Recl. Trav. Chim. Pays-Bas **113**, 145–152 (1994)
SSDI 0165-0513(94)00002-J

0165–0513/94/03145–08$07.00

Synthesis of bicyclic 3-pyrazolidinones via π-cyclization reactions of exocyclic *N*-acylhydrazonium ions

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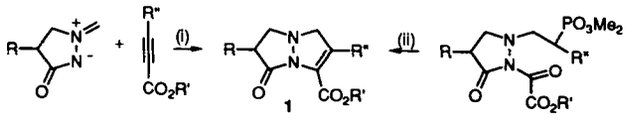
(Received October 11, 1993)

Abstract. The preparation of several *a*-fused 3-pyrazolidinones is described starting from 5,5-dimethyl-3-pyrazolidinone and using an acid-induced cyclization of a π-nucleophile tethered to N-1 onto a cationic carbon bonded to N-2 (an exocyclic *N*-acylhydrazonium intermediate). The cyclization reactions proceed best with activated π-nucleophiles such as allyl- and propargylsilanes. In the case of an ester substituent at the cationic carbon, structural analogues of antibacterial bicyclic pyrazolidinones are obtained. The stereochemistry of one product is established by X-ray crystallographic analysis. Two cyclization products showed NMR spectra with very broad signals due to relatively high nitrogen-inversion barriers (*ca.* 13 kcal/mole).

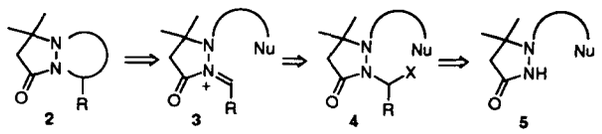
Introduction

The recently discovered antibacterial activity[1] of bicyclic pyrazolidinones of type **1** (Eqn. 1) has aroused considerable interest in the synthesis of this compound class[2]. While the preparation of the 3-pyrazolidinone ring itself is well established [2,3], improved methods have been developed for the construction of the *a*-fused 5- (or 6-) membered rings. These procedures include (*i*) the 1,3-dipolar cycloaddition reaction of azomethine imines, obtained from condensation of 3-pyrazolidinones with formaldehyde[4], and (*ii*) the intramolecular Wadsworth–Horner–Emmons reaction (Eqn. 1)[5].



(1)

In this paper we report a versatile procedure for the preparation of bicyclic 3-pyrazolidin-ones through ring closure of the fused ring using *N*-acylhydrazonium ions as intermediates. In earlier papers we have shown the usefulness of acyclic and endocyclic *N*-acylhydrazonium ions [6,7]. The key feature of the present methodology[8] is the use of exocyclic *N*-acylhydrazonium ions of type **3**, which react in an intramolecular fashion to give the fused pyrazolidinones **2** (Eqn. 2). The cationic species **3** are generated from the *N,X*-acetals **4**. The latter compounds arise via addition of the alkylated pyrazolidinones **5** to formaldehyde (R = H) or methyl glyoxylate (R = CO_2Me) or synthetic equivalents thereof. The preparation of the 5,5-dimethyl-3-pyrazolidinones **5** by alkylation of the parent compound at N-1 was described before[7]. The presence of the methyl substituents at C-5 greatly improved the yield of this latter alkylation step[5,9].



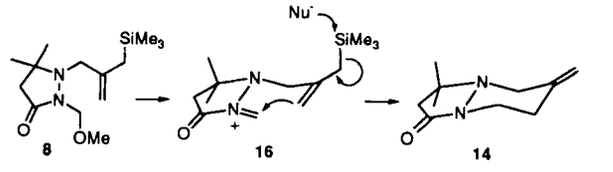
(2)

Results and discussion

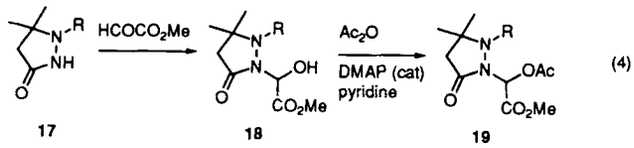
The precursors **6–9** (Table I) were obtained in moderate to good yields by deprotonation of pyrazolidinones **5**[7] with sodium hydride and subsequent alkylation with chloromethyl methyl ether. Use of other bases or solvents did not lead to more satisfactory results. A side-reaction that might possibly be responsible for the somewhat disappointing yields is alkylation at the oxygen, which has been encountered in reactions with methyl chloroformate[7]. The precursors **6** and **7** were subjected to the Lewis acid titanium tetrachloride (2 equiv, −78°C to room temperature, entries 1 and 3). Boron trifluoride etherate was used for the silanes **8** and **9** (2 equiv, 0°C to room temperature, entries 5 and 7). Furthermore, all precursors were treated with formic acid at different temperatures. The results of these reactions are summarized in Table I. Most of the Lewis-acid-promoted cyclizations occurred in good yields to give the expected products. In the case of the 3-methyl-2-butenyl precursor **7** (entry 3) treatment with titanium tetrachloride gave, in addition to chloride **11** a small amount of the elimination product **12**. The formic acid cyclizations usually gave high yields of the desired products. The phthalazine derivative **10** could also be prepared

in 66% yield in a one-pot process through treatment of 1-benzyl-5,5-dimethyl-3-pyrazolidinone[7] with 1,3,5-trioxane in formic acid for 18 h at 80°C.

The mechanistic course of the cyclization process is visualized in Eqn. 3 for the allylsilane **8**. The six-membered-ring transition state is likely to adopt a chair-like conformation as illustrated with **16**[10], which provides bicyclic product **14**.



(3)



(4)

We then turned our attention to the ester-substituted *N*-acylhydrazonium intermediates (**3**, R = CO_2Me). In analogy with our work on the synthesis of cyclization precursors from alcohols[11] and pyrrolidinones[12], the α-methoxycarbonylated precursors **19** were prepared via an addition reaction to methyl glyoxylate as shown in Eqn. 4. Thus, condensation of the pyrazolidinone **17** with either methyl glyoxylate hydrate[13] or anhydrous methyl glyoxylate[14] yielded the stable *N,O*-hemiacetals **18** upon stirring at room temperature. Without any further purification these hydroxy compounds **18** were converted into the acetates **19** by treatment with an excess of acetic anhydride.

The cyclization reactions of **20–23** were carried out under the same conditions as described for the precursors **6–9** and the results are summarized in Table II. Generally, the Lewis-acid-mediated cyclizations gave better yields than those performed in formic acid. In the case of the 3-methyl-2-butenyl precursor **21** (entries 3 and 4), mixtures of the *cis* and *trans* products were obtained. The *trans* relationship of the substituents in **25** was secured by an X-ray crystallographic analysis as depicted in Figure 1. The X-ray data show that the amidic nitrogen atom N-1 is slightly deformed from planarity, probably as a result of the strain in the fused system. The *trans* relationship in the corresponding formate **27** was inferred from a comparison of the magnitudes of the coupling constants of the α-ester hydrogens in **25** and **27** (**25**: 4.60 ppm, d, ^3J 5.2 Hz; **27**: 4.61 ppm, d, ^3J 4.9 Hz; *cf.* **26**: 5.01 ppm, d, ^3J 9.1 Hz). The predominant formation of *trans* products from **21** can be understood by considering the possible conformations leading to the transition states (Scheme 1). Cyclization can either take place via the chair-like conformation **30** or via the boat-like conformation **31**. In both cases, the iminium double bond has the *Z* geometry to avoid pseudo-allylic 1,3-strain[12b–d,15]. Cyclization in a 5-*exo* fashion via the chair-like conformation **30** will then lead to the *trans* intermediate **32** which is trapped by a nucleophile. On the other hand, 5-*exo* cyclization can also proceed via the boat-like conformation **31**, giving the intermediate *cis* cation **33**. The positive charge can be stabilized by the formation of the dioxycarbenium ion **34**, eventually leading to the lactone **26**. Such a mechanism might explain the formation of an excess of the *trans* products, as the cyclization is more likely to take place via a chair-like transition state.

The cyclizations of both silanes **22** and **23** with formic acid (entries 6 and 8) gave the desired products **28** and **29** in relatively poor yields. When the reactions were carried out at higher temperatures, protodesilylation became a major side-reaction. A better yield of the bicyclic allene **29** was obtained by using boron trifluoride etherate. Upon treatment of **29** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) isomerization took place (Eqn. 5) to the unstable conjugated product **35**, which resembles biologically active bicyclic pyrazolidinones[1]. Reaction at low temperature gave a mixture of starting material and product; only at room temperature could a complete conversion into the conjugated system **35** be effected. Application of other bases (lithium dimethylamide, potassium *tert*-butoxide,

Table I Cyclization reactions to fused pyrazolidinones.

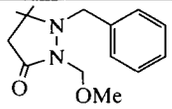
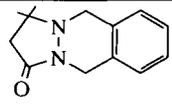
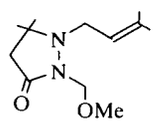
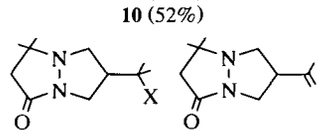
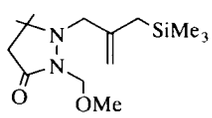
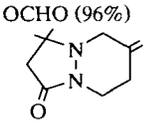
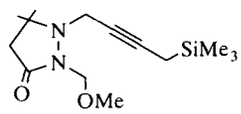
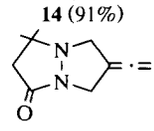
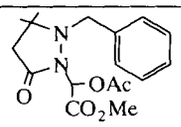
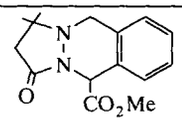
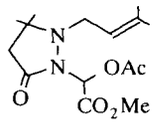
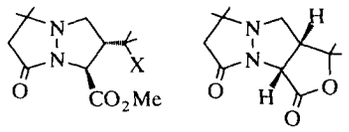
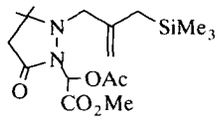
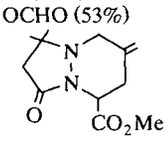
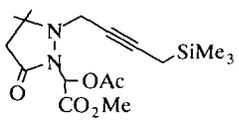
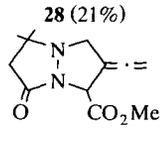
entry	cyclization precursor (yield)	acid	cyclization product(s) (yield)
			
1	**6** (86%)	$TiCl_4$	**10** (98%)
2		HCO_2H	**10** (52%)
			
3	**7** (35%)	$TiCl_4$	**11** X = Cl (76%) **12** (17%)
4		HCO_2H	**13** X = OCHO (96%)
			
5	**8** (53%)	$BF_3 \cdot OEt_2$	**14** (71%)
6		HCO_2H	**14** (91%)
			
7	**9** (54%)	$BF_3 \cdot OEt_2$	**15** (88%)
8		HCO_2H	**15** (94%)

Table II. Cyclization reactions of glyoxylate precursors.

entry	cyclization precursor (yield)	acid	cyclization product(s) (yield)
			
1	**20** (71%)	$TiCl_4$	**24** (68%)
2		HCO_2H	**24** (33%)
			
3	**21** (97%)	$TiCl_4$	**25** X = Cl (36%) **26** (20%)
4		HCO_2H	**27** X = OCHO (53%) **26** (18%)
			
5	**22** (66%)	$BF_3 \cdot OEt_2$	**28** (69%)
6		HCO_2H	**28** (21%)
			
7	**23** (90%)	$BF_3 \cdot OEt_2$	**29** (68%)
8		HCO_2H	**29** (54%)

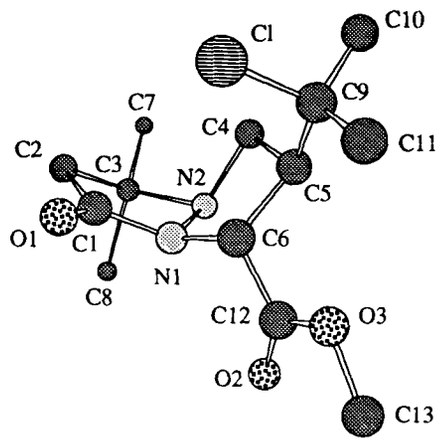
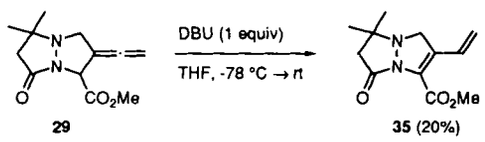


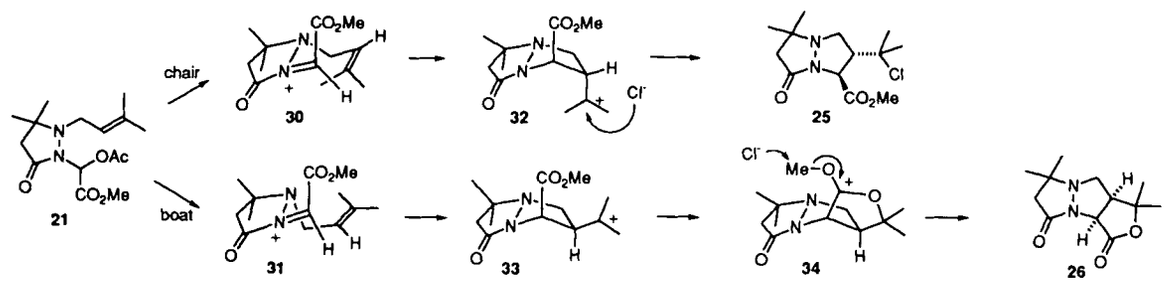
Figure 1. Chem3D™ view of the crystal structure of 25 (hydrogens omitted for clarity).

sodium hydride) did not lead to product **35** but to intractable material.

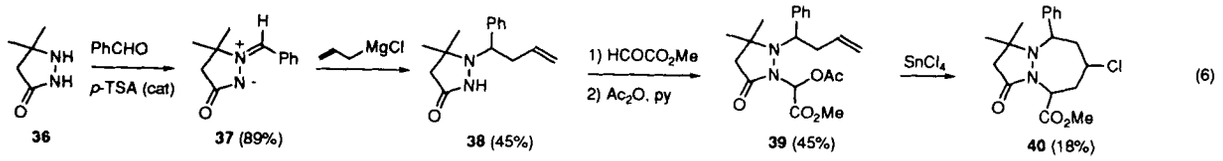


(5)

The cyclization of a 3-pyrazolidinone with a 4-butenyl substituent should lead to a pyrazolidinone fused with a 7-membered ring. Because the cyclization of unsubstituted butenyl precursors did not give the desired products, the phenyl-substituted precursor **39** was subjected to the cyclization conditions. A synthetic route to this precursor is provided by *Dorn* and *Otto*[16], who studied Grignard additions to 1,3-dipoles such as **37**.



Scheme 1. Mechanistic course of the cyclization of 21.



(6)

The zwitterion **37** was obtained by acid-catalyzed condensation of 3-pyrazolidinone **36** with benzaldehyde (Eqn. 6). Subsequent reaction with allylmagnesium chloride gave the addition product **38** after acidic work-up. The glyoxylate addition occurred in moderate yield, probably as a result of the sterically crowded environment of the nitrogen atom. The best cyclization result was obtained with tin tetrachloride, which gave the bicyclic product **40** as a single isomer in a yield of 18%. The relative configuration of **40** was not established. Cyclizations of similar precursors with a methoxy-substituted phenyl group or a more highly substituted double bond did not provide any cyclization product. Most remarkably, cyclization onto the phenyl group was not observed in either of these cases.

Finally, the ^{1}H- and ^{13}C-NMR spectra of the pyrazolidinones **10** and **14** deserve further comment. The spectra of these compounds showed some very broad signals as a result of slow inversion at one of the nitrogen atoms. This inversion process is visualized in Eqn. 7, showing the equilibrium between **14** and its enantiomeric invertomer **14'**. This nitrogen inversion is attended with a chair–chair interconversion of the six-membered ring. For example, the ^{1}H-NMR spectrum of **14** (250 MHz, solvent perdeuterotoluene) showed for the methylene hydrogens at C-5 an AB-quartet (2.73 and 3.15 ppm, J 10.6 Hz) at −40°C, whereas at +60°C a sharp singlet was observed at 2.99 ppm. From coalescence temperature measurements a nitrogen inversion barrier of 12.9 kcal/mole was determined for phthalazine derivative **10**, and of 13.2 kcal/mole for the bicyclic pyrazolidinone **14**[17]. These inversion barriers are higher than those determined several years ago[18] for monocyclic 1,2-dibenzyl-3-pyrazolidinone (11.6 kcal/mole) and 2-benzyl-1,5,5-trimethyl-3-pyrazolidinone (10.7 kcal/mole). This seems quite reasonable, as nitrogen inversion in **10** and **14** requires a concomitant conformational change of the 6-membered fused ring.

(7)

Experimental

General

All reactions were carried out under an inert atmosphere of dry nitrogen, unless otherwise described. Standard syringe techniques were applied for transfer of Lewis acids and dry solvents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions, unless indicated otherwise, using a Perkin-Elmer 298 or Perkin-Elmer 1310 spectrophotometer and wavelengths (ν) are reported in cm^{-1}. Proton-nuclear magnetic-resonance (^{1}H NMR) spectra were determined in $CDCl_3$ (unless indicated otherwise) using a JEOL PMX 60 (60 MHz), a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or a Bruker AMX 300 (300 MHz) spectrometer. The latter three instruments were also used for ^{13}C NMR (APT) spectra (50, 63 and 75 MHz, respectively) in $CDCl_3$ (unless indicated otherwise). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. Elemental analyses were performed by Dornis und 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)[19] 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 4 Å 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.

General procedure A for the N-alkylation with chloromethyl methyl ether

Sodium hydride (purchased as a 55% dispersion in oil) was washed prior to use with pentane, removing the pentane by syringe after the sodium hydride had settled. The dry solid was then mixed with DMF and the hydrazide, dissolved in DMF was added dropwise to the suspension at room temperature (rt). After being stirred for 15 min at rt, the resulting clear solution was cooled to 0°C and a solution of chloromethyl methyl ether in DMF was added. After being stirred for 15 min at 0°C and 3 h at rt, the mixture was poured into aq.satd. NaCl, extracted with 1,1,1-trichloroethane (6×), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by fc.

General procedure B for the N-functionalization with methyl glyoxylate or methyl glyoxylate hydrate

To a solution of the alkylated pyrazolidinone in benzene or toluene was added at rt an excess of freshly distilled methyl glyoxylate (hydrate)[13,14]. After complete reaction (TLC), the solution was concentrated *in vacuo*, taken up in pyridine and treated with an excess of acetic anhydride and a catalytic amount of DMAP. After being stirred at rt for 18 h, the dark brown solution was concentrated *in vacuo* and the residue purified by fc.

General procedure C for the π-cyclization reactions with $TiCl_4$

To a 0.1 M solution of the hydrazide in CH_2Cl_2 was added $TiCl_4$ (2 equiv, as a solution of $TiCl_4$ in CH_2Cl_2) at −78°C by a syringe. The mixture was stirred at −78°C for 15 min and for 5–18 h at rt. The reaction mixture was poured into cold aq. satd. $NaHCO_3$ and the resulting suspension was filtered over Celite and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by fc gave the pure cyclization product(s).

1-Benzyl-5,5-dimethyl-2-(methoxymethyl)-3-pyrazolidinone (6)

According to general procedure A, 1-benzyl-5,5-dimethyl-3-pyrazolidinone[7] (500 mg, 2.45 mmol) was deprotonated with NaH (65 mg, 2.70 mmol) and alkylated with chloromethyl methyl ether (220 μl, 2.97 mmol), while all compounds were dissolved in DMF (5 ml). Work-up and fc (ethyl acetate/hexane 1:2) afforded **6** (523 mg, 2.11 mmol, 86%) as a colourless oil, R_f 0.35. IR ν: 3085, 3060, 3030, 1690, 1450, 1370, 1070, 690. ^{1}H NMR (200 MHz) δ; 1.26, s, 6 H, $(CH_3)_2C$; 2.47, s, 2 H, $C(O)CH_2$; 3.29, s, 3 H, OCH_3; 4.01, s, 2 H, CH_2Ph; 4.35, s, 2 H, NCH_2; 7.20–7.40, m, 5 H, ArH.

2-(Methoxymethyl)-5,5-dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone (7)

According to general procedure A, 5,5-dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone[7] (385 mg, 2.12 mmol) was deprotonated with NaH (56 mg, 2.33 mmol) and chloromethyl methyl ether (240 μl, 3.16 mmol), all compounds dissolved in DMF (5 ml). Work-up and fc (ethyl acetate/hexane 1:1) afforded **7** (166 mg, 0.73 mmol, 35%) as a colourless oil, R_f 0.30. IR ν 1685, 1450, 1405, 1370, 1305, 1245, 1090, 1070, 910. ^{1}H NMR (200 MHz) δ; 1.26, s, 6 H, $(CH_3)_2C$; 1.62, s, 3 H, CH_3; 1.71, s, 3 H, CH_3; 2.40, s, 2 H, $C(O)CH_2$; 3.39, s, 3 H, CO_2CH_3; 3.52, d, J 6.8 Hz, 2 H, NCH_2; 4.76, s, 2 H, OCH_2; 5.29, tt, J 1.4, 6.8 Hz, 1 H, =CH.

2-(Methoxymethyl)-5,5-dimethyl-1-[2-[(trimethylsilyl)methyl]-2-propenyl]-3-pyrazolidinone (8)

According to general procedure A, 5,5-dimethyl-1-[2-[(trimethylsilyl)methyl]-2-propenyl]-3-pyrazolidinone[7] (931 mg, 3.88 mmol) was treated with NaH (105 mg, 4.37 mmol) and chloromethyl methyl ether (480 μl, 6.25 mmol); all compounds dissolved in DMF (5 ml). Work-up and fc (ethyl acetate/hexane 1.2:1) afforded **8** (585 mg, 2.06 mmol, 53%) as a yellowish oil, R_f 0.35. IR ν: 3075, 1690, 1370, 1245, 1070, 850. ^{1}H NMR (250 MHz) δ; 0.02, s, 9 H, $(CH_3)_3Si$; 1.25, s, 6 H, $(CH_3)_2C$; 1.68, s, 2 H, CH_2Si; 2.39, s, 2 H, $C(O)CH_2$; 3.28, s, 2 H, NCH_2; 3.37, s, 3 H, OCH_3; 4.64, br s, 1 H, =C*H*H; 4.70, s, 2 H, OCH_2; 4.85, d, J 1.5 Hz, 1 H, =CH*H*.

*2-(Methoxymethyl)-5,5-dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone (**9**)*

Following general procedure A, 5,5-dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone[7] (200 mg, 0.84 mmol) was treated with NaH (22 mg, 0.92 mmol) and chloromethyl methyl ether (107 μl, 1.27 mmol), all compounds dissolved in DMF (2 ml). Work-up and fc (ethyl acetate/hexane 1:2) afforded **9** (127 mg, 0.45 mmol, 54%) as a colourless oil, R_f 0.30. IR ν: 2200, 1685, 1400, 1370, 1250, 1075, 850. ^{1}H NMR (200 MHz) δ: 0.05, s, 9 H, $(CH_3)_3Si$; 1.29, s, 6 H, $(CH_3)_2C$; 1.43, t, J 2.4 Hz, 2 H, CH_2Si; 2.57, br s, 2 H, $C(O)CH_2$; 3.71, br s, NCH_2; 4.80, s, 2 H, OCH_2.

*2,3-Dihydro-3,3-dimethyl-1H-pyrazolo[1,2-b]phthalazin-1-one (**10**)*

According to general procedure C, a solution of **6** (322 mg, 1.30 mmol) in CH_2Cl_2 (8 ml) was treated with $TiCl_4$ (2.16 ml of a 1.2 M solution, 2.60 mmol). Work-up and fc (ethyl acetate) afforded **10** (275 mg, 1.27 mmol, 98%) as white crystals, m.p. 78–79°C (ether/hexane 10:1), R_f 0.30. IR ν: 3060, 1670, 1430, 1410, 1250, 1120, 890. ^{1}H NMR (200 MHz) δ; 1.39, br s, 6 H, $(CH_3)_2C$; 2.47, br s, 2 H, $C(O)CH_2$; 3.92, br s, 2 H, NCH_2; 4.75, br s, 2 H, NCH_2; 7.07–7.26, m, 4 H, ArH. ^{1}H NMR (250 MHz, −40°C, toluene-d_8) δ: 0.98, s, 3 H, CH_3; 1.33, s, 3 H, CH_3; 2.17, d, J 16.3 Hz, 1 H, $C(O)CHH$; 2.44 d, J 16.3 Hz, 1 H, $C(O)CHH$; 3.41, d, J 13.2 Hz, 1 H, $NCHH$; 3.55, d, J 13.2 Hz, 1 H, $NCHH$; 4.31, d, J 16.5 Hz, 1 H, $NCHH$; 5.44, d, J 16.6 Hz, 1 H, $NCHH$; 6.80–7.22, m, 4 H, ArH. ^{1}H NMR (250 MHz, 60°C, toluene-d_8) δ; 1.23, s, 6 H, $(CH_3)_2C$; 2.27, s, 2 H, $C(O)CH_2$; 3.65, s, 2 H, NCH_2; 4.77, s, 2 H, NCH_2; 6.90–7.20, m, 4 H, ArH; ^{13}C NMR (50 MHz) δ; 41.8, $C(O)CH_2$; 42.9, NCH_2; 51.2, NCH_2; 59.2, NC; 125.8, 126.6, 127.2, 127.5, ArH; 130.9, 132.2, ArC; 170.6 C(O). ^{13}C NMR (63 MHz, −30°C) δ; 22.2, CH_3; 28.3, CH_3; 40.8, $C(O)CH_2$; 42.1, NCH_2; 50.8, NCH_2; 58.8, NC; 125.3, 126.1, 126.8, 127.1, ArH; 130.0, 131.4, ArC; 170.3, C(O). MS (70 eV) m/z (%; fragment): 216 (62, M^+), 201 (100), 118 (13), 104 (45). HRMS calcd. for $C_{13}H_{16}N_2O$: 216.1263; found: 216.1274. Anal. calcd. for $C_{13}H_{16}N_2O$: C 72.19, H 7.46, N 12.95; found: C 72.10, H 7.49, N 12.86%.

This cyclization was also conducted in formic acid. A solution of **6** (268 mg, 1.08 mmol) in HCOOH (10 ml) was stirred at 50°C for 17 h. Concentration *in vacuo* and purification by fc (ethyl acetate) afforded **10** (122 mg, 0.56 mmol, 52%) as a white solid. A more straightforward way to prepare **10** is the following. A mixture of 1-benzyl-5,5-dimethyl-3-pyrazolidinone[7] (345 mg, 1.69 mmol) and trioxane (209 mg, 2.32 mmol) was heated in formic acid (5 ml) at 80°C for 20 h. Concentration *in vacuo* and purification by fc (ethyl acetate) gave **10** (157 mg, 0.73 mmol, 66%) as colourless crystals.

*6-(1-Chloro-1-methylethyl)tetrahydro-3,3-dimethyl-1H,5H-pyrazolo[1,2-a]pyrazol-1-one (**11**) and tetrahydro-6-isopropenyl-3,3-dimethyl-1H,5H-pyrazolo[1,2-a]pyrazol-1-one (**12**)*

According to general procedure C, a solution of **7** (69 mg, 0.31 mmol) in CH_2Cl_2 (3 ml) was treated with $TiCl_4$ (0.50 ml of a 1.2 M solution, 0.61 mmol). Work-up and fc (ethyl acetate) afforded **12** (10 mg, 0.052 mmol, 17%) as a colourless oil. R_f 0.40 and **11** (49 mg, 0.21 mmol, 76%) as white crystals, m.p. 91–92.5°C (ether). R_f 0.30. Data for **12**: IR ν: 1680, 1450, 1360. ^{1}H NMR (200 MHz) δ; 1.29, s, 3 H, CH_3; 1.30, s, 3 H, CH_3; 1.72, s, 3 H, CH_3; 2.38, d, J 16.7 Hz, 1 H, $C(O)CHH$; 2.52, d, J 17.4 Hz, 1 H, $C(O)CHH$; 2.61, t, J 8.0 Hz, 1 H, $NCHH$; 2.75–2.90, m, 1 H, CH; 2.97, t, J 7.4 Hz, 1 H, $NCHH$; 3.25–3.55, m, 2 H, NCH_2; 4.80, br s, 2 H, $=CH_2$; ^{13}C NMR (63 MHz) δ:20.4, 24.4, 27.3, 3 CH_3; 44.4, 45.4, $C(O)CH_2$ and NCH_2; 47.7, CH; 51.5, NCH_2; 57.4, NC; 111.9, $=CH_2$; 142.7, =C; 175.0, C(O). MS (70 eV) m/z (%; fragment): 194(40, M^+), 179 (65), 111 (45), 83 (30), 67 (40), 56 (40). HRMS calcd. for $C_{11}H_{18}N_2O$: 194.1419; found: 194.1402.

Data for **11**: IR ν; 1660, 1450, 1360. ^{1}H NMR (200 MHz) δ; 1.32, s, 6 H, $(CH_3)_2C$; 1.54, s, 3 H, CH_3; 1.55, s, 3 H, CH_3; 2.38, d, J 16.6 Hz, 1 H, $C(O)CHH$; 2.51, d, J 17.2 Hz, 1 H, $C(O)CHH$; 2.61, t, J 8.0 Hz, 1 H, $NCHH$; 2.75–2.90 m, 1 H, CH; 2.97, t, J 7.4 Hz, 1 H, $NCHH$; 3.37, br dd, J 9.2, 11.1 Hz, 1 H, $NCHH$; 3.66, dd, J 6.3, 11.3 Hz, 1 H, $NCHH$; ^{13}C NMR (50 MHz) δ; 24.1, 27.9, 31.1, 4 CH_3; 43.5, 43.8, NCH_2 and $C(O)CH_2$; 49.6, NCH_2; 57.3, NC; 69.7, CCl; 175.0 C(O). MS (70 eV) m/z (%; fragment): 230 (50, M^+), 215 (100), 179 (30), 127 (40), 111 (45), 83 (40), 69 (60). HRMS calcd. for $C_{11}H_{19}N_2OCl$: 230.1185; found: 230.1181. Anal. calcd. for $C_{11}H_{19}N_2OCl$: C 57.26, H 8.30, N 12.14; found: C 57.18, H 8.38, N, 12.03%.

*6-[1-(Formyloxy)-1-methylethyl]tetrahydro-3,3-dimethyl-1H,5H-pyrazolo[1,2-a]pyrazol-1-one (**13**)*

A solution of **7** (82 mg, 0.36 mmol) in HCOOH (4 ml) was stirred at rt for 17 h. Concentration *in vacuo* and fc (ethyl acetate) afforded **13** (83 mg, 0.35 mmol, 96%) as white crystals, m.p. 65–67°C (ether), R_f 0.15. IR ν; 1680, 1660, 1360. ^{1}H NMR (200 MHz) δ; 1.26, s, 6 H, $(CH_3)_2C$; 1.46, s, 3 H, CH_3; 1.47, s, 3 H, CH_3; 2.32, d, J 17.1 Hz, 1 H, $C(O)CHH$; 2.45, d, J 17.1 Hz, 1 H, $C(O)CHH$; 2.41–2.49, m, 1 H, $NCHH$, 2.69–2.87, m, 2 H, $NCHH$ and CH; 3.23–3.33, m, 1 H, $NCHH$; 3.48–3.57, m, 1 H, $NCHH$; 7.89, s, 1 H, CHO. ^{1}H NMR (250 MHz, toluene-d_8, 80°C) δ: 1.24, s, 3 H, CH_3; 1.30, s, 3 H, CH_3; 1.46, s, 3 H, CH_3; 1.47, s, 3 H, CH_3; 2.26, d, J 16.8 Hz, 1 H, $C(O)CHH$; 2.36 d, J 17.0 Hz, 1 H, $C(O)CHH$; 2.51 t, J 8.1 Hz, 1 H, $NCHH$; 2.67, t, J 8.1 Hz, 1 H, $NCHH$; 2.76–2.88 m, 1 H, CH; 3.42, dd, J 9.2, 11.4 Hz, 1 H, $NCHH$; 3.55, dd, J 6.4, 11.4 Hz, 1 H, $NCHH$; 7.80 s, 1 H, CHO. ^{13}C NMR (63 MHz) δ: 24.3, 24.4, 26.1, 27.8, 4 CH_3; 42.5, $C(O)CH_2$; 43.4, NCH_2; 48.3, NCH_2; 51.6, CH; 57.1, NC; 82.0, CO; 160.0, 175.3, C(O). MS (70 eV) m/z (%; fragment): 240 (60, M^+), 225 (60), 179 (40), 137 (30), 111 (100), 83 (25), 69 (70). HRMS calcd. for $C_{12}H_{20}N_2O_3$: 240.1469; found: 240.1488.

*Hexahydro-3,3-dimethyl-6-methylene-1H-pyrazolo[1,2-a] pyridazin-1-one (**14**)*

To a solution of **8** (312 mg, 1.10 mmol) in CH_2Cl_2 (6 ml) was added at 0°C $BF_3 \cdot OEt_2$ (270 μl, 2.20 mmol) and the mixture was stirred at 0°C for 15 min and for 3 h at rt. The solution was poured into aq. satd. NaCl (100 ml) and extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate) to give **14** (138 mg, 0.77 mmol, 71%) as a colourless oil, R_f 0.30. IR ν: 1670, 1415, 1260, 1115, 905. ^{1}H NMR (200 MHz) δ: 1.28, s, 6 H, $(CH_3)_2C$; 2.21, t, J 5.8 Hz, 2 H, NCH_2CH_2, 2.42, s, 2 H, $C(O)CH_2$; 3.10–4.10, br s, 2 H, NCH_2CH_2; 3.20, s, 2 H, $NCH_2C=$; 4.96, s, 1 H, $=CHH$; 4.98, s, 1 H, $=CHH$. ^{1}H NMR (250 MHz, −40°C, toluene-d_8) δ: 0.98, s, 3 H, CH_3; 1.25, s, 3 H, CH_3; 1.93, dd, J 3.3, 13.4 Hz, 1 H, NCH_2CHH; 2.07, dt, J 5.8, 12.4 Hz, 1 H, NCH_2CHH; 2.18, d, J 16.5 Hz, 1 H, $C(O)CHH$; 2.45, d, J 16.5 Hz, 1 H, $C(O)CHH$; 2.73, d, J 10.5 Hz, 1 H, $NCHHC=$; 2.92 dt, J 3.9, 12.5 Hz, 1 H, $NCHHCH_2$; 3.15, d, J 10.6 Hz, 1 H, $NCHHC=$; 4.46, dd, J 5.5, 12.5 Hz, 1 H, $NCHHCH_2$; 4.92, s, 1 H, $=CHH$; 4.98, s, 1 H, $=CHH$. ^{1}H NMR (250 MHz, 60°C, toluene-d_8) δ: 1.16, s, 6 H, $(CH_3)_3C$; 2.07, t, J 6.0 Hz, 2 H, NCH_2CH_2; 2.28, s, 2 H, $C(O)CH_2$; 3.06, s, 2 H, $NCH_2C=$; 3.61, br s, 2 H, NCH_2CH_2; 4.90, s, 1 H, $=CHH$; 4.93, s, 1 H, $=CHH$. ^{13}C NMR (50 MHz) δ: 31.7, NCH_2CH_2; 40.9, NCH_2CH_2; 42.5, $C(O)CH_2$; 55.7, $NCH_2C=$; 58.3, NC; 112.4, $=CH_2$; 140.7, =C; 170.6 C(O). ^{13}C NMR (63 MHz, −30°C) δ: 22.3, CH_3; 28.4, CH_3; 31.7, NCH_2CH_2; 40.8, NCH_2CH_2; 41.9, $C(O)CH_2$; 56.0, $NCH_2C=$; 58.5, NC; 113.4, $=CH_2$; 139.9, =C; 170.8, C(O). ^{13}C NMR (63 MHz, 70°C, benzene-d_6) δ: 25.1, $(CH_3)_2C$, 32.2, NCH_2CH_2; 41.6, NCH_2CH_2; 43.2, $C(O)CH_2$, 55.8, $NCH_2C=$; 58.2, NC, 111.2, $=CH_2$; 142.7, =C, 170.5, C(O). MS (70 eV) m/z (%; fragment): 180 (24, M^+), 165 (96), 137 (15), 83 (24), 67 (63), 53 (58), 41 (100). HRMS calcd. for $C_{10}H_{16}N_2O$: 180, 1262; found: 180.1267.

This cyclization was also conducted in formic acid. A solution of **8** (300 mg, 1.06 mmol) in HCOOH (8 ml) was stirred at rt for 5 h. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:1) afforded **14** (174 mg, 0.97 mmol, 91%) as a colourless oil.

*Tetrahydro-3,3-dimethyl-6-vinylidene-1H,5H-pyrazolo[1,2-a]pyrazol-1-one (**15**)*

To a solution of **9** (90 mg, 0.31 mmol) in CH_2Cl_2 (3 ml) was added at 0°C $BF_3 \cdot OEt_2$ (79 μl, 0.63 mmol) and the mixture was stirred at 0°C for 15 min and for 3 h at rt. The solution was poured into aq. satd. NaCl (50 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:1) to give **15** (49 mg, 0.28 mmol, 88%) as a colourless oil, R_f 0.25. IR ν; 1960, 1680. ^{1}H NMR (200 MHz) δ: 1.31 (s, 6 H, $(CH_3)_2C$; 2.41, s, 2 H, $C(O)CH_2$; 3.38, br s, 2 H, NCH_2; 4.07, br s, 2 H, NCH_2; 4.89, quintet, J 4.0 Hz, 2 H, $=CH_2$. ^{13}C NMR (50 MHz) δ: 26.0, br, 2 CH_3; 42.9, $C(O)CH_2$; 44.5, 51.3, 2 NCH_2; 57.2, NC; 80.0, $=CH_2$; 98.4, $C=C=CH_2$; 176.8, C(O); 199.4, $C=C=CH_2$. ^{13}C NMR (63 MHz, toluene-d_8, 90°C) δ: 27.3, br, 2 CH_3; 43.8 $C(O)CH_2$; 46.3, 52.7, 2 NCH_2, 58.1 NC; 80.1, $=CH_2$; 101.1, $C=C=CH_2$, 178.0 C(O); 200.7, $C=C=CH_2$. HRMS calcd. for $C_{10}H_{14}N_2O$: 178.1106; found: 178.1102.

This cyclization was also conducted in formic acid. A solution of **9** (88 mg, 0.31 mmol) in HCOOH (3 ml) was stirred at rt for 5 h.

Concentration *in vacuo* and fc (ethyl acetate/hexane 1:1) afforded **15** (50 mg, 0.28 mmol, 94%) as a colourless oil.

*α-Acetoxy-1-benzyl-5,5-dimethyl-3-oxopyrazolidineacetic acid methyl ester (**20**)*

According to general procedure B, a solution of 1-benzyl-5,5-dimethyl-3-pyrazolidinone[7] (374 mg, 1.83 mmol) in benzene (20 ml) was treated with methyl glyoxylate hydrate (409 mg, 3.86 mmol) and acetylated with Ac_2O (0.86 ml, 9.15 mmol) in pyridine (20 ml). Work-up and fc (ethyl acetate/hexane 1:1) afforded **20** (433 mg, 1.30 mmol, 71%) as a colourless oil, R_f 0.45. IR ν: 1750, 1705, 1370, 1230, 1040, 955, 690. ^{1}H NMR (200 MHz) δ: 1.15, s, 3 H, CH_3; 1.20, s, 3 H, CH_3; 2.07, s, 3 H, C(O)CH_3; 2.21, d, J 16.4 Hz, 1 H, C(O)CHH; 2.69, d, J 16.5 Hz, 1 H, C(O)CHH; 3.82, s, 3 H, CO_2CH_3; 4.14, d, J 14.4 Hz, 1 H, NCHH; 4.24, d, J 14.5 Hz, 1 H, NCHH; 6.45, s, 1 H, NCH; 7.23–7.38, m, 5 H, ArH. ^{13}C NMR (50 MHz) δ: 20.5, CH_3; 24.7, CH_3; 27.6, CH_3; 41.1, C(O)CH_2; 52.7, CO_2CH_3; 58.0, CH_2Ph; 63.0, NC; 76.4, NCH; 127.2, 128.2, 128.4, ArH; 138.2, ArC; 164.9, 169.4, 173.5, 3 C(O).

*α-Acetoxy-5,5-dimethyl-1-(3-methyl-2-butenyl)-3- oxopyrazolidineacetic acid methyl ester (**21**)*

Following general procedure B, a solution of 5,5-dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone[7] (5.00 g, 28.0 mmol) in toluene (100 ml) was treated with methyl glyoxylate (5.86 g, 66 mmol) and acetylated with Ac_2O (10.5 ml, 110 mmol) in pyridine (75 ml). Work-up and fc (ethyl acetate/hexane 1:2; afforded **21** (8.47 g, 27 mmol, 97%) as a colourless oil, R_f 0.30. IR ν: 1750, 1705, 1435, 1370, 1230, 1040, 960. ^{1}H NMR (200 MHz) δ: 1.15, s, 3 H, CH_3; 1.35, s, 3 H, CH_3; 1.62, s, 3 H, CH_3; 1.69, s, 3 H, CH_3; 2.11, s, 3 H, C(O)CH_3; 2.15, d, J 16.4 Hz, 1 H, C(O)CHH; 2.60, d, J 16.4 Hz, 1 H, C(O)CHH; 3.40–3.65, m, 2 H, NCH_2; 3.76, s, 3 H, CO_2CH_3; 5.28, t, J 7.4 Hz, 1 H, =CH; 6.56, s, 1 H, NCH.

*α-Acetoxy-5,5-dimethyl-3-oxo-1-[2-[(trimethylsilyl)methyl]-2-propenyl]-3-pyrazolidineacetic acid methyl ester (**22**)*

Following general procedure B, a solution of 5,5-dimethyl-1-[2-[(trimethylsilyl)methyl]-2-propenyl]-3-pyrazolidinone[7] (453 mg, 1.89 mmol) in benzene (20 ml) was treated with methyl glyoxylate hydrate (717 mg, 6.76 mmol) and acetylated with Ac_2O (0.89 ml, 9.45 mmol) in pyridine (8 ml). Work-up and fc (ethyl acetate/hexane 1:1) afforded **22** (443 mg, 1.25 mmol, 66%) as a colourless oil, R_f 0.45. IR ν: 3070, 1750, 1705, 1435, 1370, 1245, 1225, 1040, 855. ^{1}H NMR (250 MHz) δ: 0.02, (s, 9 H, $(CH_3)_3$Si; 1.21, s, 3 H, CH_3; 1.27, s, 3 H, CH_3; 1.48, d, J 13.5 Hz, 1 H, CHHSi; 1.67, d, J 13.5 Hz, 1 H, CHHSi; 2.10, s, 3 H, C(O)CH_3; 2.17, d, J 16.4 Hz, 1 H, C(O)CHH; 2.62, d, J 16.4 Hz, 1 H, C(O)CHH; 3.43, s, 2 H, NCH_2; 3.76, s, 3 H, CO_2CH_3; 4.66, br s, 1 H, =CHH; 4.89, d, J 1.5 Hz, 1 H, =CHH; 6.44, s, 1 H, NCH. ^{13}C NMR (50 MHz) δ: −0.4, $(CH_3)_3$Si; 20.5, CH_3; 23.8, CH_2Si; 24.1, CH_3; 27.2, CH_3; 41.1, C(O)CH_2; 52.6, CO_2CH_3; 60.2, NCH_2; 62.5, NC; 76.3, NCH; 110.7, =CH_2; 143.2, =C; 164.7, 169.4, 173.4, 3 C(O).

*α-Acetoxy-5,5-dimethyl-3-oxo-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidineacetic acid methyl ester (**23**)*

According to general procedure B, a solution of 5,5-dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone[7] (400 mg, 1.68 mmol) in benzene (5 ml) was treated with methyl glyoxylate hydrate (356 mg, 3.36 mmol) and acetylated with Ac_2O (0.80 ml, 7.26 mmol) in pyridine (7 ml). Work-up and fc (ethyl acetate/hexane 1:2) afforded **23** (556 mg, 1.51 mmol, 90%) as a colourless oil, R_f 0.30. IR ν: 2200, 1755, 1710, 1370, 1250, 1040, 850. ^{1}H NMR (200 MHz) δ: 0.05, s, 9 H, $(CH_3)_3$Si; 1.13, s, 3 H, CH_3; 1.39, s, 3 H, CH_3; 1.42, t, J 2.4 Hz, 2 H, CH_2Si; 2.12, s, 3 H, C(O)CH_3; 2.15, br s, 1 H, C(O)CHH; 3.0, br s, 1 H, C(O)CHH; 3.50, dt, J 18.6, 2.3 Hz, 1 H, NCHH; 3.75, s, 3 H, CO_2CH_3; 3.84, d, J 18.6 Hz, 1 H, NCHH; 6.77, s, 1 H, NCH.

*2,3,5,10-Tetrahydro-1,1-dimethyl-3-oxo-1H-pyrazolo[1,2-b]phthalazine-5-carboxylic acid methyl ester (**24**)*

Following general procedure C, a solution of **20** (112 mg, 0.336 mmol) in CH_2Cl_2 (3 ml) was treated with $TiCl_4$ (1.23 ml of a 1.2 M solution, 0.67 mmol). Work-up and fc (ethyl acetate) afforded **24** (63 mg, 0.23 mmol, 68%) as white crystals, m.p. 123–124°C (ether/ethanol), R_f 0.60. IR ν: 3030, 1745, 1680, 1430, 1260, 1220, 1000. ^{1}H NMR (250 MHz) δ: 1.42, s, 6 H, $(CH_3)_2$C; 2.31, d, J 16.4 Hz, 1 H, C(O)CHH; 2.66, d, J 16.5 Hz, 1 H, C(O)CHH; 3.75, s, 3 H, CO_2CH_3; 3.92, s, 2 H, NCH_2; 5.76, s, 1 H, NCH; 7.07–7.09, m, 1 H, ArH; 7.21–7.26, m, 2 H, ArH; 7.53–7.56, m, 1 H, ArH. ^{13}C NMR (50 MHz) δ: 22.6, CH_3; 28.0, CH_3; 41.5, C(O)CH_2; 50.9, NCH_2; 52.6, CO_2CH_3; 54.1, NCH; 59.5, NC; 127.1; 127.3, 127.6, 128.0, ArH; 128.0, 132.7, ArC; 169.1, 170.4, 2 C(O). MS (70 eV) m/z (%; fragment): 274 (25, M^+), 259 (7), 215 (35), 199 (7), 173 (47), 131 (13), 116 (9), 40 (24), 32 (86). HRMS calcd. for $C_{15}H_{18}N_2O_3$: 274.1317; found: 274.1340.

This cyclization was also conducted in formic acid. A solution of **20** (48 mg, 0.14 mmol) in HCOOH (2 ml) was stirred at 50°C for 17 h. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:1) afforded **24** (13 mg, 0.047 mmol, 33%) as a white solid.

*trans-2-(1-Chloro-1-methylethyl)tetrahydro-5,5-dimethyl-7-oxo-1H,5H-pyrazolo[1,2-a]pyrazole-1-carboxylic acid methyl ester (**25**) and cis-hexahydro-1,1,7,7-tetramethyl-1H,5H-furo[3,4-c]pyrazolo[1,2-a]pyrazolo[1,2-a]pyrazole-3,5-dione (**26**)*

According to general procedure C, a solution of **21** (220 mg, 0.705 mmol) in CH_2Cl_2 (7 ml) was treated with $TiCl_4$ (1.2 ml of a 1.2 M solution, 1.57 mmol). Work-up and fc (ethyl acetate/hexane 1:1) afforded **25** (73 mg, 0.25 mmol, 36%) as an inseparable mixture with **26** (34 mg, 0.14 mmol, 20%) as a colourless oil, R_f 0.35. A sample of **25** could be obtained in pure form after another purification by fc, which solidified upon standing, m.p. 91–93°C (ethyl acetate/hexane 1:5).

Data for **25**. IR ν: 1750, 1710. ^{1}H NMR (200 MHz) δ: 1.32, s, 3 H, CH_3; 1.35, s, 3 H, CH_3; 1.52, s, 3 H, CH_3; 1.61, s, 3 H, CH_3; 2.31, d, J 17.3 Hz, 1 H, C(O)CHH; 2.54, d, J 17.3 Hz, 1 H, C(O)CHH; 2.64, dd, J 9.4, 8.0 Hz, 1 H, NCHH; 3.03–3.11, t, J 8.0 Hz, 1 H, NCHH and ddd, J 9.5, 5.3, 7.8 Hz, 1 H, CH; 3.73, s, 3 H, CO_2CH_3; 4.60, d, J 5.2 Hz, 1 H, NCH. ^{13}C NMR (50 MHz) δ; 23.5, 29.1, 31.5, 32.0, 4 CH_3; 41.7, C(O)CH_2; 51.0, NCH_2; 52.8, CO_2CH_3; 56.9, NC; 57.5, CH; 57.8, NCH; 69.9, CCl; 171.0, 176.8, 2 C(O). MS (70 eV) m/z (%; fragment): 288 (25, M^+), 273 (40), 238 (20), 187 (20), 99 (100), 43 (40). HRMS calcd. for $C_{13}H_{21}N_2O_3Cl$: 288.1240; found: 288.1205.

Data for **26**. ^{1}H NMR (200 MHz) δ: 1.31, s, 3 H, CH_3; 1.35, s, 3 H, CH_3; 1.44, s, 3 H, CH_3; 1.49, s, 3 H, CH_3; 2.33, d, J 17.7 Hz, 1 H, CHH; 2.49, d, J 17.2 Hz, 1 H, CHH; 2.45–2.52, m, 1 H, NCHH; 2.91, t, J 8.3 Hz, 1 H, CH; 3.09, d, J 9.8 Hz, 1 H, NCHH; 4.99, d, J 9.1 Hz, 1 H, NCH.

X-ray crystal-structure determination of **25**

$C_{13}H_{21}N_2O_3Cl$, M_r = 288.8; monoclinic, $P2_1/c$, a = 10.129(2), b = 16.521(1), c = 10.270(1) Å, α = 90°, β = 119.237(8)°, γ = 90°, V = 1499.7(4) Å^3, Z = 4, D_x = 1.28 g/cm^3, λ(CuKα) = 1.5418 Å, μ(CuKα) = 23.3 cm^{-1}, F(000) = 616, rt. Final R = 0.059 for 2402 observed reflections.

A crystal with dimensions 0.35×0.60×0.80 mm approximately was used for data collection on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated CuKα radiation and θ–2θ scan. A total of 3082 unique reflections was measured within range $-10 \leq h \leq 12$, $-20 \leq k \leq 0$, $-12 \leq l \leq 0$. Of these, 2402 were above the significance level of 2.5 $\sigma(I)$. The maximum value of $\sin(\theta)/\lambda$ was 0.63 Å^{-1}. Unit-cell parameters were refined by a least-squares fitting

Table III Fractional coordinates of the non-hydrogen atoms and equivalent isotropic thermal parameters.

Atom	x	y	z	U_{eq}
Cl	0.2015(2)	0.72350(9)	0.4863(2)	0.104(1)
C(1)	0.5662(6)	0.7617(3)	0.4839(5)	0.068(3)
C(2)	0.6964(5)	0.7631(3)	0.6420(6)	0.072(3)
C(3)	0.7553(5)	0.6763(3)	0.6709(5)	0.065(3)
C(4)	0.5015(4)	0.6116(3)	0.6036(4)	0.055(2)
C(5)	0.3609(5)	0.5977(3)	0.4526(5)	0.059(2)
C(6)	0.3953(6)	0.6498(3)	0.3442(5)	0.069(3)
C(7)	0.8143(5)	0.6459(3)	0.8284(5)	0.075(3)
C(8)	0.8760(6)	0.6650(3)	0.6224(6)	0.084(4)
C(9)	0.2111(5)	0.6151(3)	0.4520(6)	0.076(3)
C(10)	0.2093(6)	0.5698(4)	0.5801(7)	0.090(4)
C(11)	0.0711(5)	0.5969(3)	0.2933(7)	0.091(4)
C(12)	0.3956(9)	0.6007(3)	0.2202(6)	0.110(5)
C(13)	0.284(1)	0.5328(5)	−0.0012(8)	0.22(1)
N(1)	0.5421(4)	0.6825(2)	0.4387(4)	0.062(2)
N(2)	0.6209(4)	0.6269(2)	0.5627(4)	0.057(2)
O(1)	0.4960(4)	0.8188(2)	0.4054(4)	0.087(2)
O(2)	0.5087(6)	0.5843(3)	0.2142(5)	0.130(4)
O(3)	0.2601(6)	0.5796(3)	0.1203(4)	0.134(4)

Table IV Bond distances of the non-hydrogen atoms with standard deviations in parentheses.

Bond	Distance (Å)	Bond	Distance (Å)
Cl–C(9)	1.836(5)	C(5)–C(6)	1.576(8)
C(1)–C(2)	1.511(6)	C(5)–C(9)	1.542(8)
C(1)–N(1)	1.371(6)	C(6)–C(12)	1.511(9)
C(1)–O(1)	1.218(5)	C(6)–N(1)	1.426(6)
C(2)–C(3)	1.527(7)	C(9)–C(10)	1.52(1)
C(3)–C(7)	1.510(7)	C(9)–C(11)	1.581(6)
C(3)–C(8)	1.540(9)	C(12)–O(2)	1.21(1)
C(3)–N(2)	1.509(5)	C(12)–O(3)	1.297(8)
C(4)–C(5)	1.526(5)	C(13)–O(3)	1.59(1)
C(4)–N(2)	1.484(7)	N(1)–N(2)	1.452(5)

procedure using 23 reflections with $80 < 2\theta < 90°$. Corrections for Lorentz and polarisation effects were applied. The structure was solved by Direct Methods. The hydrogen atoms were calculated. Block-diagonal least-squares refinement on F, anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms, restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.09 Å, converged to $R = 0.059$, $R_w = 0.072$, $(\Delta/\sigma)_{max} = 0.93$. A weighting scheme $w = (3.5 + F_{obs} + 0.006 \cdot F_{obs}^2)^{-1}$ was used. An empirical absorption correction (DIFABS)[20] was applied, with coefficients in the range of 0.71–1.50. A final difference-Fourier map revealed a residual electron density between −0.4 and 0.4 eÅ^{-3}. Atom C-13 is remarkably anisotropic, so the hydrogen atoms attached to it were refined with a fixed temperaturefactor of $U = 0.15$ Å^2. Scattering factors were taken from *Cromer* and *Mann*[21]. The anomalous scattering of Cl was taken into account. All calculations were performed with XTAL[22], unless stated otherwise. Tables III–V show fractional coordinates, bond distances and bond angles of the non-hydrogen atoms. Details of the crystal structure determination have been deposited at the Cambridge Crystallographic Data Centre.

*trans-2-[1-(Formyloxy)-1-methylethyl]tetrahydro-5,5-dimethyl-7-oxo-1H,5H-pyrazolo[1,2-a]pyrazole-1-carboxylic acid methyl ester (**27**)*

A solution of **21** (200 mg, 0.64 mmol) in HCOOH (6 ml) was stirred at rt for 40 h. Concentration *in vacuo* and purification by fc (ethyl acetate/hexane 1:1) afforded an inseparable mixture of **27** (101 mg, 0.34 mmol, 53%) and **26** (29 mg, 0.12 mmol, 18%) as a colourless oil, R_f 0.10. Crystallization from ether gave **27** in pure form as white crystals, m.p. 108–109°C. IR ν: 1715, 1460, 1435, 1390, 1370, 1260, 1180, 1140. ^{1}H NMR (200 MHz) δ: 1.33, s, 3 H, CH_3; 1.37, s, 3 H, CH_3; 1.53, s, 3 H, CH_3; 1.60, s, 3 H, CH_3; 2.34, d, J 17.4 Hz, 1 H, C(O)CHH; 2.55, d, J 17.4 Hz, 1 H, C(O)CHH; 2.49–2.54, m, 1 H, NCHH; 2.98, m, 2 H, NCHH and CH; 3.74, s, 3 H, CO_2CH_3; 4.59, d, J 4.9 Hz, 1 H, NCH; 7.91, s, 1 H, CHO. ^{13}C NMR (50 MHz) δ: 23.5, 24.4, 25.0, 29.0, 4 CH_3; 41.7, CH_2; 49.4 NCH_2; 52.7, CO_2CH_3; 56.4, 56.3, 2 CH; 56.8 NC; 81.6, CO; 159.7, 170.9, 177.0, 3 C(O). HRMS calcd. for $C_{14}H_{22}N_2O_5$: 298.1529; found: 298.1519. Anal. calcd. for $C_{14}H_{22}N_2O_5$: C 56.36, H 7.43, N 9.39; found: C 56.22, H 7.31, N 9.26%.

Table V Bond angles of the non-hydrogen atoms with standard deviations in parentheses.

Bond	Angle (°)
C(2)–C(1)–N(1)	107.2(4)
C(2)–C(1)–O(1)	128.3(4)
N(1)–C(1)–O(1)	124.4(4)
C(1)–C(2)–C(3)	104.3(4)
C(2)–C(3)–C(7)	115.7(5)
C(2)–C(3)–C(8)	110.3(5)
C(2)–C(3)–N(2)	103.8(3)
C(7)–C(3)–C(8)	110.2(4)
C(7)–C(3)–N(2)	110.6(4)
C(8)–C(3)–N(2)	105.6(4)
C(5)–C(4)–N(2)	102.9(4)
C(4)–C(5)–C(6)	102.5(4)
C(4)–C(5)–C(9)	113.8(4)
C(6)–C(5)–C(9)	116.8(4)
C(5)–C(6)–C(12)	113.2(4)
C(5)–C(6)–N(1)	104.0(3)
C(12)–C(6)–N(1)	110.2(6)
Cl–C(9)–C(5)	109.0(3)
Cl–C(9)–C(10)	106.8(4)
Cl–C(9)–C(11)	106.2(3)
C(5)–C(9)–C(10)	109.3(4)
C(5)–C(9)–C(11)	110.7(5)
C(10)–C(9)–C(11)	114.5(4)
C(6)–C(12)–O(2)	123.8(5)
C(6)–C(12)–O(3)	111.9(7)
O(2)–C(12)–O(3)	124.3(6)
C(1)–N(1)–C(6)	123.1(4)
C(1)–N(1)–N(2)	112.1(3)
C(6)–N(1)–N(2)	107.5(3)
C(3)–N(2)–C(4)	116.8(4)
C(3)–N(2)–N(1)	102.5(3)
C(4)–N(2)–N(1)	100.4(3)
C(12)–O(3)–C(13)	104.0(7)

*Hexahydro-1,1-dimethyl-7-methylene-3-oxo-1H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester (**28**)*

To a solution of **22** (98 mg, 0.28 mmol) in CH_2Cl_2 (3 ml) was added at 0°C $BF_3 \cdot OEt_2$ (68 μl, 0.55 mmol) and the mixture was stirred at 0°C for 15 min and for 3 h at rt. The solution was poured into aq. satd. NaCl (50 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate) to afford **28** (45 mg, 0.19 mmol, 69%) as white crystals, m.p. 65–66°C (hexane), R_f 0.30. IR ν: 3080, 1740, 1670, 1435, 1410, 1270, 1230, 1050, 910. ^{1}H NMR (250 MHz) δ: 1.16, s, 3 H, CH_3; 1.27, s, 3 H, CH_3; 2.29, d, J 16.5 Hz, 1 H, C(O)CHH; 2.32, d, J 13.3 Hz, 1 H, CHCHH; 2.54, d, J 16.6 Hz, 1 H, C(O)CHH; 2.85, d, J 14.0 Hz, 1 H, CHCHH; 3.06, d, J 10.8 Hz, 1 H, NCHH; 3.31, d, J 10.7 Hz, 1 H, NCHH; 3.69, s, 3 H, CO_2CH_3; 4.94–5.00, m, 3 H, $=CH_2$ and NCH). ^{13}C NMR (63 MHz) δ: 22.2, CH_3; 27.8, CH_3; 32.6, $CHCH_2$; 42.7, C(O)CH_2; 52.1, CO_2CH_3; 52.3, NCH; 55.1, NCH_2; 58.8, NC; 114.2, $=CH_2$; 138.2, =C; 169.5, 171.1, 2 C(O). HRMS calcd. for $C_{12}H_{18}N_2O_3$: 238.1317; found: 238.1307. Anal. calcd. for $C_{12}H_{18}N_2O_3$: C 60.49, H 7.61, N 11.76; found: C 60.55, H 7.68, N 11.68%.
This cyclization was also conducted in formic acid. A solution of **22** (120 mg, 0.33 mmol) in HCOOH (3 ml) was stirred at rt for 5 h. Concentration *in vacuo* and fc (ethyl acetate) afforded **28** (16 mg, 0.067 mmol, 21%) as a white solid.

*Tetrahydro-5,5-dimethyl-7-oxo-2-vinylidene-1H,5H-pyrazolo[1,2-a]pyrazole-1-carboxylic acid methyl ester (**29**)*

To a solution of **23** (195 mg, 0.54 mmol) in CH_2Cl_2 (5 ml) was added at 0°C $BF_3 \cdot OEt_2$ (136 μl, 1.09 mmol) and the mixture was stirred at 0°C for 15 min and for 3 h at rt. The solution was poured into aq. satd. NaCl (50 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:1) to give **29** (85 mg, 0.36 mmol, 68%) as a colourless oil, R_f 0.30. IR ν: 1960, 1730, 1700, 1430, 1370, 1300, 1240, 990, 860. ^{1}H NMR (200 MHz) δ: 1.32, s, 3 H, CH_3; 1.43, s, 3 H, CH_3; 2.45, d, J 17.2 Hz, 1 H, C(O)CHH; 2.54, d, J 17.2 Hz, 1 H, C(O)CHH; 3.34, dt, J 11.2, 4.0 Hz, 1 H, NCHH; 3.59, dt J 11.2, 2.1 Hz, 1 H, NCHH; 3.76, s, 3 H, CO_2CH_3; 5.02–5.08, m, 3 H, $=CH_2$ and NCH. ^{13}C NMR (50 MHz) δ: 23.2, 28.0, 2 CH_3; 43.4, CH_2; 50.6, NCH_2; 52.7, CO_2CH_3; 56.7, NCH; 58.2, NC; 81.6, $=CH_2$; 99.3, C=C=CH_2; 168.3, 171.2, 2 C(O); 200.8, C=C=CH_2. MS (70 eV) m/z (%; fragment): 236 (45, M^+), 221 (25), 204 (50), 186 (55), 146 (100), 135 (50), 59 (35). HRMS calcd. for $C_{12}H_{16}N_2O_3$: 236.1161; found: 236.1172.
This cyclization was also conducted in formic acid. A solution of **23** (220 mg, 0.60 mmol) in HCOOH (6 ml) was stirred at rt for 5 h. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:1) afforded **29** (77 mg, 0.33 mmol, 54%) as a colourless oil.

*2,3-Dihydro-5,5-dimethyl-7-oxo-2-vinyl-1H,5H-pyrazolo[1,2-a]pyrazole-1-carboxylic acid methyl ester (**35**)*

To a solution of **29** (80 mg, 0.34 mmol) in THF (2 ml) was added at −78°C DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 50 μl, 0.34 mmol) and the mixture was allowed to warm to rt in 2 h. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:1) afforded **35** (16 mg, 0.068 mmol, 20%) as a yellow oil, R_f 0.40. IR ν: 1745, 1700, 900. ^{1}H NMR (200 MHz) δ: 1.26, s, 6 H, 2 CH_3; 2.63, s, 2 H, CH_2; 3.89, s, 3 H, CO_2CH_3; 4.04, s, 2 H, NCH_2; 5.16, d, J 17.7 Hz, 1 H, =CHH; 5.38, d, J 10.9 Hz, 1 H, =CHH; 6.98, dd, J 10.9, 17.6 Hz, 1 H, =CH. ^{13}C NMR (50 MHz) δ: 22.5, CH_3; 49.0, 49.5, NCH_2 and CH_2; 52.4, CO_2CH_3; 62.7, NCH_2; 119.4, $=CH_2$; 127.6, =CH; 130.8, C=CC(O); 159.5, C(O), 165.5, C=CC(O); 171.0, C(O).

*5,5-Dimethyl-1-(1-phenyl-3-butenyl)-3-pyrazolidinone (**38**)*

To a solution of 5,5-dimethyl-3-pyrazolidinone (**36**, 1.65 g, 14.5 mmol) in toluene (20 ml) were added benzaldehyde (1.54 g, 14.5 mmol) and a catalytic amount of *p*TSA (4-toluenesulphonic acid). The resulting solution was refluxed under azeotropic removal of water for 18 h. Filtration and recrystallization (CH_2Cl_2/ether 1:5) afforded **37** (2.59, 12.9 mmol, 89%) as white crystals, m.p. 143–144°C. IR ν: 3060, 1655, 1580. ^{1}H NMR δ: 1.71, s, 6 H, $(CH_3)_2C$; 2.72, s, 2 H, $C(O)CH_2$; 7.08, s, 1 H, CH; 7.43–7.47, m, 3 H, ArH; 8.32–8.37, m, 2 H, ArH. To a solution of **37** (1.50 g, 7.43 mmol) in THF (15 ml) was added dropwise at 0°C allylmagnesium chloride (3.7 ml of a 2.0 M solution in THF, 7.4 mmol) and the mixture was allowed to warm to rt. After being stirred at ambient temperature for 2 h, the mixture was refluxed for another hour and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (10 ml) and 0.95 ml of 8 N aq. HCl was added dropwise. After addition of CH_2Cl_2 (50 ml), the organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:1) to afford **38** (821 mg, 3.36 mmol, 45%) as a white solid, m.p. 108–110°C, R_f 0.35. IR ν: 3410, 1680, 910, 690. ^{1}H NMR (250 MHz) δ: 1.18, s, 3 H, CH_3; 1.29, s, 3 H, CH_3; 1.78, d, *J* 16.1 Hz, 1 H, C(O)C*H*H; 2.05, d, *J* 16.1 Hz, 1 H, C(O)CH*H*; 2.58–3.99, m, 2 H, $CHCH_2$, 3.96, dd, *J* 6.0, 8.6 Hz, 1 H, NCH; 4.87–5.00, m, 2 H, $=CH_2$; 5.47–5.59, m, 1 H, =CH; 7.18–7.36, m, 5 H, ArH; 9.03, br s, 1 H, NH. ^{13}C NMR (63 MHz) δ: 25.0, 27.9, 2 CH_3; 40.0, $CHCH_2$; 43.6, $C(O)CH_2$; 63.5, NC; 65.6, NCH; 116.7, $=CH_2$; 127.4, 128.2, 128.7, ArH; 134.9, =CH; 140.6, ArC; 176.0 C(O).

*α-Acetoxy-5,5-dimethyl-3-oxo-1-(1-phenyl-3-butenyl)-3-pyrazolidineacetic acid methyl ester (**39**)*

According to general procedure B, a solution of **38** (939 mg, 3.84 mmol) in benzene (20 ml) was treated with methyl glyoxylate hydrate (814 mg, 7.7 mmol) and acetylated with Ac_2O (1.81 ml, 19.1 mmol) in pyridine (15 ml). Work-up and fc (ethyl acetate/hexane 1:3.5) afforded **39** (650 mg, 1.74 mmol, 45%) as a colourless oil, 1:1 mixture of diastereomers, R_f 0.30. IR ν: 1765, 1750, 1715, 1370, 1220, 690. ^{1}H NMR (200 MHz) δ (two diastereomers); 1.17, 1.23, s, 3 H, CH_3; 1.27, 1.32, s, 3 H, CH_3; 1.63, 1.78, br s, 2 H, $C(O)CH_2$; 2.17, 2.19, s, 3 H, $C(O)CH_3$; 2.74–2.79, m, 2 H, CH_2; 3.81, 3.89, s, 3 H, CO_2CH_3; 4.07–4.15, m, 1 H, CH; 4.93–5.06, m, 2 H, $=CH_2$; 5.50–5.70, m, 1 H, =CH; 6.18, 6.59, s, 1 H, NCH; 7.24–7.54, m, 5 H, ArH.

*7-Chlorohexahydro-1,1-dimethyl-3-oxo-9-phenyl-1H,5H-pyrazolo[1,2-a][1,2]diazepine-5-carboxylic acid methyl ester (**40**)*

According to general procedure C, a solution of **39** (100 mg, 0.27 mmol) in CH_2Cl_2 (3 ml) was treated with $SnCl_4$ (0.27 ml of a 2.0 M solution, 0.54 mmol). Work-up and fc (ethyl acetate/hexane 1:1.3) afforded **40** (18 mg, 0.051 mmol, 18%) as white crystals, single isomer, m.p. 153–154°C (ether), R_f 0.40. IR ν: 1740, 1680, 1390, 690. ^{1}H NMR (250 MHz) δ: 0.92, s, 3 H, CH_3; 1.46, s, 3 H, CH_3; 2.10, d, *J* 16.3 Hz, 1 H, C(O)C*H*H; 2.15–2.45, m, 3 H, CH_2 and CH*H*; 2.83, d, *J* 16.3 Hz, 1 H, C(O)CH*H*; 2.89–3.01, m, 1 H, CH*H*; 3.78, s, 3 H, CO_2CH_3; 4.07–4.19, m, 1 H, CHCl; 4.50, dd, *J* 2.3, 5.1 Hz, 1 H, NC*H*Ph, 4.81; dd, *J* 10.8, 3.1 Hz, 1 H, NCHC(O); 7.25–7.38, m, 5 H, ArH. ^{13}C NMR (63 MHz) δ: 24.2, 29.0, 2 CH_3); 37.7, 42.2, 2 CH_2; 43.6, $C(O)CH_2$; 52.4, CO_2CH_3; 53.4, 53.6, 2 CH; 63.2, CH; 63.4, NC; 126.5, 127.4, 128.8, ArH; 142.4, ArC; 170.3, 172.0, C(O). Anal. calcd. for $C_{18}H_{23}N_2O_3Cl$: C 61.62, H 6.61, N 7.98; found: C 61.68, H 6.56, N 7.94%.

Acknowledgements

We thank *J.A.J. Geenevasen* for his help in recording the temperature-dependent NMR spectra of compounds **10** and **14**. *K. Goubitz* and *J. Fraanje* (Laboratory of Crystallography, University of Amsterdam) are kindly acknowledged for the X-ray crystal-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).

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