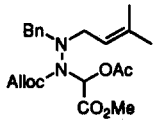
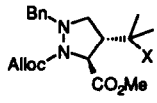
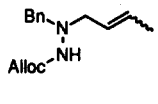
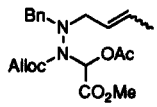
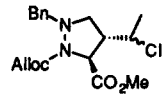
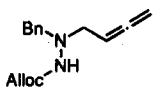
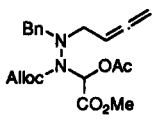
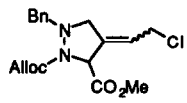
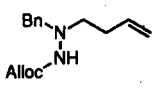
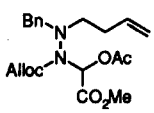
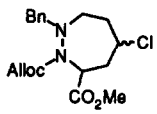
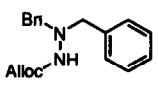
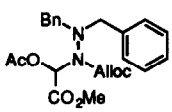
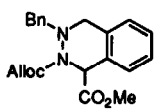
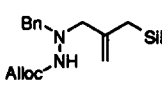
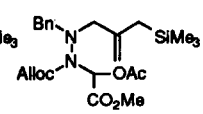
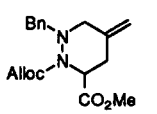
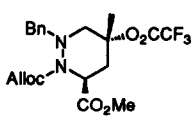
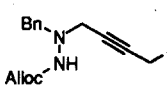
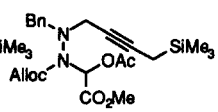
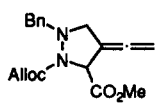
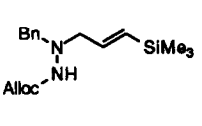
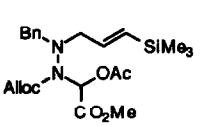
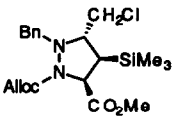
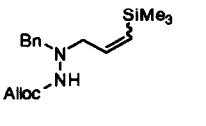
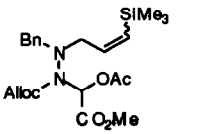
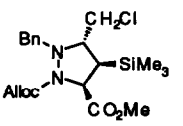
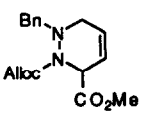
entry	alkylation product (yield)	glyoxylate adduct (yield)	acid	cyclization products (yield)	
					
1	**13** R = H (89%)	**24** R = H (91%)	$SnCl_4$	**35** R = H (75%) *c/tr* 1:5	
2	**14** R = Me (78%)	**25** R = Me (98%)	Et_2AlCl	**36** R = Me (27%) *c/tr* 1:1.8	**37** X = Cl (59%) *c/tr* 1:8.8
3			HCOOH		**38** X = OCHO (68%) *trans*
					
4	**15** (66%)	**26** (57%)	$SnCl_4$	**39** X = Cl (58%)	
5			HCOOH	**40** X = OCHO (66%)	
					
6	**16** (73%) (*E*)/(*Z*) 3.3 :1	**27** (82%)[a]	$SnCl_4$	**41** (56%) 5:1 mixture of isomers	
					
7	**17** (23%)	**28** (83%)	$TiCl_4$	**42** (45%) 1.2:1 mixture of isomers	
					
8	**18** (39%)	**29** (48%)	$SnCl_4$	**43** (65%) 1:1 mixture of isomers	
					
9	**19** (83%)[b]	**30** (99%)	$SnCl_4$	**44** (91%)	
					
10	**20** (58%)	**31** (79%)	Et_2AlCl	**45** (83%)	
11			CF_3COOH		**46** (70%)
					
12	**21** (81%)	**32** (82%)	$BF_3{\cdot}OEt_2$	**47** (30%)	

Table I (continued). Synthesis of cyclic α-hydrazino acid derivatives.

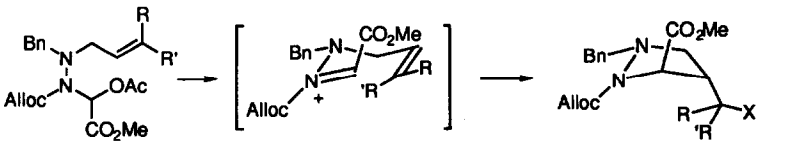
entry	alkylation product (yield)	glyoxylate adduct (yield)	acid	cyclization products (yield)	
					
13	**22** (88%)	**33** (74%)	$SnCl_4$	**48** (68%)	
					
14	**23** (52%) (*E*)/(*Z*) 1:1.9	**34** (79%) (*E*)/(*Z*) 1:1.2	$SnCl_4$	**48** (32%)	**49** (50%)

a) The (*E*)/(*Z*)-ratio could not be determined from the ^{1}H NMR spectrum. b) Yield in one step from allylcarbazate (**10**).

The formation of the *trans*-five-membered ring was confirmed by reduction of the *trans*-cyclization product **35** with tri-*n*-butyltin hydride to give **56** (Chart 1), clearly showing the characteristic doublet of the methyl substituent in the ^{1}H NMR spectrum (0.98 ppm, d, J = 7.1 Hz). The structure was further proven by an X-ray crystallographic analysis of the deprotected product **66** (Fig I). The formation of the *cis*-five-membered ring product **35** was concluded by comparison of the ^{13}C NMR data of the *cis*- and *trans*-isomers of **35**.

An analogous mechanism in the case of the methallyl substituent **25** (entry 2) accounts for the formation of the mixture of the five- and six-membered rings **36** and **37**, respectively. The formation of the five-membered rings **36** was proven by reduction of the mixture with tri-*n*-butyltin hydride to give **57** (Chart I). The relative configuration of *trans*-**36** was secured by NOE difference ^{1}H NMR techniques. Irradiation of the methylene group adjacent to the chlorine atom showed an enhancement of H3, whereas irradiation of the methyl function did not. The more stable tertiary carbocation **50** (R = Me, eq 3) is less prone to be stabilized by the nitrogen atom and thus leads to a considerable amount of the six-membered rings **37**. The stereochemistry of the the *cis*- and *trans*-products was assigned by subjecting *trans*-**37** to NOE difference ^{1}H NMR techniques; irradiation of the methyl function showed an enhancement of the signal of one of the H6 protons and of the broad signal of both H4 protons. The fact that the signal of only one of the H6 protons was enhanced leads to the conclusion that the methyl group is in the axial position. In view of the proposed conformation of the intermediate hydrazonium species, the ester function is expected to be axially oriented. When formic acid was used for the cyclization (entry 3), only the *trans* six-membered ring **38** was found. The tertiary carbocation **50** (R = Me) probably gives a faster reaction with formate as a result of the large excess of the nucleophile so that ring contraction is less likely to occur.

Cyclization of the prenyl precursor **26** (entries 4 and 5) afforded the expected five-membered rings **39** and **40** with a *trans*-relationship between both substituents. Surprisingly, the crotyl precursor **27** (entry 6) also gave only a mixture of the *trans*-five-membered ring products **41**.



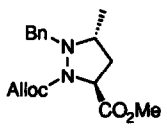
26,27 **55**

39 R = R' = Me, X = Cl
40 R = R' = Me, X = OCHO
41 R = Me, R' = H, X = Cl

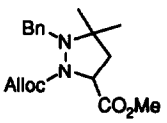
(eq 5)

The *trans*-relationship between the substituents of the products **39**, **40** and **41** is in accordance with the expected chair-like conformation **55** leading to the most favorable transition state (eq 5). The preference for the formation of a five-membered ring in the case of the crotyl precursor **27** is remarkable, because in similar cationic cyclizations six-membered rings are generally obtained. For example, comparable *N*-acyliminium ion precursors led to exclusive formation of six-membered rings.[18b] Reduction of the cyclization product **41** with tri-*n*-butyltin hydride afforded **58**, thus confirming the formation of the five-membered ring. The *trans*-orientation was deduced from NOE difference ^{1}H NMR techniques. Irradiation of the methyl substituent of **41** showed an enhancement of the signal of H3.

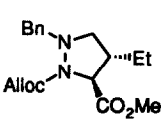
Chart I



56 (65%)

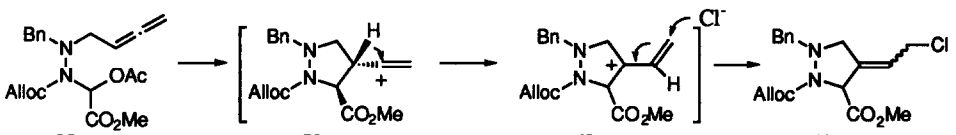


57 (51%)



58 (38%)

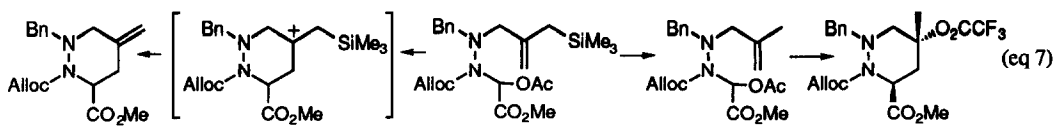
Additional evidence for the preference for the formation of five-membered rings was obtained upon cyclization of the allene precursor **28** (entry 7). Treatment of **28** with titanium tetrachloride afforded the five-membered rings **42** as a mixture of (*E*)/(*Z*)-isomers that could not be separated by flash chromatography. A mechanism that accounts for the formation of **42** is shown in eq 6. Initially, cyclization takes place to afford the vinylic cation **59**. This intermediate rearranges via a 1,2-H shift to the more stable tertiary allylic cation **60**, which is trapped by chloride to afford **42**.



28 **59** **60** **42** (eq 6)

The seven-membered rings **43** were obtained upon cyclization of the butenyl precursor **29** (entry 8). Cyclisation of the dibenzyl precursor **30** took place smoothly to give **44** in excellent yield (entry 9) although cyclisation involving the benzyl function was not observed in any of the other reactions in table I. This is remarkable and might be partly explained by the difference in nucleophilicity with the other substituents, but also by the strong preference for the formation of five-membered rings. Presumably, other systems are likely to adopt a conformation in which the relatively large benzyl function is moved away from the glyoxylate moiety and thus will be less available for cyclization.

Another way to inhibit the ring contraction was observed upon cyclization of the allylsilane **31** (entry 10). Treatment with diethylaluminum chloride initially led to the silicon stabilized carbocation **61** (eq 7) which gave a fast elimination to the exocyclic double bond. An indication that formation of six-membered rings in such systems is a relatively slow process, is seen in entry 11. Treatment of the allylsilane precursor **31** with trifluoroacetic acid afforded **46** as a single product, which is explained by protodesilylation of **31** to the methallyl precursor **25** (not isolated), followed by cyclization to the expected six-membered ring **46** (treatment of **31** with formic acid gave the corresponding formate **38** in 58% yield).

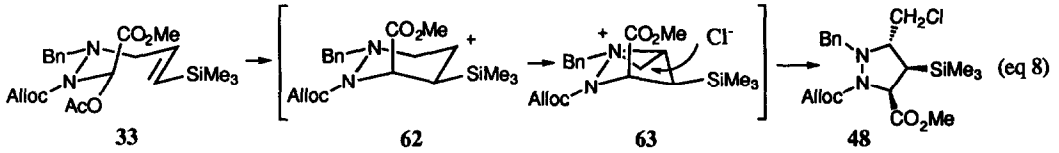


45 **61** **31** **25** **46** (eq 7)

The fact that the cyclization product **45** appeared to be stable in formic acid indicates that the formation of **46** is not simply a result of addition of formic acid to the double bond after cyclization.

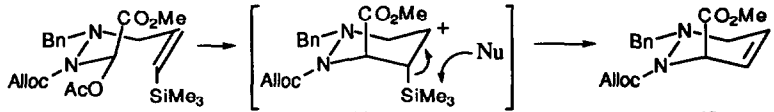
In an analogous way, the propargylsilane **32** (entry 12) was treated with boron trifluoride etherate to give the allene **47** in a rather poor yield.

A striking difference was observed between cyclization of the (*E*)- and (*Z*)-vinylsilanes **33** and **34** (entries 13 and 14). The chair-like transition state conformations of both starting materials are visualized in eqs 8 and 9, respectively. The (*E*)-vinylsilane **33** will react via a chair-like conformation to the cyclic cationic intermediate **62** in which the trimethylsilyl group occupies the equatorial position. Because the β-C-Si bond is not coplanar with the vacant *p*-orbital, stabilization of the positive charge by the silicon atom and subsequent elimination is not likely to take place, thus leading to a ring contraction via the aziridinium intermediate **63**. Attack of chloride affords the final product **48**. The stereochemistry of the product was confirmed by subjecting **48** to NOE difference ^{1}H NMR techniques, showing an enhancement of only H3 upon irradiation of the proton adjacent to the silicon atom.



33 62 63 48 (eq 8)

Cyclization of the (*Z*)-precursor **34** will occur via conformation **64** in which the trimethylsilyl group is axially oriented. In this orientation, maximal σ–π hyperconjugative stabilization of the developing positive charge is possible, followed by fast elimination to the unsaturated six-membered ring **49**, thereby excluding the formation of the aziridinium intermediate. Considering these mechanistic details, starting from the precursor **34**, that was obtained as a 1:1.2 mixture of (*E*)- and (*Z*)-isomers, the corrected yields for **48** and **49** (entry 14) are 70% and 90%, respectively. Comparing the yield of the five-membered ring product **48**, with the yield of **48** from the pure (*E*)-precursor **33** (entry 13), it is evident that the (*Z*)-isomer leads to exclusive formation of the six-membered ring **49**.

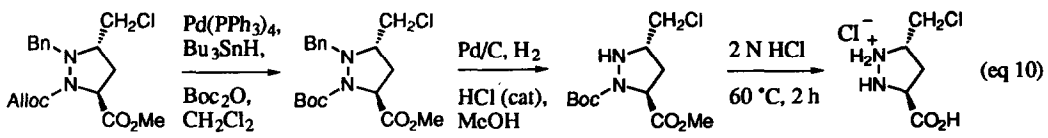


34 64 49 (eq 9)

These observations are in full accord with results published by Overman and co-workers,[31] who reported the (*Z*)-vinylsilane to be at least 7000 times more reactive than its (*E*)-analog in iminium ion cyclizations.

DEPROTECTION REACTIONS

The sequence of deprotection reactions developed for compound **35** is shown in eq 10. First, the Alloc group was converted into the acid-labile Boc group (eq 10) in a one-pot procedure via a so-called transprotection reaction {$Pd(PPh_3)_4$ (cat), Bu_3SnH (1,1 equiv), Boc_2O (2 equiv), CH_2Cl_2, rt}.[20]



35 65 (77%) 66 (90%) 67 (82%) (eq 10)

Hydrogenation of **65** {10% Pd/C, HCl (cat)} led to smooth removal of the benzyl group to give **66**, which was readily hydrolyzed to the HCl-salt **67** of the free α-hydrazino acid.

The structure of the five-membered ring **66**, including the *trans*-relationship between the substituents was secured by an X-ray crystallographic analysis of **66** as depicted in Fig I. Beside the *trans*-relationship, it clearly shows the difference between the almost planar carbamate nitrogen atom (N2) and the pyramidal amine nitrogen atom (N1).

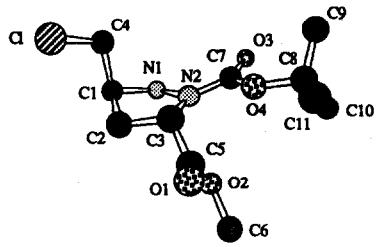
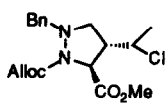
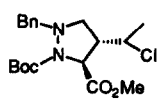
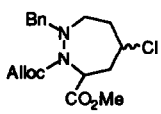
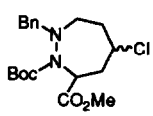
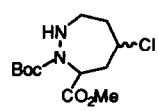
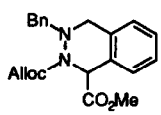
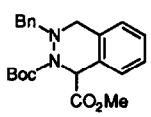
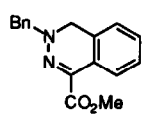
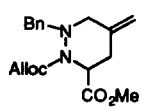
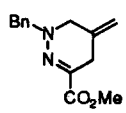
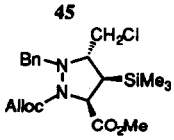
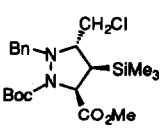
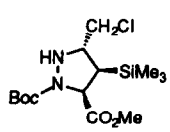


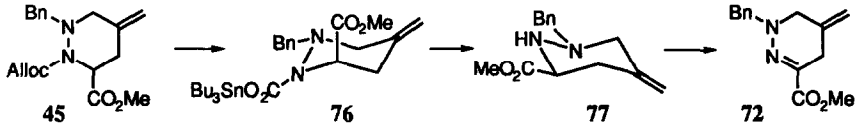
Figure I. Chem3D™ view of the crystal structure of **66** (hydrogens are not shown).

Some of the cyclization products were subjected to these deprotection reactions of which the results are summarized in Table II.

Table II. Deprotection reactions.

entry	cyclization product(s)	transprotection product(s) (yield)		reduction product(s) (yield)
1	 **41**	 **68** (54%)		
2	 **42**	 **69** (64%)		 **74** (65%)
3	 **44**	 **70** (56%)	 **71** (22%)	
4	 **45**		 **72** (78%)	
5	 **48**	 **73** (64%)		 **75** (81%)

The desired transprotected products could not be obtained in all cases. Transprotection of the five-membered rings proceeded in reasonable yields (entries 1 and 5), whereas the six-membered rings **44** and **45** also gave deprotection of the Alloc group to give the corresponding oxidized products **71** and **72** (entries 3 and 4). Apparently, the reaction with di-*tert*-butyl dicarbonate is very sensitive to steric hindrance caused by the benzyl substituent and the methyl ester, which is more pronounced in the six-membered rings. The formation of the oxidized products might be explained by decarboxylation of the initially formed tin carbamate **76**,[32] which will give a ring inversion to the thermodynamically more stable hydrazine **77** (eq 11).[33] Once the ring inversion has taken place, oxidation occurs to give **72**. Attempts to introduce smaller electrophiles like an acetyl function also failed.



(eq 11)

The seven-membered ring **42** (entry 3), however, afforded the transprotected product **69** in a reasonable yield. Probably, the methyl ester causes less steric strain in a larger, more flexible ring.

Analogous to the hydrazino acid derivative **65**, debenzylation of **69** and **73** provided a good yield of the corresponding hydrazines **74** and **75** (entries 2 and 5).

CONCLUSIONS

It is evident that a large variety of cyclic α-hydrazino acid derivatives can be efficiently synthesized via this method. Several conclusions can be drawn from the outcome of the cyclization reactions. The cyclizations show a strong preference for the formation of five-membered rings, particularly illustrated by the crotyl and allene precursor, which both produced the corresponding five- instead of six-membered rings. Furthermore, if a six-membered ring is formed during the cyclization, stabilization of the cationic intermediate by the amine nitrogen atom may take place, leading to a five-membered ring via an aziridinium intermediate. This ring contraction can be inhibited by stabilization of the developing positive charge by a β-silicon substituent, followed by a fast elimination process. A remarkable difference in reactivity is observed between the benzyl group and the non-aromatic π-nucleophiles; cyclization of the benzyl group only takes place if no other nucleophile is present in the molecule. Deprotection is carried out by the transprotection method. This method fails in most six-membered ring cases, probably due to steric hindrance.

ACKNOWLEDGEMENT

K. Goubitz and J. Fraanje (Department of Crystallography, University of Amsterdam) are gratefully acknowledged for the X-ray structure determination. This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

EXPERIMENTAL

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 1310 spectrophotometer and wavelenghts (ν) are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$ (unless indicated otherwise) using 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. Low and high resolution mass spectra were recorded by 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)[34] 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. $BF_3{\cdot}OEt_2$ was distilled and stored under a dry nitrogen atmosphere. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use.

Allyl carbazate (10). To a solution of hydrazine hydrate (128 mL, 2.64 mmol) in EtOH (1.3 L) was added dropwise in 1.5 h allyl chloroformate (70.0 mL, 0.66 mmol) while the temperature inside the flask was kept around -20 °C. The mixture was allowed to warm to rt, stirred at ambient temperature for 1 h and after addition of K_2CO_3 (91.2 g, 0.66 mol), it was stirred for an additional hour. After filtration and concentration *in vacuo*, the residue was distilled to afford **10** (59.2 g, 0.51 mol, 77%) as a colorless oil, bp 82 °C (0.3 mm), R_f 0.35 (ethyl acetate/hexane 1:1). IR ν 3460, 3350, 1710, 1625, 995, 935; ^{1}H NMR (200 MHz) δ 3.66 (br s, 2 H, NH_2), 4.56 (d, J = 5.6 Hz, 2 H, OCH_2), 5.15-5.31 (m, 2 H, $=CH_2$), 5.77-5.97 (m, 1 H, =CH), 6.61 (br s, 1 H, NH).

1-Benzyl-2-hydrazinecarboxylic acid allyl ester (12). To a solution of allyl carbazate (**10**), (10.0 g, 86.2 mmol) in toluene (170 mL) was added benzaldehyde (9.1 mL, 90.5 mmol) and the mixture was stirred at rt for 18 h. Filtration and recrystallization (ethyl acetate/hexane/methanol 5:10:1) afforded the hydrazone **11** (16.5 g, 80.9 mmol, 94%) as white crystals, mp 147-148 °C. IR ν 3400, 3340, 1730, 690; ^{1}H NMR (250 MHz) δ 4.64 (d, J = 5.4 Hz, 2 H, OCH_2), 5.24-5.41 (m, 2 H, $=CH_2$), 5.90-6.06 (m, 1 H, =CH), 7.24 (s, 1 H, ArH), 7.34 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.86 (s, 1 H, NH), 8.01 (s, 1 H, N=CH). A solution of *p*TSA (23.6 g, 124 mmol) in THF (125 mL) was added dropwise in 2.5 h to a solution of the hydrazone **11** (25.3 g, 124 mmol) and $NaBH_3CN$ (9.18 g, 124 mmol) in THF (300 mL) and the mixture was stirred for one additional hour at rt. The resulting mixture was diluted with ethyl acetate (600 mL) and extracted subsequently with aq satd NaCl (600 mL), aq satd $NaHCO_3$ (600 mL) and aq satd NaCl (600 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, taken up in 1 N NaOH (250 mL), stirred at ambient temperature for 1.5 h, neutralized with 2 M HCl and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **12** (25.3 g, 123 mmol, 99%) as a colorless oil, R_f 0.45 (ethyl acetate/hexane 4:1). IR ν 3440, 3340, 1710, 990, 930, 690; ^{1}H NMR (200 MHz) δ 4.00 (s, 2 H, CH_2Ph), 4.25 (br s, 1 H, NH), 4.61 (d, J = 5.5 Hz, 2 H, OCH_2), 5.20-5.35 (m, 2 H, $=CH_2$), 5.82-6.01 (m, 1 H, =CH), 6.44 (br s, 1 H, NH), 7.26-7.36 (m, 5 H, ArH).

General procedure A for the alkylation reactions. To a solution of **12** in 2-butanone, EtOH or acetone were added the alkylating agent (1.1-2 equiv), K_2CO_3 (1.1-2 equiv) and a catalytic amount of LiI. After heating at reflux temperature for 18 h, the mixture was concentrated *in vacuo*, taken up in H_2O 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 alkylated hydrazine.

1-Benzyl-1-(2-propenyl)-2-hydrazinecarboxylic acid allyl ester (13). Following the general procedure A, **12** (3.00 g, 14.6 mmol) was alkylated by using allyl bromide (3.52 g, 29.1 mmol) and K_2CO_3 (2.00 g, 14.6 mmol) in EtOH (100 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **13** (3.20 g, 13.0 mmol, 89%) as a white solid, mp 34-36.5 °C, R_f 0.30. IR ν 3430, 3330, 1720, 690; ^{1}H NMR (200 MHz) δ 3.45 (br s, 2 H, NCH_2), 3.99 (br s, 2 H, CH_2Ph), 4.52 (d, J = 5.4 Hz, 2 H, OCH_2), 5.15-5.28 (m, 4 H, 2 × $=CH_2$), 5.76-6.03 (m, 3 H, 2 × =CH and NH), 7.30-7.35 (m, 5 H, ArH).

1-Benzyl-1-(2-methyl-2-propenyl)-2-hydrazinecarboxylic acid allyl ester (14). According to the general procedure A, **12** (10.0 g, 48.5 mmol) was alkylated by using 3-chloro-2-methyl-2-propene (5.28 mL, 53.4 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in EtOH (250 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **14** (9.81 g, 37.7 mmol, 78%) as a light yellow oil, R_f 0.30. IR ν 3440, 3340, 1720, 695; ^{1}H NMR (200 MHz) δ 1.83 (s, 3 H, CH_3), 3.41 (br s, 2 H, NCH_2), 4.02 (br s, 2 H, CH_2Ph), 4.53 (d, J = 5.2 Hz, 2 H, OCH_2), 4.90 (d, J = 6.6 Hz, 2 H, C=CH_2), 5.16-5.28 (m, 2 H, CH=CH_2), 5.75-5.95 (m, 2 H, =CH and NH), 7.26-7.38 (m, 5 H, ArH).

1-Benzyl-1-(3-methyl-2-butenyl)-2-hydrazinecarboxylic acid allyl ester (15). According to the general procedure A, **12** (7.04 g, 34.2 mmol) was alkylated by using 4-bromo-2-methyl-2-butene (5.60 g, 37.6 mmol) and K_2CO_3 (5.20 g, 37.6 mmol) in EtOH (300 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **15** (2.89 g, 10.5 mmol, 66% (after correction)) as a light yellow oil, R_f 0.40. IR ν 3440, 3340, 1725, 690; ^{1}H NMR (200 MHz) δ 1.63 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 3.45 (br s, 2 H, NCH_2), 3.97 (br s, 2 H, CH_2Ph), 4.52 (d, J = 5.3 Hz, 2 H, OCH_2), 5.14-5.36 (m, 3 H, =CH_2 and NCH_2CH), 5.75-5.95 (m, 2 H, =CH and NH), 7.23-7.34 (m, 5 H, ArH).

1-Benzyl-1-(2-butenyl)-2-hydrazinecarboxylic acid allyl ester (16). According to the general procedure A, **12** (10.0 g, 48.5 mmol) was alkylated by using 4-bromo-2-butene ((*E*)/(*Z*) 3.3:1, 5.28 mL, 53.4 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in EtOH (250 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **16** (9.18 g, 35.3 mmol, 73%) as a light yellow oil, (*E*)/(*Z*) 3.3:1, R_f 0.35. IR ν 3440, 3340, 1720, 690; ^{1}H NMR (200 MHz) δ 1.64 (d, J = 6.4 Hz, 3 H, CH_3 (*Z*)), 1.70 (d, J = 5.0 Hz, 3 H, CH_3(*E*)), 3.38 (br s, 2 H, NCH_2), 3.95 (br s, 2 H, CH_2Ph), 4.52 (d, J = 5.3 Hz, 2 H, OCH_2), 5.14-5.26 (m, 2 H, =CH_2), 5.45-5.92 (m, 4 H, =CH, NH and CH=CH), 7.26-7.32 (m, 5 H, ArH).

1-Benzyl-1-(ethenylidenemethyl)-2-hydrazinecarboxylic acid allyl ester (17). According to the general procedure A, **12** (2.32 g, 11.3 mmol) was alkylated by using 4-iodo-1-(trimethylsilyl)-2-butyne[24] (4.09 g, 12.4 mmol) and K_2CO_3 (1.71 g, 12.4 mmol) in EtOH (100 mL). Work-up and fc (ethyl acetate/hexane 1:5) afforded **17** (670 mg, 2.60 mmol, 23%) as an orange oil, R_f 0.40. IR ν 3440, 3340, 1950, 1725, 690; ^{1}H NMR (200 MHz) δ 3.64 (br s, 2 H, NCH_2), 4.00 (br s, 2 H, CH_2Ph), 4.54 (d, J = 5.5 Hz, 2 H, OCH_2), 4.76 (dt, J = 6.5, 2.3 Hz, 2 H, C=CH_2), 5.16-5.28 (m, 3 H, CH=CH_2 and CH=C=CH_2), 5.77-5.96 (m, 2 H, =CH and NH), 7.27-7.36 (m, 5 H, ArH).

1-Benzyl-1-(3-butenyl)-2-hydrazinecarboxylic acid allyl ester (18). According to the general procedure A, **12** (2.91 g, 14.1 mmol) was alkylated by using 4-bromo-1-butene (2.10 g, 15.5 mmol) and K_2CO_3 (2.15 g, 15.5 mmol) in EtOH (150 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **18** (384 mg, 1.50 mmol, 39% (after correction)) as white crystals, mp 50-51 °C, R_f 0.45. IR ν 3440, 3340, 1740, 690; ^{1}H NMR (200 MHz) δ 2.26-2.34 (m, 2 H, NCH_2CH_2), 2.70-2.95 (br s, 2 H, NCH_2), 3.80-4.15 (m, 2 H, CH_2Ph), 4.55 (d, J = 5.4 Hz, 2 H, OCH_2), 4.98-5.21 (m, 4 H, 2 × =CH_2), 5.55-5.95 (m, 3 H, 2 × =CH and NH), 7.26-7.35 (m, 5 H, ArH).

1,1-Dibenzyl-2-hydrazinecarboxylic acid allyl ester (19). According to the general procedure A, **10** (15.0 g, 130 mmol) was alkylated by using benzyl chloride (29.7 mL, 260 mmol) and K_2CO_3 (36 g, 260 mmol) in EtOH (300 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **19** (31.9 g, 110 mmol, 83%) as a white solid, mp 52-54 °C, R_f 0.45. IR ν 3440, 3340, 1725, 690; ^{1}H NMR (200 MHz) δ 3.96 (br s, 4 H, 2 × CH_2Ph), 4.49 (d, J = 5.5 Hz, 2 H, OCH_2), 5.12-5.19 (m, 2 H, =CH_2), 5.73-5.92 (m, 2 H, =CH and NH), 7.24-7.32 (m, 10 H, ArH); Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.90; H, 6.75; N, 9.54.

1-Benzyl-1-{2-[(trimethylsilyl)methyl]-2-propenyl}-2-hydrazinecarboxylic acid allyl ester (20). According to the general procedure A, **12** (3.42 g, 16.6 mmol) was alkylated by using 2-(chloromethyl)-3-(trimethylsilyl)-1-propene (2.97 g, 18.3 mmol) and K_2CO_3 (2.52 g, 18.3 mmol) in 2-butanone (175 mL).

Work-up and fc (ethyl acetate/hexane 1:4) afforded **20** (3.20 g, 9.60 mmol, 58%) as a colorless oil, R_f 0.55. IR ν 3440, 3340, 1720, 1240, 850, 690; ^{1}H NMR (200 MHz) δ -0.04 (s, 9 H, $(CH_3)_3Si$), 1.69 (s, 2 H, CH_2Si), 3.35 (br s, 2 H, NCH_2), 4.03 (br s, 2 H, CH_2Ph), 4.53 (d, J = 5.2 Hz, 2 H, OCH_2), 4.68 (s, 1 H, C=C*H*H), 4.85 (s, 1 H, C=CH*H*), 5.16-5.28 (m, 2 H, CH=CH_2), 5.75-5.90 (m, 2 H, =CH and NH), 7.24-7.35 (m, 5 H, ArH).

1-Benzyl-1-[4-(trimethylsilyl)-2-butenyl]-2-hydrazinecarboxylic acid allyl ester (21). According to the general procedure A, **12** (1.40 g, 6.80 mmol) was alkylated by using 4-iodo-1-(trimethylsilyl)-2-butyne[24] (1.88 g, 7.50 mmol) and K_2CO_3 (1.03 g, 7.50 mmol) in acetone (50 mL) by stirring at rt for 18 h. Work-up and fc (ethyl acetate/hexane 1:6) afforded **21** (1.82 g, 5.50 mmol, 81%) as a colorless oil, R_f 0.35. IR ν 3440, 3340, 2190, 1730, 1240, 850, 690; ^{1}H NMR (200 MHz) δ 0.16 (s, 9 H, $(CH_3)_3Si$), 1.56 (t, J = 2.4 Hz, 2 H, CH_2Si), 3.60 (t, J = 2.3 Hz, 2 H, NCH_2), 3.90 (s, 2 H, CH_2Ph), 4.54 (dt, J = 5.5, 1.3 Hz, 2 H, OCH_2), 5.15-5.29 (m, 2 H, =CH_2), 5.77 (m, 2 H, =CH and NH), 7.26-7.41 (m, 5 H, ArH).

1-Benzyl-1-[(*E*)-3-(trimethylsilyl)-2-propenyl]-2-hydrazinecarboxylic acid allyl ester (22). According to the general procedure A, **12** (6.23 g, 30.2 mmol) was alkylated by using (*E*)-3-bromo-1-(trimethylsilyl)-1-propene (4.09 g, 21.2 mmol) and K_2CO_3 (4.18 g, 30.2 mmol) in 2-butanone (250 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **22** (5.93 g, 18.6 mmol, 88%) as a colorless oil, R_f 0.50. IR ν 3440, 3340, 1740, 1245, 835, 690; ^{1}H NMR (200 MHz) δ 0.06 (s, 9 H, $(CH_3)_3Si$), 3.48 (br s, 2 H, NCH_2), 3.98 (br s, 2 H, CH_2Ph), 4.52 (d, J = 5.0 Hz, 2 H, OCH_2), 5.15-5.27 (m, 2 H, =CH_2), 5.70-5.91 (m, 2 H, C*H*=CH_2, NH and CHSi), 6.12 (dt, J = 18.6, 5.8 Hz, 1 H, CH_2CH), 7.27-7.35 (m, 5 H, ArH).

1-Benzyl-1-[(*Z*)-3-(trimethylsilyl)-2-propenyl]-2-hydrazinecarboxylic acid allyl ester (23). According to the general procedure A, **12** (3.71 g, 18.0 mmol) was alkylated by using 3-bromo-1-(trimethylsilyl)-1-propene[26] (2.31 g, 12.0 mmol, (*E*)/(*Z*) 1:2.5) and K_2CO_3 (2.65 g, 19.2 mmol) in 2-butanone (130 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **23** (1.97 g, 6.19 mmol, 52%) as a colorless oil, (*E*)/(*Z*) 1:1.9, R_f 0.50. IR ν 3440, 3340, 1740, 1245, 835, 690; ^{1}H NMR (250 MHz) δ 0.07 (s, 9 H, $(CH_3)_3Si$), 3.55 (br s, 2 H, NCH_2), 4.00 (br s, 2 H, CH_2Ph), 4.52 (d, J = 4.8 Hz, 2 H, OCH_2), 5.18-5.28 (m, 2 H, =CH_2), 5.75-5.88 (m, 2 H, C*H*=CH_2, NH and CHSi), 6.41 (dt, J = 14.3, 7.2 Hz, 1 H, CH_2CH), 7.27-7.35 (m, 5 H, ArH).

General procedure B for the reactions with methyl glyoxylate. To a solution of the hydrazine in toluene was added an excess of freshly distilled methyl glyoxylate at rt.[29] After complete reaction (according to TLC), the solution was concentrated *in vacuo*. The residue was taken up in pyridine and treated with an excess of acetic anhydride and a catalytic amount of DMAP. After stirring at rt for 18 h, the dark brown solution was concentrated *in vacuo* and purified by fc to afford the pure product.

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-propenyl)hydrazineacetic acid methyl ester (24). Following the general procedure B, a solution of **13** (3.20 g, 13.0 mmol) in toluene (100 mL) was reacted with methyl glyoxylate (2.29 g, 26.0 mmol) for 4 h and acetylated with Ac_2O (6.15 mL, 65.0 mmol) in pyridine (100 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:5) afforded **24** (4.45 g, 11.8 mmol, 91%) as a colorless oil, R_f 0.45. IR ν 1760, 1740, 1710, 1360, 690; ^{1}H NMR (200 MHz) δ (some signals appear as rotamers) 1.97, 2.00 (s, 3 H, $C(O)CH_3$), 3.50-3.81 (m, 2 H, NCH_2), 3.66, 3.73 (s, 3 H, CO_2CH_3), 4.17-4.25 (m, 2 H, CH_2Ph), 4.68 (br s, 2 H, OCH_2), 4.98-5.34 (m, 4 H, 2 × =CH_2), 5.54-6.03 (m, 2 H, 2 × =CH), 6.55, 6.57 (s, 1 H, NCH), 7.21-7.33 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-methyl-2-propenyl)hydrazineacetic acid methyl ester (25). Following the general procedure B, a solution of **14** (4.00 g, 15.4 mmol) in toluene (150 mL) was reacted with methyl glyoxylate (9.5 g, 0.11 mol) for 18 h and acetylated with Ac_2O (7.3 mL, 0.08 mol) in pyridine (150 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:5) afforded **25** (5.88 g, 15.1 mmol, 98%) as a colorless oil, R_f 0.30. IR ν 1760, 1740, 1720, 690; ^{1}H NMR (250 MHz) δ 1.80 (s, 3 H,

CH_3), 1.91 (s, 3 H, $C(O)CH_3$), 3.41-3.74 (m, 2 H, NCH_2), 3.64 (s, 3 H, CO_2CH_3), 3.95-4.25 (m, 2 H, CH_2Ph), 4.60 (br s, 2 H, OCH_2), 4.80-4.90 (m, 2 H, $C=CH_2$), 5.10-5.45 (m, 2 H, $CH=CH_2$), 5.75-6.05 (m, 1 H, =CH), 6.44 (br s, 1 H, NCH), 7.20-7.33 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-methyl-2-butenyl)hydrazineacetic acid methyl ester (26). According to the general procedure B, a solution of **15** (800 mg, 2.90 mmol) in toluene (30 mL) was reacted with methyl glyoxylate (2.6 g, 29 mmol) for 18 h and acetylated with Ac_2O (2.76 mL, 29 mmol) in pyridine (50 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **26** (670 mg, 1.70 mmol, 57%) as a colorless oil, R_f 0.40. IR ν 1760, 1735, 1715, 690; ^{1}H NMR (250 MHz) δ 1.53-1.73 (m, 6 H, $(CH_3)_2C$), 1.98 (s, 3 H, $C(O)CH_3$), 3.40-3.75 (m, 5 H, NCH_2 and CO_2CH_3), 4.10-4.25 (m, 2 H, CH_2Ph), 4.60-4.80 (m, 2 H, OCH_2), 5.15-5.45 (m, 3 H, CH_2 and C=CH), 5.75-6.05 (m, 1 H, $CH_2=CH$), 6.51 (s, 1 H, NCH), 7.19-7.34 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-butenyl)hydrazineacetic acid methyl ester (27). Following the general procedure B, a solution of **16** (3.00 g, 11.5 mmol) in toluene (120 mL) was reacted with methyl glyoxylate (7.1 g, 80 mmol) for 4 h and acetylated with Ac_2O (7.5 mL, 80 mmol) in pyridine (125 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **27** (3.70 g, 9.5 mmol, 82%) as a colorless oil, R_f 0.30. IR ν 1760, 1710, 690; ^{1}H NMR (300 MHz) δ (some signals appear as rotamers) 1.58, 1.64 (m, 3 H, CH_3), 2.01, 2.05 (s, 3 H, $C(O)CH_3$), 3.50-3.73 (m, 2 H, NCH_2), 3.66, 3.74 (s, 3 H, CO_2CH_3), 4.10-4.25 (m, 2 H, CH_2Ph), 4.60-4.75 (m, 2 H, OCH_2), 5.23-5.35 (m, 2 H, $=CH_2$), 5.48-5.57 (m, 2 H, CH=CH), 5.80-6.10 (m, 1 H, $CH_2=CH$), 6.54 (s, 1 H, NCH), 7.22-7.33 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(ethenylidenemethyl)hydrazineacetic acid methyl ester (28). Following the general procedure B, a solution of **17** (530 mg, 2.10 mmol) in toluene (25 mL) was reacted with methyl glyoxylate (720 mg, 8.2 mmol) for 4 h and acetylated with Ac_2O (0.97 mL, 10.3 mmol) in pyridine (25 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:6) afforded **28** (660 mg, 1.70 mmol, 83%) as a yellow oil, R_f 0.40. ^{1}H NMR δ (some signals appear as rotamers) 2.01 (s, 3 H, $C(O)CH_3$), 3.48-3.91 (m, 2 H, NCH_2), 3.68, 3.74 (s, 3 H, CO_2CH_3), 4.05-4.40 (m, 2 H, CH_2Ph), 4.55-4.95 (m, 4 H, OCH_2 and $C=CH_2$), 5.10-5.50 (m, 3 H, $CH=CH_2$ and C=CH), 5.75-6.10 (m, 1 H, $CH_2=CH$), 6.57, 6.60 (s, 1 H, NCH), 7.26-7.34 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-butenyl)hydrazineacetic acid methyl ester (29). Following the general procedure B, a solution of **18** (384 mg, 1.48 mmol) in toluene (15 mL) was reacted with methyl glyoxylate (650 mg, 7.4 mmol) for 5 h and acetylated with Ac_2O (0.70 mL, 7.38 mmol) in pyridine (15 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **29** (279 mg, 0.72 mmol, 48%) as a colorless oil, R_f 0.45. IR ν 1765, 1740, 1715, 690; ^{1}H NMR (200 MHz) δ (some signals appear as rotamers) 2.03, 2.06 (s, 3 H, $C(O)CH_3$), 2.25-2.35 (m, 2 H, NCH_2CH_2), 2.75-3.35 (m, 2 H, NCH_2), 3.70, 3.73 (s, 3 H, CO_2CH_3), 4.10-4.30 (m, 2 H, CH_2Ph), 4.68 (br s, 2 H, OCH_2), 4.88-5.03 (m, 2 H, $=CH_2$), 5.20-5.45 (m, 2 H, $=CH_2$), 5.50-6.00 (m, 2 H, 2 × =CH), 6.54 (s, 1 H, NCH), 7.22-7.40 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2,2-dibenzylhydrazineacetic acid methyl ester (30). According to the general procedure B, a solution of **19** (10.0 g, 33.8 mmol) in toluene (200 mL) was reacted with methyl glyoxylate (5.95 g, 68 mmol) for 40 h and acetylated with Ac_2O (16.0 mL, 169 mmol) in pyridine (200 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **30** (14.3 g, 33.6 mmol, 99%) as a colorless oil, R_f 0.30. IR ν 1760, 1735, 1715, 1220, 690; ^{1}H NMR (200 MHz) δ 1.77 (br s, 3 H, $C(O)CH_3$), 3.57 (s, 3 H, CO_2CH_3), 4.10-4.41 (m, 4 H, 2 × CH_2Ph), 4.69 (br s, 2 H, OCH_2), 5.15-5.40 (m, 2 H, $=CH_2$), 5.60-6.10 (m, 1 H, =CH), 6.42 (s, 1 H, NCH), 7.21-7.37 (m, 10 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-{2-[(trimethylsilyl)methyl]-2-propenyl}hydrazineacetic acid methyl ester (31). Following the general procedure B, a solution of **20** (1.00 g, 3.01 mmol) in toluene (30 mL) was reacted with methyl glyoxylate (2.65 g, 30.1 mmol) for 18 h (2 ×)

and acetylated with Ac_2O (1.42 mL, 15.1 mmol) in pyridine (30 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **31** (1.10 g, 2.38 mmol, 79%) as a colorless oil, R_f 0.50. IR ν 1760, 1735, 1715, 1240, 850, 690; ^{1}H NMR (200 MHz) δ (some signals appear as rotamers) -0.10, -0.09 (s, 9 H, $(CH_3)_3Si$), 1.43, 1.63 (s, 2 H, CH_2Si), 1.91 (s, 3 H, $C(O)CH_3$), 3.25-3.70 (m, 2 H, NCH_2), 3.66 (s, 3 H, CO_2CH_3), 3.85-4.35 (m, 2 H, CH_2Ph), 4.50-4.75 (m, 3 H, OCH_2 and C=C*H*H), 4.88 (s, 1 H, C=CH*H*), 5.15-5.50 (m, 2 H, CH=CH_2), 5.75-6.10 (m, 1 H, =CH), 6.42 (s, 1 H, NCH), 7.22-7.34 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[4-(trimethylsilyl)-2-butynyl]hydrazineacetic acid methyl ester (32). According to the general procedure B, a solution of **21** (150 mg, 0.45 mmol) in toluene (5 mL) was reacted with methyl glyoxylate (9.5 g, 0.11 mol) for 4 h at 80 °C and acetylated with Ac_2O (220 μL, 2.27 mmol) in pyridine (5 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:6) afforded **32** (170 mg, 0.37 mmol, 82%) as a light yellow oil, R_f 0.35. IR ν 2210, 1765, 1735, 1715, 1245, 845, 690; ^{1}H NMR δ (some signals appear as rotamers) 0.08, 0.09 (s, 9 H, $(CH_3)_3Si$), 1.40-1.55 (m, 2 H, CH_2Si), 1.75-2.00 (m, 3 H, $C(O)CH_3$), 3.55-3.95 (m, 5 H, NCH_2 and CO_2CH_3), 4.24 (br s, 2 H, CH_2Ph), 4.66 (m, 2 H, OCH_2), 5.15-5.36 (m, 2 H, $=CH_2$), 5.82-5.96 (m, 1 H, =CH), 6.50 (s, 1 H, NCH), 7.26-7.37 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[(*E*)-3-(trimethylsilyl)-2-propenyl)hydrazineacetic acid methyl ester (33). Following the general procedure B, a solution of **22** (5.93 g, 18.6 mmol) in toluene (200 mL) was reacted with methyl glyoxylate (13.1 g, 150 mmol) for 42 h and acetylated with Ac_2O (17.6 mL, 0.19 mol) in pyridine (200 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:3) afforded **33** (6.20 g, 13.8 mmol, 74%) as a light yellow oil, R_f 0.50. IR ν 1765, 1700, 1240, 840, 690; ^{1}H NMR (200 MHz) δ (some signals appear as rotamers) -0.06, 0.00 (s, 9 H, $(CH_3)_3Si$), 2.00, 2.05 (s, 3 H, $C(O)CH_3$), 3.68 (br s, 2 H, NCH_2), 3.75 (s, 3 H, CO_2CH_3), 4.05-4.25 (m, 2 H, CH_2Ph), 4.55-4.80 (m, 2 H, OCH_2), 5.15-5.50 (m, 2 H, $=CH_2$), 5.68-5.77 (m, 2 H, CH=CH), 5.80-6.15 (m, 1 H, CH_2=C*H*), 6.50, 6.60 (s, 1 H, NCH), 7.24-7.32 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[(*Z*)-3-(trimethylsilyl)-2-propenyl)hydrazineacetic acid methyl ester (34). Following the general procedure B, a solution of **23** (1.95 g, 6.13 mmol) in toluene (60 mL) was reacted with methyl glyoxylate (2.70 g, 30.7 mmol) for 42 h and acetylated with Ac_2O (5.8 mL, 61 mmol) in pyridine (60 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **34** (2.17 g, 4.84 mmol, 79%) as a light yellow oil, (*E*)/(*Z*) 1:1.2, R_f 0.50. IR ν 1760, 1740, 1720, 1240, 835, 690; ^{1}H NMR (250 MHz) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.94 (s, 3 H, $C(O)CH_3$), 3.64 (br s, 2 H, NCH_2), 3.70 (s, 3 H, CO_2CH_3), 4.05-4.22 (m, 2 H, CH_2Ph), 4.65-4.75 (m, 2 H, OCH_2), 5.15-5.35 (m, 2 H, $=CH_2$), 5.40-6.00 (m, 2 H, CHSi and =CH), 6.42 (dt, J = 14.3, 7.2 Hz, 1 H, CH_2C*H*), 6.63 (s, 1 H, NCH), 7.22-7.32 (m, 5 H, ArH).

General procedure C for the cyclization reactions with Lewis acids. To a 0.1 M solution of the hydrazide in CH_2Cl_2 was added $TiCl_4$, $SnCl_4$ (2 equiv of a solution in CH_2Cl_2) or Et_2AlCl (2 equiv of a 1.0 M solution in toluene) 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).

***rel*-(3*S*,5*S*)-2-(Allyloxycarbonyl)-1-benzyl-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (*trans*-35).** According to the general procedure C, a solution of **24** (500 mg, 1.33 mmol) in CH_2Cl_2 (13 mL) was cyclized by using $SnCl_4$ (1.33 mL of a 2.0 M solution, 2.66 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **35** (352 mg, 1.00 mmol, 75%) as a colorless oil, *c/tr* 1:5, R_f 0.25. ***trans*-35**: IR ν 1740, 1680, 1375, 690; ^{1}H NMR δ 2.46-2.72 (m, 2 H, 2 × H4), 3.11 (dd, J = 8.8, 10.6 Hz, 1 H, C*H*HCl), 3.31-3.44 (m, 2 H, CH*H*Cl and H5), 3.80 (d, J = 12.6 Hz, 1 H, C*H*HPh), 3.81 (s, 3 H, CO_2CH_3),

4.24 (d, J = 12.6 Hz, 1 H, CH*H*Ph), 4.50-4.60 (m, 2 H, OCH_2), 4.67 (t, J = 8.8 Hz, 1 H, H3), 5.17-5.35 (m, 2 H, $=CH_2$), 5.79-5.97 (m, 1 H, =CH), 7.27-7.47 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 31.9 (C4), 45.0 (CH_2Cl), 52.6 (CO_2CH_3), 59.4 (C3), 62.1 (CH_2Ph), 64.1 (C5), 66.4 (OCH_2), 117.5 ($=CH_2$), 127.7, 128.4, 129.4 (ArH), 132.5 (=CH), 137.0 (ArC), 172.6 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 352 (M^+, 90), 267 (55), 217 (52), 91 (100); HRMS calcd for $C_{17}H_{21}N_2O_4$ 354.1160, found 354.1171. ***cis*-35**: ^{13}C NMR (50 MHz) δ 31.3 (C4), 44.5 (CH_2Cl), 52.4 (CO_2CH_3), 58.6 (C3), 60.6 (CH_2Ph), 64.0 (C5), 66.4 (OCH_2), 117.7 ($=CH_2$), 127.8, 128.4, 129.4 (ArH), 132.4 (=CH), 136.2 (ArC), 171.6 (C(O)).

Cyclization of 25 with Et_2AlCl. Following the general procedure C, a solution of **25** (982 mg, 2.52 mmol) in CH_2Cl_2 (25 mL) was treated with Et_2AlCl (7.55 mL of a 1.0 M solution in toluene, 7.55 mmol). Work-up and fc (ethyl acetate/hexane 1:5) afforded ***rel*-(3*S*,5*S*)-2-(allyloxycarbonyl)-1-benzyl-5-chloro-5-methylhexahydro-3-pyridazinecarboxylic acid methyl ester (*trans*-37)** (488 mg, 1.33 mmol, 53%) as a colorless oil, ***rel*-(3*S*,5*S*)-2-(allyloxycarbonyl)-1-benzyl-5-(chloromethyl)-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (*trans*-36)** (178 mg, 0.49 mmol, 19%) as an inseparable mixture with ***cis*-37** (59 mg, 0.16 mmol, 6%) and ***cis*-36** (76 mg, 0.21 mmol, 8%) as a colorless oil, R_f 0.20. ***trans*-37**: IR ν 1735, 1700, 690; ^{1}H NMR (200 MHz) δ 1.51 (s, 3 H, CH_3), 2.35 (br s, 2 H, H4), 2.86 (d, J = 13.5 Hz, 1 H, H6), 3.20 (d, J = 13.5 Hz, 1 H, H6), 3.76 (s, 3 H, CO_2CH_3), 4.30 (d, J = 14.0 Hz, 1 H, C*H*HPh), 4.41 (d, J = 14.0 Hz, 1 H, CH*H*Ph), 4.63-4.65 (m, 2 H, OCH_2), 4.70-4.90 (m, 1 H, H3), 5.22-5.36 (m, 2 H, $=CH_2$), 5.68-6.05 (m, 1 H, =CH), 7.26-7.40 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 30.6 (CH_3), 40.0 (C4), 52.3 (CO_2CH_3), 52.5 (C3), 60.2 (CH_2Ph), 66.8 (OCH_2), 118.3 ($=CH_2$), 127.8, 128.2, 129.2 (ArH), 132.2 (=CH), 137.7 (ArC); MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 6), 331 (14), 281 (8), 231 (5), 160 (41), 91 (100); HRMS calcd for $C_{18}H_{23}N_2O_4Cl$ 366.1346, found 366.1318. ***cis*-37**: ^{1}H NMR (300 MHz) δ 1.30 (s, 3 H, CH_3), 2.06 (dd, J = 14.6, 7.2 Hz, 1 H, H4), 2.86-2.88 (m, 2 H, H4 and H6), 3.02 (d, J = 14.7 Hz, 1 H, H6), 3.82 (s, 3 H, CO_2CH_3), 4.01 (d, J =13.0 Hz, 1 H, C*H*HPh), 4.10 (d, J = 13.0 Hz, 1 H, CH*H*Ph), 4.15-4.90 (m, 3 H, OCH_2 and H3), 4.95-5.40 (m, 2 H, $=CH_2$), 5.92-6.03 (m, 1 H, =CH), 7.20-7.52 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 30.8 (CH_3), 40.0 (C4), 52.3 (CO_2CH_3), 57.9 (CH_2Ph), 59.6 (C6), 59.7 (C3), 63.0 (C5), 67.0 (OCH_2), 117.6 ($=CH_2$), 127.2, 128.2, 129.6 (ArH), 132.5 (=CH), 138.1 (ArC), 172.6 (C(O)). ***trans*-36**: IR ν 1745, 1685, 690; ^{1}H NMR (200 MHz) δ 1.43 (s, 3 H, CH_3), 2.19 (dd, J = 13.2 Hz, 10.6 Hz, 1 H, H4), 2.88 (dd, J = 13.2, 8.9 Hz, 1 H, H4), 3.18 (d, J = 11.3 Hz, 1 H, C*H*HCl), 3.37 (d, J = 11.3, 1 H, CH*H*Cl), 3.82 (s, 3 H, CO_2CH_3), 4.00 (d, J = 13.2 Hz, 1 H, C*H*HPh), 4.11 (d, J = 13.2 Hz, 1 H, NCH*H*Ph), 4.41-4.55 (m, 3 H, H3 and OCH_2), 5.10-5.23 (m, 2 H, $=CH_2$), 5.55-5.80 (m, 1 H, =CH), 7.22-7.53 (m, 5 H, ArH); ^{13}C NMR (63 MHz) δ 19.7 (CH_3), 37.1 (C4), 49.2 (CH_2Cl), 52.5 (CO_2CH_3), 58.1 (CH_2Ph), 59.6 (C3), 66.4 (C9), 69.3 (C5), 118.2 ($=CH_2$), 127.0, 128.0, 129.4 (ArH), 132.3 (=CH), 138.0 (ArC), 172.6 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 45), 331 (31), 317 (14), 281 (18), 231 (31), 91 (100); HRMS calcd for $C_{18}H_{23}N_2O_4Cl$ 366.1346, found 366.1381. ***cis*-36**: IR ν 1745, 1685, 690; ^{1}H NMR (200 MHz) δ 1.27 (s, 3 H, CH_3), 2.37-2.43 (m, 2 H, 2 × H4), 3.51 (d, J = 11.2 Hz, 1 H, C*H*HCl), 3.76 (d, J = 11.2 Hz, 1 H, CH*H*Cl), 3.79 (s, 3 H, CO_2CH_3), 3.96 (s, 2 H, CH_2Ph), 4.25-4.45 (m, 2 H, OCH_2), 4.50-4.70 (m, 1 H, H3), 5.09-5.21 (m, 2 H, $=CH_2$), 5.55-5.80 (m, 1 H, =CH), 7.24-7.49 (m, 5 H, ArH); ^{1}H NMR (250 MHz, 50 °C) δ 1.25 (s, 3 H, CH_3), 2.30-2.44 (m, 2 H, 2 × H4), 3.47 (d, J = 11.3 Hz, 1 H, C*H*HCl), 3.73 (d, J = 11.3 Hz, 1 H, CH*H*Cl), 3.78 (s, 3 H, CO_2CH_3), 3.97 (s, 2 H, CH_2Ph), 4.25-4.45 (m, 2 H, OCH_2), 4.57 (dd, J = 9.1, 7.7 Hz, 1 H, H3), 5.08-5.20 (m, 2 H, $=CH_2$), 5.60-5.80 (m, 1 H, =CH), 7.18-7.47 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 22.3 (CH_3), 38.4 (C4), 48.8 (CH_2Cl), 52.5 (CO_2CH_3), 56.9 (CH_2Ph), 59.5 (C3), 66.3 (OCH_2), 68.4 (C5), 117.4 ($=CH_2$), 127.2, 128.0, 129.6 (ArH), 132.4 (=CH), 137.3 (ArC), 173.1 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 68), 331 (10), 317 (20), 307 (6), 281 (35), 255 (9), 231 (59), 91 (100); HRMS calcd for $C_{18}H_{23}N_2O_4Cl$ 366.1346, found 366.1387.

***rel*-(3*S*,5*S*)-2-(Allyloxycarbonyl)-1-benzyl-5-formyloxy-5-methylhexahydro-3-pyridazinecarboxylic acid methyl ester (38).** A solution of **25** (565 mg, 1.45 mmol) in HCOOH (15 mL) was stirred for 18 h at rt. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **38** (369 mg,

0.98 mmol, 68%) as a colorless oil, R_f 0.30. IR ν 1740, 1700, 690; ^{1}H NMR (200 MHz) δ 1.51 (s, 3 H, CH_3), 2.20-2.40 (m, 1 H, H4), 2.40-2.60 (m, 1 H, H4), 2.87 (d, J = 13.7 Hz, 1 H, H6), 3.38 (d, J = 13.7 Hz, 1 H, H6), 3.74 (s, 3 H, CO_2CH_3), 4.20 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.27 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.64 (d, J = 5.5 Hz, 2 H, OCH_2 and br s, 1 H, H3), 5.22-5.36 (m, 2 H, $=CH_2$), 5.80-6.05 (m, 1 H, =CH), 7.22-7.33 (m, 5 H, ArH), 7.91 (s, 1 H, CHO); ^{13}C NMR (50 MHz) δ 24.4 (CH_3), 34.9 (C4), 52.2 (CO_2CH_3), 54.5 (C3), 56.7 (CH_2Ph), 61.0 (C6), 66.6 (OCH_2), 79.4 (C5), 118.1 ($=CH_2$), 127.3, 128.1, 128.9 (ArH), 132.2 (=CH), 137.6 (ArC), 157.0, 159.7, 172.0 (3 × C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 376 (M^+, 43), 331 (14), 317 (7), 259 (13), 245 (26), 91 (100); HRMS calcd for $C_{19}H_{24}N_2O_6Cl$ 376.1634, found 376.1609.

***rel*-(3*S*,4*S*)-2-(Allyloxycarbonyl)-1-benzyl-4-(1-chloromethylethyl)-3-pyrazolidinecarboxylic acid methyl ester (39).** Following the general procedure C, a solution of **26** (140 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) was treated with $SnCl_4$ (0.58 mL of a 1.2 M solution, 0.70 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **39** (76 mg, 0.20 mmol, 58%) as a colorless oil, R_f 0.25. IR ν 1735, 1690, 690; ^{1}H NMR (200 MHz) δ 1.54 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 3.13-3.28 (m, 3 H, H4 and 2 × H5), 3.81 (d, J = 12.5 Hz, 1 H, C*H*HPh), 3.82 (s, 3 H, CO_2CH_3), 4.17 (d, J = 12.5 Hz, 1 H, CH*H*Ph), 4.56 (d, J = 5.3 Hz, 2 H, OCH_2), 4.70 (d, J = 6.2 Hz, 1 H, H3), 5.15-5.31 (m, 2 H, $=CH_2$), 5.70-5.95 (m, 1 H, =CH), 7.26-7.44 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 31.5, 31.9 (2 × CH_3), 52.7 (CO_2CH_3), 54.9 (C5), 55.8 (C4), 61.9 (CH_2Ph), 62.6 (C3), 66.5 (OCH_2), 69.4 (CCl), 117.6 ($=CH_2$), 127.5, 128.2, 129.4 (ArH), 132.3 (=CH), 137.2 (ArC), 173.4 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 380 (M^+, 67), 344 (36), 295 (44), 245 (51), 91 (100); HRMS calcd for $C_{19}H_{25}N_2O_4Cl$ 380.1503, found 380.1548.

***rel*-(3*S*,4*S*)-2-(allyloxycarbonyl)-1-benzyl-4-[1-(formyloxy)-1-methylethyl)-3-pyrazolidinecarboxylic acid methyl ester (40).** A solution of **26** (173 mg, 0.43 mmol) in HCOOH (5 mL) was stirred at rt for 18 h. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **40** (110 mg, 0.28 mmol, 66%) as a colorless oil, R_f 0.25. IR ν 1735, 1715, 1690, 690; ^{1}H NMR (200 MHz) δ 1.53 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 3.06 (d, J = 8.7 Hz, 2 H, 2 × H5), 3.26-3.39 (m, 1 H, H4), 3.81 (s, 3 H, CO_2CH_3), 3.82 (d, J = 12.3 Hz, 1 H, C*H*HPh), 4.20 (d, J = 12.3 Hz, 1 H, CH*H*Ph), 4.56 (d, J = 5.5 Hz, 2 H, OCH_2), 4.62 (d, J = 7.4 Hz, 1 H, H3), 5.16-5.32 (m, 2 H, $=CH_2$), 5.75-5.95 (m, 1 H, =CH), 7.27-7.43 (m, 5 H, ArH), 7.93 (s, 1 H, OCHO); ^{13}C NMR (50 MHz) δ 24.2, 25.0 (2 × CH_3), 52.6 (CO_2CH_3), 53.3 (C5), 53.7 (C4), 61.3 (C3), 61.7 (CH_2Ph), 66.5 (OCH_2), 81.6 (CO), 117.7 ($=CH_2$), 127.4, 128.2, 129.4 (ArH), 132.3 (=CH), 137.1 (ArC), 159.8, 173.2 (2 × C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 390 (M^+, 34), 345 (6), 227 (20), 91 (100); HRMS calcd for $C_{20}H_{26}N_2O_6$ 390.1791, found 390.1749.

***rel*-(3*S*,4*S*)-2-(Allyloxycarbonyl)-1-benzyl-4-(1-chloroethyl)-3-pyrazolidinecarboxylic acid methyl ester (41).** According to the general procedure C, a solution of **27** (513 mg, 1.32 mmol) in CH_2Cl_2 (15 mL) was treated with $SnCl_4$ (2.19 mL of a 1.2 M solution, 2.63 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **41** (267 mg, 0.73 mmol, 56%) as a colorless oil, 1:5 mixture of isomers, R_f 0.30. IR ν 1740, 1690, 690; ^{1}H NMR (250 MHz) δ (mixture) 1.57 (d, J = 6.4 Hz, 3 H, CH_3), 3.05-3.17 (m, 3 H, H4 and 2 × H5), 3.72-3.82 (m, 1 H, C*H*HPh), 3.80 (s, 3 H, CO_2CH_3), 4.16 (d, J = 12.4 Hz, 1 H, CH*H*Ph), 4.24-4.28 (m, 1 H, H3), 4.46-4.53 (m, 3 H, CHCl and OCH_2), 5.13-5.27 (m, 2 H, $=CH_2$), 5.72-5.90 (m, 1 H, =CH), 7.24-7.43 (m, 5 H, ArH); ^{1}H NMR (250 MHz, 50 °C) δ 1.56 (d, J = 6.7 Hz, 3 H, CH_3), 3.05-3.18 (m, 3 H, H4 and 2 × H5), 3.76 (d, J = 12.3 Hz, 1 H, C*H*HPh), 3.81 (s, 3 H, CO_2CH_3), 4.19 (d, J = 12.5 Hz, 1 H, CH*H*Ph), 4.25-4.27 (m, 1 H, H3), 4.48-4.50 (m, 1 H, CHCl), 4.55 (d, J = 5.5 Hz, 2 H, OCH_2), 5.14-5.29 (m, 2 H, $=CH_2$), 5.72-5.95 (m, 1 H, =CH), 7.22-7.43 (m, 5 H, ArH); ^{13}C NMR (63 MHz) δ (mixture) 23.5, 24.1 (CH_3), 51.5, 51.8 (C4), 52.5, 52.7 (CO_2CH_3), 54.6, 55.3 (C5), 57.5, 56.8 (CHCl), 61.7, 62.0 (CH_2Ph), 63.2, 63.0 (C3), 66.6, 66.7 (OCH_2), 117.7, 118.3 ($=CH_2$), 127.5, 127.7, 128.3, 128.4, 129.5, 129.8 (ArH), 132.2, 132.3 (=CH), 137.1, 137.2 (ArC), 154.2, 154.3, 172.4, 172.5 (2 × C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 38), 330 (6), 281 (21), 231 (24), 91 (100); HRMS calcd for $C_{18}H_{23}N_2O_4Cl$ 366.1346, found 366.1369.

2-(Allyloxycarbonyl)-1-benzyl-4-[(chloromethyl)methylene]-3-pyrazolidinecarboxylic acid methyl ester (42). According to the general procedure C, a solution of **28** (660 mg, 1.70 mmol) in CH_2Cl_2 (17 mL) was treated with $TiCl_4$ (2.84 mL of a 1.2 M solution, 3.40 mmol). Work-up and fc (ethyl acetate/hexane 1:6) afforded **42** (280 mg, 0.77 mmol, 45%) as a yellowish oil, 1.2:1 mixture of two isomers, R_f 0.40. IR ν 1740, 1700, 690; ^{1}H NMR (200 MHz) δ (one isomer) 2.61-2.75 (m, 1 H, C*H*HCl), 3.31 (dd, *J* = 6.4, 3.1 Hz, 1 H, CH*H*Cl), 3.55-4.00 (m, 2 H, 2 × H5), 3.71 (s, 3 H, CO_2CH_3), 4.35 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 4.47 (d, *J* = 13.4 Hz, 1 H, CH*H*Ph), 4.65 (m, 2 H, OCH_2), 4.90 (dd, *J* = 12.2, 5.4 Hz, 1 H, C=CH), 5.21-5.45 (m, 2 H, $=CH_2$), 5.56-5.60 (br s, 1 H, H3), 5.83-6.10 (m, 1 H, CH_2=C*H*), 7.26-7.41 (m, 5 H, ArH); (other isomer) 2.61-2.75 (m, 1 H, C*H*HCl), 3.25 (dd, *J* = 6.5, 3.1 Hz, 1 H, CH*H*Cl), 3.55-4.00 (m, 2 H, 2 × H5), 3.71 (s, 3 H, CO_2CH_3), 4.11 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 4.46 (d, *J* = 13.4 Hz, 1 H, CH*H*Ph), 4.77 (d, *J* = 5.7 Hz, 2 H, OCH_2), 5.05 (dd, *J* = 12.6, 5.4 Hz, 1 H, C=CH), 5.21-5.45 (m, 2 H, $=CH_2$), 5.56-5.60 (br s, 1 H, H3), 5.83-6.10 (m, 1 H, CH_2=C*H*), 7.26-7.41 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ (mixture) 36.5, 36.6 (CH_2Cl), 51.2, 51.8 (C5), 52.4, 52.5 (CO_2CH_3), 59.9, 60.9 (CH_2Ph), 60.8, 61.1 (C3), 66.1, 66.9 (OCH_2), 117.3, 118.5 ($=CH_2$), 124.9, 125.7 (C=*C*H), 127.0, 127.3 (C4), 127.5, 128.4, 128.9 (ArH), 132.3, 132.4 (CH_2=*C*H), 138.2, 138.3 (ArC), 154.5, 171.3, 171.4 (2 × C(O)); MS (EI, 70 eV), *m/z* (relative intensity) 364 (M^+, 6), 329 (25), 305 (11), 273 (42), 193 (21), 91 (100); HRMS calcd for $C_{18}H_{21}N_2O_4Cl$ 364.1190, found 364.1159.

2-(Allyloxycarbonyl)-1-benzyl-5-chloro-1*H*-1,2-diazepine-3-carboxylic acid methyl ester (43). Following the general procedure C, a solution of **29** (279 mg, 0.72 mmol) in CH_2Cl_2 (7 mL) was treated with $SnCl_4$ (1.19 mL of a 1.2 M solution, 1.43 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **43** (170 mg, 0.46 mmol, 65%) as a colorless oil, 1:1 mixture of isomers, R_f 0.25. IR ν 1745, 1685, 690; ^{1}H NMR (200 MHz) δ (mixture) 1.50-1.75 (m, 2 H, 2 × H6), 2.23 (dd, *J* = 12.7, 9.0 Hz, 1 H, H4), 2.61 (ddd, *J* = 13.0, 9.2, 7.2 Hz, 1 H, H4), 3.15-3.50 (m, 3 H, 2 × H7 and H5), 3.73 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 3.81 (s, 3 H, CO_2CH_3), 4.17 (d, *J* = 12.4 Hz, 1 H, CH*H*Ph), 4.48-4.67 (m, 3 H, OCH_2 and H3), 5.18-5.33 (m, 2 H, $=CH_2$), 5.77-5.94 (m, 1 H, =CH), 7.26-7.44 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ (mixture) 30.4, 34.3, 35.9, 36.0 (C4 and C6), 41.9 (C7), 52.6 (CO_2CH_3), 59.6 (C3), 59.2, 61.2 (C5), 61.6 (CH_2Ph), 66.3 (OCH_2), 117.5 ($=CH_2$), 127.3, 128.1, 129.5 (ArH), 132.2 (=CH), 137.0 (ArC), 172.7 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 52), 325 (9), 303 (6), 275 (23), 91 (100).

2-(Allyloxycarbonyl)-3-benzyl-1,2,3,4-tetrahydro-1-phthalazinecarboxylic acid methyl ester (44). According to the general procedure C, a solution of **30** (2.00 g, 4.69 mmol) in CH_2Cl_2 (45 mL) was treated with $SnCl_4$ (7.82 mL of a 1.2 M solution, 9.38 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **44** (1.55 mg, 4.23 mmol, 91%) as a colorless oil, R_f 0.30. IR ν 1740, 1685, 1400, 690; ^{1}H NMR δ 3.65-3.75 (m, 2 H, NCH_2), 3.78 (br s, 3 H, CO_2CH_3), 3.95-4.20 (m, 1 H, C*H*HPh), 4.45-4.70 (m, 3 H, OCH_2 and CH*H*Ph), 5.15-5.40 (m, 2 H, $=CH_2$), 5.63 (br s, 1 H, NCH), 5.80-6.05 (m, 1 H, =CH), 7.00-7.50 (m, 9 H, ArH); ^{13}C NMR (50 MHz) δ 51.5 (NCH), 52.6 (CO_2CH_3), 57.7 (NCH_2), 59.3 (CH_2Ph), 66.7 (OCH_2), 117.9 ($=CH_2$), 118.6, 127.1, 127.5, 128.3, 128.8, 129.3 (ArH), 132.5 (=CH), 134.0, 135.1, 137.0 (ArC), 171.0 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 32), 307 (15), 226 (32), 105 (100), 91 (100); HRMS calcd for $C_{21}H_{22}N_2O_4$ 366.1580, found 366.1579.

2-(Allyloxycarbonyl)-1-benzyl-5-methylenehexahydro-3-pyridazinecarboxylic acid methyl ester (45). According to the general procedure C, a solution of **31** (1.10 g, 2.38 mmol) in CH_2Cl_2 (25 mL) was treated with Et_2AlCl (5.95 mL of a 1.0 M solution, 5.95 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **45** (517 mg, 1.57 mmol, 83% (after correction)) as a colorless oil, R_f 0.35. IR ν 1735, 1680, 690; ^{1}H NMR (200 MHz) δ 2.59-2.70 (m, 1 H, H4), 3.01 (d, *J* = 14.1 Hz, 1 H, H4), 3.20 (m, 1 H, H6), 3.40 (d, *J* = 14.3 Hz, 1 H, H6), 3.75 (s, 3 H, CO_2CH_3), 3.86 (d, *J* = 12.5 Hz, 1 H, C*H*HPh), 4.05 (d, *J* = 12.5 Hz, 1 H, CH*H*Ph), 4.62-4.80 (m, 2 H, OCH_2), 4.88 (s, 1 H, C=C*H*H), 5.05 (m, 1 H, H3), 5.15 (s, 1 H, C=CH*H*), 5.24-5.43 (m, 2 H, CH=CH_2), 5.96-6.04 (m, 1 H, =CH), 7.23-7.40 (m, 5 H, ArH); ^{1}H NMR (250 MHz, 50 °C) δ 2.64 (dd, *J* = 14.2, 7.4 Hz, 1 H, H4), 2.96 (dd, *J* = 14.2, 3.3 Hz, 1 H, H4), 3.21 (d, *J* = 14.5 Hz, 1 H,

H6), 3.42 (d, J = 14.5 Hz, 1 H, H6), 3.73 (s, 3 H, CO_2CH_3), 3.91 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.08 (d, J = 12.5 Hz, 1 H, NCH*H*Ph), 4.65-4.80 (m, 2 H, OCH_2), 4.84 (s, 1 H, C=C*H*H), 4.97 (br s, 1 H, H3), 5.10 (s, 1 H, C=CH*H*), 5.22-5.40 (m, 2 H, CH=CH_2), 5.91-6.07 (m, 1 H, =CH), 7.20-7.39 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 32.0 (C4), 52.2 (CO_2CH_3), 53.9 (C6), 55.5 (C3), 57.9 (CH_2Ph), 66.6 (OCH_2), 91.5 (C5), 113.7 (C=CH_2), 117.6 (CH=CH_2), 127.2, 128.1, 129.0 (ArH), 132.5 (=CH), 137.4 (ArC), 172.0 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 330 (M^+, 46), 271 (24), 245 (44), 195 (20), 185 (24), 159 (69), 142 (29), 135 (42), 91 (100); HRMS calcd for $C_{18}H_{22}N_2O_4$ 330.1580, found 330.1548.

***rel*-(3*S*,5*S*)-2-(allyloxycarbonyl)-1-benzyl-5-methyl-5-(trifluoroacetoxy)hexahydro-3-pyridazinecarboxylic acid methyl ester (46).** A solution of **31** (232 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was treated with CF_3CO_2H (155 μL, 2.00 mmol) at 0 °C. After being stirred at rt for 18 h, the mixture was poured into aq satd $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:4) to afford **46** (155 mg, 0.35 mmol, 70%) as a light yellow oil, R_f 0.35. IR ν 1775, 1735, 1710, 690; ^{1}H NMR (200 MHz) δ 1.54 (s, 3 H, CH_3), 2.30-2.55 (m, 2 H, 2 × H4), 2.89 (d, J = 13.7 Hz, 1 H, H6), 3.39 (d, J = 13.7 Hz, 1 H, H6), 3.76 (s, 3 H, CO_2CH_3), 4.27 (s, 2 H, CH_2Ph), 4.65 (d, J = 5.5 Hz, 2 H, OCH_2), 4.75-4.95 (m, 1 H, H3), 5.24-5.37 (m, 2 H, =CH_2), 5.80-6.05 (m, 1 H, =CH), 7.26-7.34 (m, 5 H, ArH); MS (EI, 70 eV) *m/z* (relative intensity) 444 (M^+, 8), 348 (13), 277 (8), 263 (7), 245 (10), 160 (42), 121 (29), 91 (100); HRMS calcd for $C_{20}H_{23}N_2O_6F_3$ 444.1508, found 444.1543.

2-(Allyloxycarbonyl)-1-benzyl-4-ethenylidene-3-pyrazolidinecarboxylic acid methyl ester (47). To a solution of **32** (250 mg, 0.53 mmol) in CH_2Cl_2 (25 mL) was added at 0 °C BF_3·OEt_2 (0.40 mL, 3.15 mmol) and the mixture was stirred at 0 °C for 15 min. After stirring at rt for 4 h, the mixture was poured into aq satd NaCl (100 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 1:5) to afford **47** (51 mg, 0.16 mmol, 30% (after correction)) as a light yellow oil, R_f 0.20. IR ν 1950, 1745, 1685, 690; ^{1}H NMR (200 MHz) δ 3.65 (m, 2 H, 2 × H5), 3.81 (s, 3 H, CO_2CH_3), 3.83 (d, J = 12.4 Hz, 1 H, C*H*HPh), 4.10 (d, J = 12.4 Hz, 1 H, CH*H*Ph), 4.59 (d, J = 5.5 Hz, 2 H, OCH_2), 4.65-4.75 (m, 1 H, H3), 5.08-5.11 (m, 2 H, C=CH_2), 5.18-5.34 (m, 2 H, CH=CH_2), 5.77-5.97 (m, 1 H, =CH), 7.28-7.46 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 52.6 (CO_2CH_3), 55.5 (C5), 61.3 (C3), 61.8 (CH_2Ph), 66.6 (OCH_2), 81.1 (C=CH_2), 99.0 (C4), 117.9 (CH=CH_2), 127.6, 128.3, 129.7 (ArH), 132.3 (=CH), 136.8 (ArC), 169.6 (C(O)), 200.3 (C=C=CH_2); MS (EI, 70 eV) *m/z* (relative intensity) 328 (M^+, 53), 243 (18), 193 (11), 124 (6), 91 (100); HRMS calcd for $C_{18}H_{20}N_2O_4$ 328.1423, found 328.1401.

***rel*-(3*R*,4*S*,5*S*)-2-(Allyloxycarbonyl)-1-benzyl-5-(chloromethyl)-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (48).** According to the general procedure C, a solution of **33** (925 mg, 2.06 mmol) in CH_2Cl_2 (25 mL) was treated with $SnCl_4$ (3.44 mL of a 1.2 M solution, 4.13 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **48** (591 mg, 1.39 mmol, 68%) as a colorless oil, R_f 0.45. IR ν 1735, 1685, 1250, 940, 690; ^{1}H NMR (200 MHz) δ 0.12 (s, 9 H, $(CH_3)_3$Si), 2.00 (t, J = 9.1 Hz, 1 H, H4), 3.07 (dd, J = 11.5, 4.3 Hz, 1 H, C*H*HCl), 3.25 (dd, J = 11.5, 3.4 Hz, 1 H, CH*H*Cl), 3.47-3.56 (m, 1 H, H5), 3.78 (s, 3 H, CO_2CH_3), 3.99 (d, J = 12.8 Hz, 1 H, C*H*HPh), 4.36 (d, J = 12.7 Hz, 1 H, CH*H*Ph), 4.56 (ddt, J = 13.6, 5.3, 1.4 Hz, 1 H, OC*H*H), 4.67 (ddt, J = 13.6, 5.3, 1.4 Hz, 1 H, OCH*H*), 5.01 (d, J = 9.0 Hz, 1 H, H3), 5.18-5.40 (m, 2 H, =CH_2), 5.91-5.98 (m, 1 H, =CH), 7.26-7.51 (ArH); ^{13}C NMR (63 MHz) δ 1.5 $(CH_3)_3$Si), 35.3 (C4), 47.7 (CH_2Cl), 52.1 (CO_2CH_3), 62.4 (C3), 63.4 (CH_2Ph), 66.5 (OCH_2), 68.8 (C5), 117.4 (=CH_2), 127.5, 128.2, 129.4 (ArH), 132.6 (=CH), 137.8 (ArC), 156.0, 172.3 (2 × C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 424 (M^+, 57), 409 (10), 339 (13), 289 (10), 243 (20), 185 (23), 91 (100); HRMS calcd for $C_{20}H_{29}N_2O_4ClSi$ 424.1585, found 424.1569.

2-(Allyloxycarbonyl)-1-benzyl-1,2,3,6-tetrahydro-3-pyridazinecarboxylic acid methyl ester (49). According to the general procedure C, a solution of **34** (500 mg, 1.12 mmol) in CH_2Cl_2 (12 mL) was

treated with $SnCl_4$ (1.86 mL of a 1.2 M solution, 2.23 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **48** (152 mg, 0.36 mmol, 32%) as a colorless oil, R_f 0.45 and **49** (176 mg, 0.56 mmol, 50%) as a colorless oil, R_f 0.25. **49**: IR ν 1740, 1680, 1400, 985, 690; ^{1}H NMR (250 MHz) δ 3.09 (dd, J = 17.6, 4.2 Hz, 1 H, H6), 3.46 (br d, J = 19.3 Hz, 1 H, H6), 3.78 (s, 3 H, CO_2CH_3), 3.82 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.22 (d, J = 12.5 Hz, 1 H, CH*H*Ph), 4.60-4.80 (m, 2 H, OCH_2), 5.10 (br s, 1 H, H3), 5.23-5.45 (m, 2 H, $=CH_2$), 5.65-6.15 (m, 3 H, CH_2=C*H*, H4 and H5), 7.22-7.39 (m, 5 H, ArH); ^{13}C NMR (63 MHz) δ 46.9 (C6), 52.4 (CO_2CH_3), 52.5 (C3), 59.3 (CH_2Ph), 66.6 (OCH_2), 117.6 ($=CH_2$), 121.0, 124.6 (C4 and C5), 127.3, 127.5, 128.0 (ArH), 132.7 (CH_2=CH), 138.0 (ArC), 155.0, 170.2 (2 × C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 316 (M^+, 10), 257 (10), 231 (13), 171 (14), 91 (100), 41 (43); HRMS calcd for $C_{17}H_{20}N_2O_4$ 316.1423, found 316.1401.

***rel*-(3*S*,5*R*)-2-(Allyloxycarbonyl)-1-benzyl-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (56).** To a refluxing solution of *n*-Bu_3SnH (160 mL, 0.60 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of **35** (55 mg, 0.15 mmol) and AIBN (5 mg, 0.030 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated *in vacuo* and chromatographed (hexane, then ethyl acetate/hexane 1:4) to afford **56** (31 mg, 0.097 mmol, 65%) as a colorless oil, R_f 0.25. IR ν 1740, 680, 1400, 690; ^{1}H NMR (200 MHz) δ 0.98 (d, J = 7.1 Hz, 3 H, CH_3), 2.18 (dd, J = 12.5, 8.7 Hz, 1 H, H4), 2.45-2.60 (m, 1 H, H4), 3.37 (quintet, J = 6.6. Hz, 1 H, H5), 3.74 (d, J = 12.8 Hz, 1 H, C*H*HPh), 3.80 (s, 3 H, CO_2CH_3), 4.17 (d, J = 12.8 Hz, 1 H, CH*H*Ph), 4.57 (d, J = 5.5 Hz, 2 H, OCH_2), 4.59 (t, J = 8.9 Hz, 1 H, H3), 5.14-5.32 (m, 2 H, $=CH_2$), 5.76-5.95 (m, 1 H, =CH), 7.23-7.47 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 19.9 (CH_3), 35.4 (C4), 52.5 (CO_2CH_3), 58.6, 59.5 (2 × NCH), 61.5 (CH_2Ph), 66.3 (OCH_2), 117.2 ($=CH_2$), 127.3, 128.2, 129.4 (ArH), 132.7 (=CH), 137.8 (ArC), 173.2 (C(O)).

2-(Allyloxycarbonyl)-1-benzyl-5,5-dimethyl-3-pyrazolidinecarboxylic acid methyl ester (57). To a refluxing solution of *n*-Bu_3SnH (217 μL, 0.82 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of **36** (75 mg, 0.20 mmol) and AIBN (3.4 mg, 0.02 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated *in vacuo* and chromatographed (hexane, then ethyl acetate/hexane 1:4) to afford **57** (35 mg, 0.11 mmol, 51%) as a colorless oil, R_f 0.15. IR ν 1740, 1680, 690; ^{1}H NMR (200 MHz) δ 1.20-1.30 (s, 6 H, $(CH_3)_2C$), 2.30 (d, J = 9.2 Hz, 2 H, 2 × H4), 3.80 (s, 3 H, CO_2CH_3), 3.85 (d, J = 12.4 Hz, 1 H, C*H*HPh), 3.99 (d, J = 12.4 Hz, 1 H, CH*H*Ph), 4.10-4.45 (m, 2 H, OCH_2), 4.60 (t, J = 9.3 Hz, 1 H, H3), 5.05-5.17 (m, 2 H, $=CH_2$), 5.55 (m, 1 H, =CH), 7.17-7.54 (m, 5 H, ArH).

***rel*-(3*S*,4*S*)-2-(Allyloxycarbonyl)-1-benzyl-4-ethyl-3-pyrazolidinecarboxylic acid methyl ester (58).** To a refluxing solution of *n*-Bu_3SnH (324 μL, 1.22 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of **41** (112 mg, 0.31 mmol) and AIBN (5.0 mg, 0.030 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated *in vacuo*, taken up in THF (10 mL) and stirred with KF (93 mg, 1.22 mmol) and TBAF (122 mL of a 1.0 M solution in THF, 0.12 mmol) for 17 h. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:4) to afford **58** (39 mg, 0.12 mmol, 38%) as a colorless oil, R_f 0.25. IR ν 1740, 1685, 690; ^{1}H NMR (200 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.40-1.55 (m, 1 H, C*H*HCH$_3$), 1.70-1.90 (m, 1 H, CH*H*CH$_3$), 2.65-2.73 (m, 2 H, 2 × H5), 3.15-3.18 (m, 1 H, H4), 3.82 (s, 3 H, CO_2CH_3), 3.75-3.85 (m, 1 H, C*H*HPh), 4.05-4.25 (m, 2 H, CH*H*Ph and H3), 4.53 (d, J = 5.4 Hz, 2 H, OCH_2), 5.14-5.30 (m, 2 H, $=CH_2$), 5.76-5.90 (m, 1 H, =CH), 7.23-7.46 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 12.2 (CH_2CH_3), 24.7 (CH_2CH_3), 45.5 (C4), 52.5 (CO_2CH_3), 57.8 (C5), 61.7 (CH_2Ph), 65.8 (C3), 66.5 (OCH_2), 117.7 ($=CH_2$), 127.4, 128.3, 129.6 (ArH), 132.5 (=CH), 137.4 (ArC), 173.1 (C(O)).

General procedure D for the transprotection reactions. To a solution of the Alloc compound and Boc_2O (2 equiv) in CH_2Cl_2 was added $Pd(PPh_3)_4$ (0.02 equiv), immediately followed by the full amount of *n*-Bu_3SnH (1.1 equiv) and the mixture was stirred at rt for 2 h. Concentration *in vacuo* and purification by fc (first with hexane, then with the suitable eluent) afforded the pure product(s).

***rel*-(3*S*,5*S*)-1-Benzyl-2-(*tert*-butoxycarbonyl)-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (65).** Following the general procedure D, a solution of **35** (760 mg, 2.16 mmol) in CH_2Cl_2 (25 mL) was treated with Boc_2O (990 μL, 4.31 mmol), $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) and *n*-Bu_3SnH (629 μL, 2.37 mmol). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **65** (612 mg, 1.66 mmol, 77%) as a light yellow oil, R_f 0.35. IR ν 1740, 1680, 1360, 690; ^{1}H NMR (200 MHz) δ 1.43 (s, 9 H, $(CH_3)_3$), 2.47-2.69 (m, 2 H, 2 × H4), 3.11 (dd, *J* = 8.1, 10.6 Hz, 1 H, C*H*HCl), 3.30-3.44 (m, 2 H, CH*H*Cl and H5), 3.77 (d, *J* = 12.6 Hz, 1 H, C*H*HPh), 3.81 (s, 3 H, CO_2CH_3), 4.23 (d, *J* = 12.6 Hz, 1 H, CH*H*Ph), 4.59 (t, *J* = 8.8 Hz, 1 H, H3), 7.27-7.47 (m, 5 H, ArH).

***rel*-(3*R*,5*S*)-2-(*tert*-Butoxycarbonyl)-5-chloromethyl-3-pyrazolidinecarboxylic acid methyl ester (66).** A mixture of **65** (120 mg, 0.33 mmol), Pd/C (30 mg of 10% Pd on C, 0.03 mmol) and a few drops of a 1 M HCl/MeOH solution in MeOH (10 mL) was stirred under a H_2-atmosphere for 1 h. After filtration over Celite, the solution was concentrated *in vacuo*, taken up in 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 afford **66** (81 mg, 0.29 mmol, 90%) white solid, mp 45-47 °C, R_f 0.15. IR ν 1740, 1705, 1365, 1130; ^{1}H NMR (200 MHz) δ 1.45 (s, 9 H, $(CH_3)_3C$), 2.23 (ddd, *J* = 13.2, 7.1, 5.1 Hz, 1 H, H4), 2.54 (ddd, *J* = 13.2, 9.2, 4.4 Hz, 1 H, H4), 3.43 (dd, *J* = 11.2, 7.3 Hz, 1 H, C*H*HCl), 3.60 (dd, *J* = 11.2, 4.8 Hz, 1 H, CH*H*Cl), 3.75 (s, 3 H, CO_2CH_3), 3.66-3.77 (m, 1 H, H5), 4.59 (dd, *J* = 4.9, 9.1 Hz, 1 H, H3); ^{13}C NMR (50 MHz) δ 28.3 ($(CH_3)_3C$), 35.7 (C4), 44.9 (CH_2Cl), 52.4 (CO_2CH_3), 59.0, 59.2 (C3 and C5), 81.1 ($(CH_3)_3C$); MS (EI, 70 eV) *m/z* (relative intensity) 178 (M^+-100, 90), 119 (100), 95 (45), 91 (100), 69 (60).

Crystallographic data.

Tetragonal, $P\bar{4}2_1c$, $a = b = 17.4709(7)$, $c = 9.695$ Å, $\alpha = \beta = \gamma = 90°$, V = 2959.3(2) Å^3, Z = 8, $D_x = 1.25$ gcm^{-3}, λ(CuKα) = 1.5418 Å, μ(CuKα) = 23.98 cm^{-1}, F(000) = 1184, rt. Final R = 0.076 for 1164 observed reflections.

Table 7.3. Bond distances of the atoms (Å), with standard deviations in parentheses.

C1-C4	1.777(8)	C7-N2	1.337(8)	C2-H21	1.07(6)	C9-H92	1.10(4)
C1-C2	1.553(9)	C7-O3	1.193(8)	C2-H22	1.11(3)	C9-H93	1.07(7)
C1-H4	1.51(1)	C7-O4	1.366(7)	C3-H3	1.06(4)	C10-H101	1.09(5)
C1-N1	1.467(8)	C8-C9	1.49(1)	C4-H41	1.07(4)	C10-H102	1.08(4)
C2-C3	1.548(9)	C8-C10	1.52(1)	C4-H42	1.08(6)	C10-H103	1.08(4)
C3-C5	1.496(9)	C8-C11	1.51(1)	C6-H61	1.08(7)	C11-H111	1.10(3)
C3-N2	1.441(8)	C4-O8	1.489(8)	C6-H62	1.10(4)	C11-H112	1.09(4)
C5-O1	1.21(1)	N1-N2	1.420(6)	C6-H63	1.09(6)	C11-H113	1.07(5)
C5-O2	1.306(9)	C1-H1	1.05(4)	C9-H91	1.08(5)	N1-H2	1.06(5)
C6-O2	1.47(1)						

Table 7.4. Bond angles of the atoms (°), with standard deviations in parentheses.

C2-C1-C4	113.6(5)	C1-N1-N2	103.4(4)	H61-C6-H63	90(5)
C2-C1-N1	104.4(5)	C5-O2-C6	114.5(6)	H62-C6-H63	145(5)
C4-C1-N1	107.2(5)	C7-O4-C8	121.1(5)	C8-C9-H91	100(3)
C1-C2-C3	103.0(5)	C2-C1-H1	106(2)	C8-C9-H92	99(4)

C2-C3-C5	108.9(5)	C4-C1-H1	111(3)	C8-C9-H93	98(4)
C2-C3-N2	103.1(5)	N1-C1-H1	115(2)	H91-C9-H92	128(5)
C5-C3-N2	115.8(6)	C1-C2-H21	97(4)	H91-C9-H93	115(6)
Cl-C4-C1	112.2(5)	C1-C2-H22	107(3)	H92-C9-H93	110(5)
C3-C5-O1	121.5(7)	C3-C2-H21	107(4)	C8-C10-H101	99(3)
C3-C5-O2	114.4(6)	C3-C2-H22	113(3)	C8-C10-H102	103(3)
O1-C5-O2	124.1(7)	H21-C2-H22	126(5)	C8-C10-H103	105(3)
N2-C7-O3	126.4(6)	C2-C3-H3	122(3)	H101-C10-H102	115(4)
N2-C7-O4	107.7(5)	C5-C3-H3	106(2)	H101-C10-H103	123(4)
O3-C7-O4	125.8(6)	N2-C3-H3	101(3)	H102-C10-H103	109(4)
C9-C8-C10	110.0(6)	Cl-C4-H41	94(3)	C8-C11-H111	102(4)
C9-C8-C11	112.0(6)	Cl-C4-H42	118(4)	C8-C11-H112	105(2)
C9-C8-O4	109.0(5)	C1-C4-H41	116(3)	C8-C11-H113	115(3)
C10-C8-C11	113.0(6)	C1-C4-H42	101(4)	H111-C11-H112	110(5)
C10-C8-O4	102.3(5)	H41-C4-H42	118(5)	H111-C11-H113	129(6)
C11-C8-O4	110.1(5)	O2-C6-H61-	95(4)	H112-C11-H113	94(4)
C3-N2-C7	126.5(5)	O2-C6-H62	97(3)	C1-N1-H2	107(4)
C3-N2-N1	114.3(4)	O2-C6-H63	100(4)	N2-N1-H2	108(4)
C7-N2-N1	118.9(5)	H61-C6-H62	118(5)		

***rel*-(3*R*,5*S*)-5-chloromethyl-3-pyrazolidinecarboxylic acid hydrogen chloride (67).** A solution of **66** (30 mg, 0.11 mmol) in 2 M HCl was heated at 60 °C for 2 h and concentrated *in vacuo* to afford **67** (18 mg, 0.090 mmol, 82%) as a viscous yellow oil. ^{1}H NMR (200 MHz, D_2O) δ 2.46 (dt, J = 13.8, 8.4 Hz, 1 H, H4), 2.67 (ddd, J = 4.5, 7.8, 13.9 Hz, 1 H, H4), 3.74 (dd, J = 7.5, 12.4 Hz, 1 H, C*H*HCl), 3.90 (dd, J = 3.8, 12.3 Hz, 1 H, CH*H*Cl), 4.08-4.20 (m, 1 H, H5), 4.49 (dd, J = 4.4, 8.9 Hz, 1 H, H3); ^{13}C NMR (50 MHz, D_2O) δ 34.9 (C4), 44.8 (CH_2Cl), 62.4, 62.6 (C3 and C5), 174.5 (C(O)).

***rel*-(3*S*,4*S*)-1-Benzyl-2-(*tert*-butoxycarbonyl)-4-(1-chloroethyl)-3-pyrazolidinecarboxylic acid methyl ester (68).** According to the general procedure D, a solution of **41** (90 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (124 μL, 0.54 mmol), $Pd(PPh_3)_4$ (8.5 mg, $7.4\cdot10^{-3}$ mmol) and *n*-Bu_3SnH (72 μL, 0.27 mmol). Concentration *in vacuo* and flash chromatography (ethyl acetate/hexane 1:4) afforded **68** (49 mg, 0.13 mmol, 54%) as a light yellow oil, R_f 0.35. IR ν 1745, 1700, 1680, 690; ^{1}H NMR (200 MHz) δ 1.39 (s, 9 H, $(CH_3)_3C$), 1.56 (d, J = 6.7 Hz, 3 H, CH_3), 3.03-3.10 (m, 3 H, H4 and 2 × H5), 3.69-3.85 (m, 2 H, CH_2Ph), 3.82 (s, 3 H, CO_2CH_3), 4.15-4.30 (m, 2 H, H3 and CHCl), 7.26-7.46 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 24.1 (CH_3), 28.2 (($CH_3)_3$C), 51.5 (C4), 52.6 (CO_2CH_3), 54.5 (C5), 57.5 (CHCl), 61.8 (CH_2Ph), 63.2 (C3), 81.0 (($CH_3)_3$C), 127.4, 128.3, 129.6 (ArH), 137.5 (ArC), 172.9 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 382 (M^+, 4), 281 (58), 245 (15), 231 (9), 91 (100); HRMS calcd for $C_{19}H_{27}N_2O_4Cl$ 382.1659, found 382.1635.

1-Benzyl-2-(*tert*-butoxycarbonyl)-5-chlorohexahydro-1*H*-diazepine-3-carboxylic acid methyl ester (69). According to the general procedure D, a solution of **42** (76 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (105 μL, 0.46 mmol), $Pd(PPh_3)_4$ (7.2 mg, $6.2\cdot10^{-3}$ mmol) and *n*-Bu_3SnH (60 μL, 0.23 mmol). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **69** (51 mg, 0.13 mmol, 64%) as a colorless oil, R_f 0.50. IR ν 1740, 1680, 690; ^{1}H NMR (200 MHz) δ 1.38 (s, 9 H, $(CH_3)_3C$), 1.45-1.65 (m, 2 H, 2 × H6), 2.19 (dd, J = 12.8, 8.9 Hz, 1 H, H4), 2.59 (ddd, J = 13.0, 9.3, 7.0 Hz, 1 H, H4), 3.20-3.55 (m, 3 H, H5 and 2 × H7), 3.68 (d, J = 12.3 Hz, 1 H, C*H*HPh), 3.80 (s, 3 H, CO_2CH_3), 4.13 (d, J = 13.0 Hz, 1 H, CH*H*Ph), 4.50 (t, J = 8.8 Hz, 1 H, H3), 7.22-7.44 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ (two diastereomers) 28.2 (($CH_3)_3$C), 30.5, 34.4, 36.0, 35.9 (C4 and C6), 41.9 (C7), 52.4 (CO_2CH_3), 59.5 (C3),

60.2 (C5), 61.4 (CH_2Ph), 80.6 ($(CH_3)_3C$), 127.3, 128.1, 129.8 (ArH), 137.6 (ArC), 173.4 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 382 (M^+, 3), 327 (20), 281 (58), 163 (10), 91 (100).

Deprotection of 44. Following the general procedure D, a solution of **44** (200 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (139 μL, 0.61 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) and *n*-Bu_3SnH (160 μL, 0.61 mmol). Concentration *in vacuo* and flash chromatography (ethyl acetate/hexane 1:4) afforded **3-benzyl-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-1-phthalazinecarboxylic acid methyl ester (70)** (118 mg, 0.31 mmol, 56%) as a colorless oil, R_f 0.35 and **3-benzyl-3,4-dihydro-1-phthalazinecarboxylic acid methyl ester (71)** (35 mg, 0.12 mmol, 22%) as a colorless oil, R_f 0.32. **70**: IR ν 1735, 1670, 1130, 690; ^1H NMR (200 MHz) δ (some signals appear as rotamers) 1.52, 1.53 (s, 9 H, $(CH_3)_3C$), 3.30-4.50 (br m, 7 H, CO_2CH_3, CH_2Ph and NCH_2), 5.40, 5.60 (br s, 1 H, NCH), 7.00-7.50 (m, 9 H, ArH); ^{13}C NMR (63 MHz) δ 28.4 ($(CH_3)_3C$), 52.4 (CO_2CH_3), 52.8 (NCH), 55.6 (NCH_2), 59.1 (CH_2Ph), 81.3 ($(CH_3)_3C$), 126.1, 127.4, 127.9, 128.3, 129.4, 131.7 (ArH), 132.0, 136.1, 138.0 (ArC), 171.5 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 382 (M^+, 20), 282 (61), 223 (45), 91 (100), 57 (83); HRMS calcd for $C_{22}H_{26}N_2O_4$ 382.1892, found 382.1901. **71**: IR ν 1700, 1435, 1135, 690; ^1H NMR (200 MHz) δ 3.94 (s, 3 H, CO_2CH_3), 4.08 (s, 2 H, NCH_2), 4.69 (s, 2 H, CH_2Ph), 6.89-6.94 (m, 1 H, ArH), 7.23-7.40 (m, 7 H, ArH), 8.08-8.13 (m, 1 H, ArH).

1-Benzyl-3-methylene-1,4,5,6-tetrahydro-3-pyridazinecarboxylic acid methyl ester (72). According to the general procedure D, a solution of **45** (100 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (153 μL, 0.67 mmol), $Pd(PPh_3)_4$ (11 mg, $9.1 \cdot 10^{-3}$ mmol) and *n*-Bu_3SnH (88 μL, 0.33 mmol). Concentration *in vacuo* and flash chromatography (ethyl acetate/hexane 1:4) afforded **72** (58 mg, 0.24 mmol, 78%) as a colorless oil, R_f 0.25. ^1H NMR (200 MHz) δ 3.14 (s, 2 H, 2 × H4), 3.43 (s, 2 H, 2 × H6), 3.84 (s, 3 H, CO_2CH_3), 4.61 (s, 2 H, CH_2Ph), 4.93 (s, 1 H, C=C*H*H), 5.03 (s, 1 H, C=CH*H*), 7.24-7.35 (m, 5 H, ArH).

***rel*-(3*R*,4*S*,5*S*)-1-Benzyl-2-(*tert*-butoxycarbonyl)-5-(chloromethyl)-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (73).** Following the general procedure D, a solution of **48** (434 mg, 1.02 mmol) in CH_2Cl_2 (15 mL) was treated with Boc_2O (0.52 mL, 2.25 mmol), $Pd(PPh_3)_4$ (35 mg, 0.031 mmol) and *n*-Bu_3SnH (0.30 mL, 1.13 mmol). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **73** (288 mg, 0.65 mmol, 64%) as a light yellow oil, R_f 0.60. IR ν 1760, 1690, 1250, 840, 690; ^1H NMR (200 MHz) δ 0.11 (s, 9 H, $(CH_3)_3Si$), 1.45 (s, 9 H, $(CH_3)_3C$), 1.97 (t, J = 9.0 Hz, 1 H, H4), 3.06 (dd, J = 11.4, 4.3 Hz, 1 H, C*H*HCl), 3.24 (dd, J = 11.4, 3.4 Hz, 1 H, CH*H*Cl), 3.43-3.50 (m, 1 H, H5), 3.77 (s, 3 H, CO_2CH_3), 3.96 (d, J = 12.7 Hz, 1 H, C*H*HPh), 4.32 (d, J = 12.7 Hz, 1 H, CH*H*Ph), 4.99 (d, J = 9.0 Hz, 1 H, H3), 7.26-7.51 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 1.7 ($(CH_3)_3Si$), 28.3 ($(CH_3)_3C$), 35.1 (C4), 47.9 (CH_2Cl), 52.0 (CO_2CH_3), 62.0 (C3), 63.2 (CH_2Ph), 68.7 (C5), 80.8 ($(CH_3)_3C$), 127.4, 128.2, 129.4 (ArH), 138.1 (ArC), 155.7, 172.8 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 440 (M^+, 26), 340 (90), 325 (12), 185 (13), 159 (5), 133 (8), 91 (100); HRMS calcd for $C_{21}H_{33}N_2O_4ClSi$ 440.1898, found 440.1905.

2-(*tert*-Butoxycarbonyl)-5-chlorohexahydro-1*H*-diazepine-3-carboxylic acid methyl ester (74). A mixture of **69** (40 mg, 0.10 mmol), Pd/C (11 mg of 10% Pd on C, 0.01 mmol) and one drop of a 3 M HCl/MeOH solution in MeOH (5 mL) was stirred under a H_2-atmosphere for 1 h. After filtration over Celite, the solution was concentrated *in vacuo*, taken up in aq satd $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:2) to afford **74** (20 mg, 0.065 mmol, 65%) as a colorless oil, R_f 0.25. IR ν 3450, 1720, 1685; ^1H NMR (200 MHz) δ 1.45 (s, 9 H, $(CH_3)_3$), 1.69-1.84 (m, 2 H, 2 × H6), 2.19-2.27 (m, 2 H, 2 × H4), 3.53-3.78 (m, 3 H, H5 and 2 × H7), 3.75 (s, 3 H, CO_2CH_3), 4.50-4.63 (m, 1 H, H3); ^{13}C NMR (50 MHz) δ (mixture of isomers) 28.0 ($(CH_3)_3C$), 30.5, 35.6, 35.8, 38.2, 38.3 (C4 and C6), 42.0 (C7), 52.1 (CO_2CH_3), 56.0, 56.5 (C5), 58.8 (C3), 80.9 ($(CH_3)_3C$), 172.7 (C(O)); MS (EI, 70 eV) *m/z*

(relative intensity) 292 (M^+, 6), 236 (8), 192 (20), 175 (13), 167 (23), 153 (27), 131 (100).

***rel*-(3*R*,4*S*,5*S*)-2-(*tert*-Butoxycarbonyl)-5-chloromethyl-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (75).** A mixture of **73** (275 mg, 0.63 mmol), Pd/C (67 mg of 10% Pd on C, 0.06 mmol) and a few drops of a 3 M HCl/MeOH solution in MeOH (7 mL) was stirred under a H_2-atmosphere for 45 min. After filtration over Celite, the solution was concentrated *in vacuo*, taken up in aq satd $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:2) to afford **75** (178 mg, 0.51 mmol, 81%) as a colorless oil, R_f 0.50. IR ν 1735, 1700, 1250, 840; ^{1}H NMR (200 MHz) δ 0.10 (s, 9 H, $(CH_3)_3Si$), 1.45 (s, 9 H, $(CH_3)_3C$), 1.84 (t, J = 9.0 Hz, 1 H, H4), 3.57-3.84 (m, 6 H, CO_2CH_3, H5 and CH_2Cl), 4.65 (d, J = 8.8 Hz, 1 H, H3); ^{13}C NMR (50 MHz) δ 1.7 ($(CH_3)_3Si$), 28.2 ($(CH_3)_3C$), 36.1 (C4), 45.2 (CH_2Cl), 51.8 (CO_2CH_3), 60.6 (C3), 63.0 (C5), 81.1 ($(CH_3)_3C$), 153.2, 172.0 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 350 (M^+, 8), 279 (9), 250 (100), 191 (47), 185 (19), 133 (18); HRMS calcd for $C_{14}H_{27}N_2O_4ClSi$ 350.1429, found 350.1468.

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