SYNTHETIC BUILDING BLOCKS CONTAINING THE 1,2-DIAZINE MOIETY: *N*- AND *O*-PROTECTED 3-(4-PYRIDAZINYL)ISOSERINES[1]

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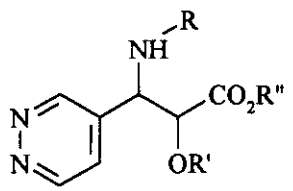
Abstract - The synthesis of pyridazinylglycidates and pyridazinylimines as potential precursors of pyridazinylisoserine derivatives, is described. Reaction of the imines (**6a,b**) with α-silyloxyketene acetals in the presence of zinc chloride led to isoserine derivatives (**7a,b**) and (**8a,b**). The mixtures of diastereoisomers obtained were separated and configurations were determined by X ray analysis.

† **Dedicated with best personal wishes to Prof. M. Tišler on the occasion of his 70th birthday.**

The α-hydroxy ß-amino acid substructure appears as the key component in various biologically active compounds.[2] Thus for instance, several endopeptidase inhibitors,[3] leukotriene antagonists[4] and antitumor agents[5] contain the isoserine moiety. The current interest in these (potential) drugs has resulted in a number of investigations aimed at the development of synthetic pathways to building blocks required for the construction of congeneric molecules with improved pharmacological and/or pharmacokinetic characteristics. In this context synthetic approaches to phenylisoserine and various heteroaromatic analogs thereof have been reported.[6] Whereas pyridylisoserines[7] have already been prepared, the 3-(4-pyridazinyl)isoserine system (**1a**) so far remained unexplored. Here we report on the synthesis of pyridazinylisoserine esters bearing suitable protecting groups at the amino and at the hydroxy function as represented in formulae (**1b**) and (**1c**).



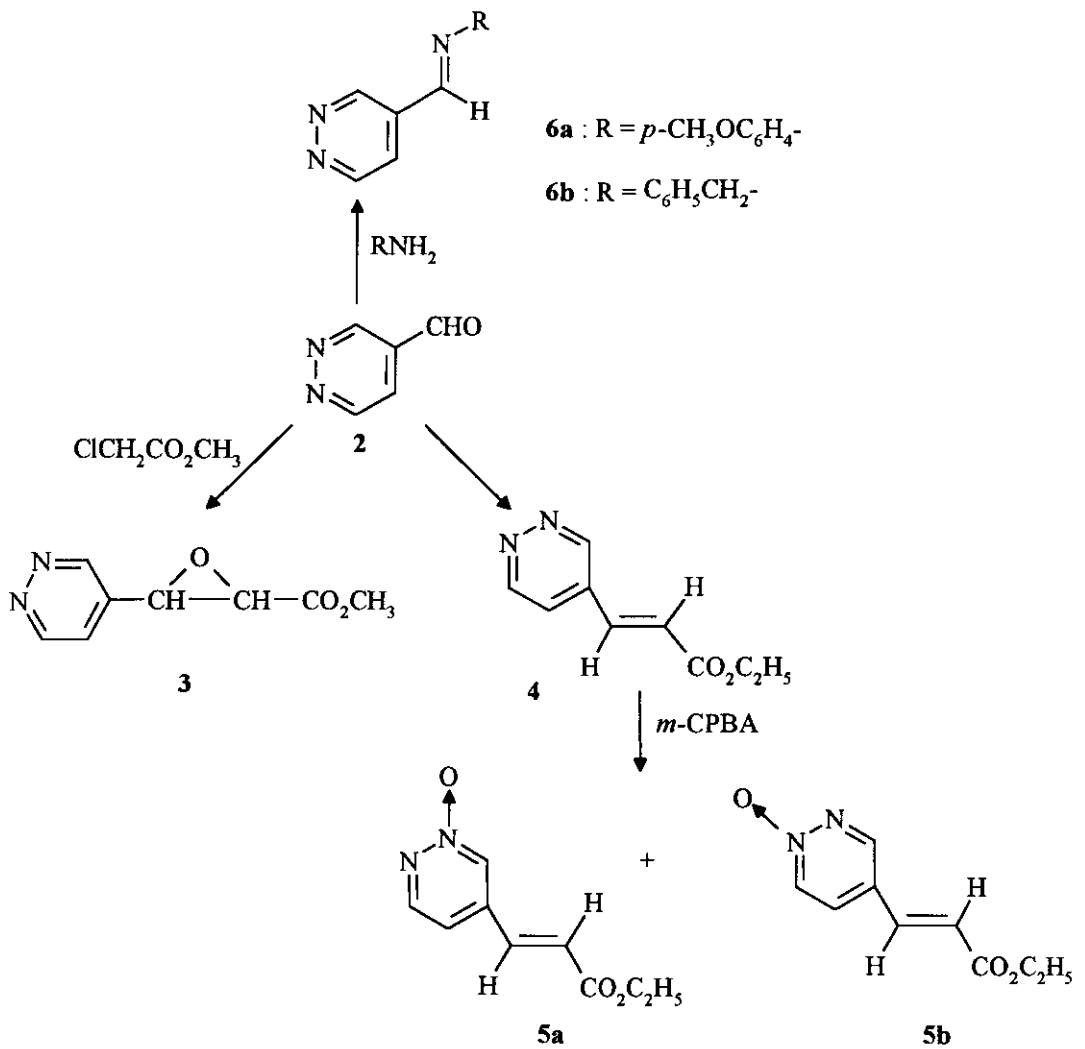
1a: R = H	R' = H	R" = H
1b: R = *p*-$CH_3OC_6H_5$-	R' = $C(CH_3)_3Si(CH_3)_2$-	R" = C_2H_5-
1c: R = $C_6H_5CH_2$-	R' = $C(CH_3)_3Si(CH_3)_2$-	R" = C_2H_5-

The present investigation was prompted by the fact that the pyridazine system represents a unique *N*-heteroarene exhibiting an extremely high dipole moment (3.95 D[8]) and that this ring system is known to be highly capable of acting as a strong acceptor of H-bonds. Thus, incorporation of the pyridazine core into bioactive compounds may well result in significant alteration of their physicochemical characteristics e.g. in a drastic enhancement of their water solubility.[9]

As key intermediates for the construction of the pyridazinylisoserine system the oxirane (**3**) and the imines (**6a,b**) derived from 4-pyridazinecarbaldehyde (**2**) were considered. Initial attempts to prepare an epoxide by reaction of conveniently available ethyl (*E*)-3-(4-pyridazinyl)acrylate[10] (**4**) with *m*-chloroperbenzoic acid (Scheme 1) following the procedure given in ref.[11] were found to result exclusively in the formation of two *N*-oxides (**5a,b**).[12] The structures of these regioisomers could be established unequivocally based on the ^1H nmr data. On the other hand, a 9:1 mixture of *E* and *Z* oxirane (**3**) was obtained albeit in only moderate yield upon reaction of 4-pyridazinecarbaldehyde with methyl chloroacetate in the presence of a

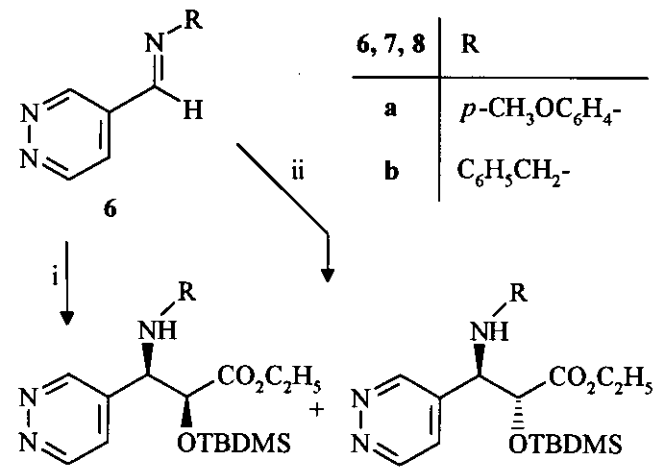
strong base.[13] Attempts to convert **3** into a hydroxy azide (methyl 3-azido-2-hydroxy-3-(4-pyridazinyl)propanoate) by reaction with sodium azide, however, remained unsuccessful.

This prompted us to prepare the so far unreported imines (**6a,b**) and to investigate their utility for the synthesis of the desired pyridazinylisoserine system bearing protecting groups removable under different conditions. Compounds (**6a,b**) could be prepared in nearly quantitative yield by reacting **2** with *p*-methoxyaniline or benzylamine, respectively, in dichloromethane solution in the presence of a dehydrating agent[14] (Scheme 1).

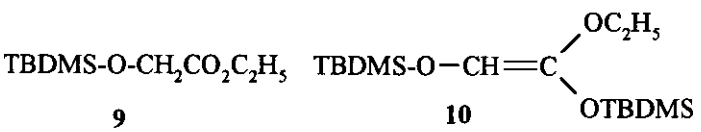


Scheme 1

According to the literature[15] reaction of *N*-arylaldimines with lithium enolates leads to ß-lactams. Upon reaction of **6a** with the enolate resulting from treatment of ethyl *tert*-butyldimethylsilyloxyacetate (**9**) with LDA we, however, isolated instead of a ß-lactam our target α-silyloxy-ß-amino ester (**7a**) as the sole product (Scheme 2). Compound (**7a**) shows syn configuration as discussed below.



i: **9**/LDA/THF/-78°C; ii: **10**/$ZnCl_2$/CH_2Cl_2



Scheme 2

The only poor yield of **7a** (12%) thus obtained prompted us to investigate reactions of **6a** and **6b** with the *E/Z* silylketene acetal (**10**) in the presence of zinc chloride. The results are summarized in Table 1. Obviously, there is no significant influence of the stereochemistry of the silylketene acetal employed on the ratio of the resulting diastereomers (**7a,8a**) in the reaction with **6a**. By contrast, in reactions of **6b** with **10** of different *E/Z* ratios, we observed preferred formation of the *anti* isomer (**8b**) upon employment of *E/Z*-**10** containing the *E* isomer as the main component, whereas reversing the *E/Z* ratio of **10** yields predominantly to the *syn* isomer (**7b**). The mixtures of the diastereomeric racemates (**7a,8a**) and (**7b,8b**)

thus obtained were separated by means of column chromatography and the configurations of the products were assigned based on the results of X ray analyses.

Table 1. Reactions of Imines (**6a,b**) with **10**

Imine	Silylketene acetal **10** ratio *Z/E*[a]	Product	ratio *syn/anti*[a]	Yield (%)[b]
6a	20/80	**7a/8a**	54/46	57
	95/5		63/37	30
6b	33/67	**7b/8b**	40/60	43
	80/20		66/34	40

[a] Ratio was determined by ^{1}H nmr. [b] Total yield of isolated products.

Crystal structure of compounds (7b) and (8a)

Technical details of the structure determination work are given in the experimental section. Atomic parameters and isotropic displacement parameters are listed in Tables 2 and 3.

Compound (7b)

The racemic diastereomer (**7b**) was recrystallized from hexane to provide crystals for the X ray determination. A view of the molecule in crystalline state is given in Figure 1. The two chiral centres of the molecule C(7) and C(16) showed *R* and *S* configuration, respectively, allowing us to assign syn configuration to this racemate. The *tert*-butyldimethylsilyl group showed a disorder and adopted two different orientations. The disorder is in principle the result of a $\approx 180^{\circ}$ rotation of this group about the C(16)-O(22) bond axis. In this way do the Si-bonded CH_3 groups of the silyl group in the first orientation roughly coincide with two of the three *tert*-butyl CH_3 groups in the second orientation and *vice versa*. The uppermost *tert*-butyl CH_3 group of both orientations occupy roughly the same space in the crystal lattice.

The tertiary carbon C(26) and Si(23) are hidden inside the bulky methyl groups and their relative positions inside the molecule are obviously of little relevance for the packing of the molecules.

Figure 1. View of **7b** in the crystal structure (only the 'A' orientation is displayed, Ortep plot, 20% ellipsoids)

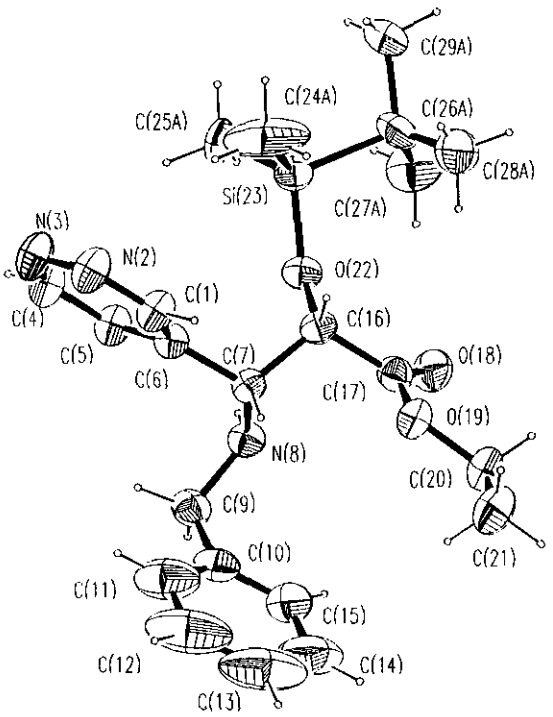


Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **7b** ($C_{22}H_{33}N_3O_3Si$); calculated H atoms omitted.

	x	y	z	Ueq
C(1)	0.26806(11)	0.2714(2)	0.2714(2)	93(1)
N(2)	0.24489(11)	0.2165(2)	0.2165(2)	111(1)
N(3)	0.22883(11)	0.1503(2)	0.1503(2)	117(1)
C(4)	0.23738(14)	0.1432(2)	0.1432(2)	107(1)
C(5)	0.26123(13)	0.1989(2)	0.1989(2)	89(1)
C(6)	0.27773(11)	0.2667(2)	0.2667(2)	74(1)
C(7)	0.30407(13)	0.3340(2)	0.3340(2)	74(1)
N(8)	0.33252(12)	0.3150(2)	0.3150(2)	85(1)
C(9)	0.3835(2)	0.2659(2)	0.2659(2)	101(1)
C(10)	0.4316(2)	0.3048(3)	0.3048(3)	109(1)
C(11)	0.4529(2)	0.2749(4)	0.2749(4)	186(2)
C(12)	0.4971(3)	0.3101(6)	0.3101(6)	272(6)
C(13)	0.5207(4)	0.3775(8)	0.3775(8)	291(10)
C(14)	0.4998(3)	0.4060(5)	0.4060(5)	247(5)
C(15)	0.4551(2)	0.3714(3)	0.3714(3)	155(2)
C(16)	0.25850(13)	0.3964(2)	0.3964(2)	81(1)
C(17)	0.2856(2)	0.4626(2)	0.4626(2)	92(1)
O(18)	0.27355(11)	0.4821(2)	0.4821(2)	123(1)
O(19)	0.32576(11)	0.49604(13)	0.49604(13)	102(1)
C(20)	0.3569(2)	0.5603(2)	0.5603(2)	126(1)
C(21)	0.3968(2)	0.5889(2)	0.5889(2)	154(2)
O(22)	0.21149(10)	0.36566(13)	0.36566(13)	88(1)
Si(23A)*	0.14174(10)	0.3582(2)	0.3582(2)	90(1)
C(24A)*	0.1324(9)	0.3589(16)	0.3589(16)	258(18)
C(25A)*	0.1101(5)	0.2691(4)	0.2691(4)	106(4)
C(26A)*	0.1038(4)	0.4469(5)	0.4469(5)	136(3)
C(27A)*	0.1162(11)	0.4429(14)	0.4429(14)	187(9)
C(28A)*	0.1258(7)	0.5199(9)	0.5199(9)	228(10)
C(29A)*	0.0385(4)	0.4369(7)	0.4369(7)	203(6)
Si(23B)*	0.14703(12)	0.4141(3)	0.4141(3)	102(2)
C(24B)*	0.1455(9)	0.5016(12)	0.5016(12)	318(24)
C(25B)*	0.1309(15)	0.4556(15)	0.4556(15)	234(16)
C(26B)*	0.0948(5)	0.3395(7)	0.3395(7)	168(5)
C(27B)*	0.1072(11)	0.2786(13)	0.2786(13)	315(18)
C(28B)*	0.1131(10)	0.3244(17)	0.3244(17)	183(10)
C(29B)*	0.0331(4)	0.3773(9)	0.3773(9)	218(8)
H(8N)	0.3078(14)	0.2961(18)	-0.0154(26)	102

*$Si(CH_3)_2(C(CH_3)_3)$ group shows orientation disorder with site occupation factors of 0.545 for 'A' sites and 1-0.545 = 0.455 for 'B' sites.

In the crystal lattice the molecules are held together by van der Waals forces and by a long (2.378 Å) and weak hydrogen bond N(8)-H(8N)····N(2) from the benzylamine nitrogen N(8) to the pyridazine nitrogen N(2) of a neighbouring molecule.

Compound (**8a**)

Suitable crystals for X ray determination were obtained by recrystallization of the minor isomer from ether. The asymmetric unit contains two independent molecules which show the same configuration and which are almost similar (only one molecule is represented in Figure 2). The two chiral centres C(1) and C(5) of the molecule represented in the Figure 2 had the *R* configuration, characterizing the anti racemate.

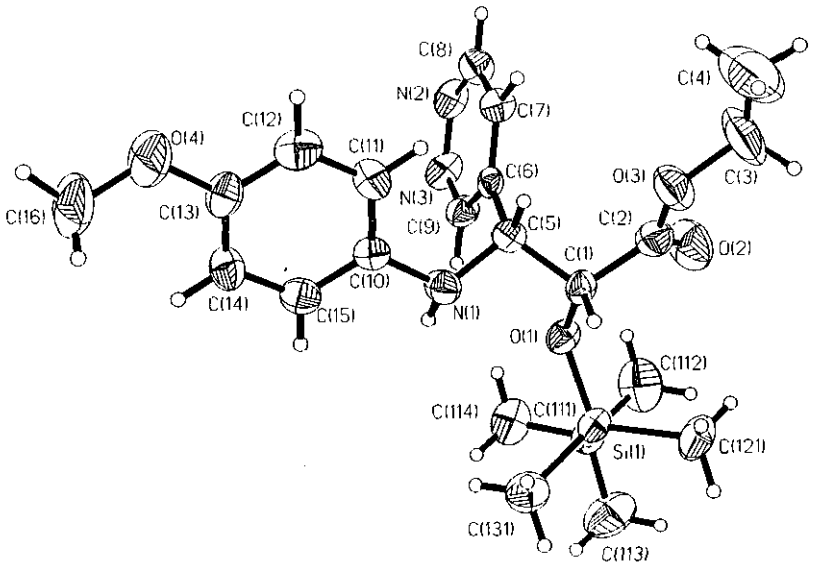


Figure 2. View of **8a** in the crystal structure (Ortep plot, 50% ellipsoids)

In the crystal lattice the molecules are held together by van der Waals forces and by a chain of two long and weak hydrogen bonds. The first one (2.514 Å) from the pyridazinyl nitrogen N(2) to the pyridazine hydrogen H(27C) of a neighbouring molecule and the other one (2.526 Å) from the pyridazinyl nitrogen N(5) (of the second molecule of the asymmetric unit) to the pyridazine hydrogen H(7C) of a neighbouring molecule.

Table 3. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **8a** ($C_{22}H_{33}N_3O_4Si$); calculated H atoms omitted (data of the two molecules of the asymmetric unit is listed).

	x	y	z	Ueq		x	y	z	Ueq
Si(2)	2614(1)	7826(1)	299(1)	33(1)	Si(1)	487(1)	2119(1)	6756(1)	37(1)
O(5)	2708(3)	7104(2)	-361(2)	38(1)	O(1)	2368(3)	2835(2)	5723(2)	36(1)
O(6)	2084(4)	8414(3)	-1994(2)	81(1)	O(2)	3086(4)	1556(3)	4748(2)	74(1)
O(7)	716(3)	7605(2)	-2249(2)	52(1)	O(3)	4507(4)	2367(3)	4171(2)	66(1)
O(8)	1625(3)	1247(3)	819(2)	68(1)	O(4)	3189(4)	8787(3)	3720(2)	76(1)
N(4)	2099(4)	5232(3)	6(3)	42(1)	N(1)	2950(4)	4752(3)	5128(3)	38(1)
N(5)	5051(4)	5195(3)	-2382(3)	44(1)	N(2)	-83(4)	4845(3)	2784(3)	42(1)
N(6)	5215(4)	5379(3)	-1616(3)	46(1)	N(3)	-211(4)	4658(3)	3648(3)	44(1)
C(21)	1725(4)	7000(3)	-847(3)	39(1)	C(1)	3351(4)	2981(3)	5196(3)	32(1)
C(22)	1553(5)	7760(4)	-1750(3)	46(1)	C(2)	3608(5)	2215(4)	4687(3)	45(1)
C(23)	497(5)	8281(4)	-3145(4)	65(2)	C(3)	4833(8)	1672(5)	3638(5)	119(3
C(24)	-413(6)	7967(4)	-3595(4)	87(2)	C(4)	5447(15)	1954(6	3018(6)	238(8
C(25)	1965(4)	5908(3)	-881(3)	35(1)	C(5)	3081(4)	4069(3)	4591(3)	33(1)
C(26)	3028(4)	5654(3)	-1432(3)	28(1)	C(6)	1992(4)	4324(3)	3930(3)	27(1)
C(27)	2889(4)	5457(3)	-2204(3)	35(1)	C(7)	2107(4)	4516(3)	3056(3)	34(1)
C(28)	3922(5)	5226(3)	-2655(3)	44(1)	C(8)	1036(5)	4773(3)	2509(3)	43(1)
C(29)	4241(5)	5598(3)	-1170(3)	39(1)	C(9)	783(5)	4407(3)	4192(3)	38(1)
C(30)	2031(4)	4217(4)	182(3)	35(1)	C(10)	2971(4)	5779(4)	4749(3)	31(1)
C(31)	1446(4)	3877(4)	-390(3)	44(1)	C(11)	3541(4)	6109(4)	3985(3)	39(1)
C(32)	1330(4)	2886(5)	-166(4)	49(1)	C(12)	3604(4)	7116(4)	3667(3)	46(1)
C(33)	1789(5)	2220(4)	644(4)	46(1)	C(13)	3091(4)	7806(4)	4097(4)	44(1)
C(34)	2376(4)	2544(4)	1220(3)	47(1)	C(14)	2520(4)	7483(4)	4850(3)	44(1)
C(35)	2501(4)	3530(4)	988(3)	44(1)	C(15)	2454(4)	6487(4)	5167(3)	42(1)
C(36)	1959(6)	588(4)	1674(4)	75(2)	C(16)	2787(6)	9494(4)	4174(4)	83(2)
C(211)	4154(4)	8157(3)	261(3)	36(1)	C(111)	968(4)	1789(3)	6933(3)	40(1)
C(212)	4339(5)	8757(4)	-672(3)	62(2)	C(112)	763(5)	1152(4)	6350(4)	75(2)
C(213)	4218(5)	8793(4)	874(3)	61(2)	C(113)	937(5)	1174(4)	7893(4)	77(2)
C(214)	5173(4)	7189(4)	550(3)	52(1)	C(114)	-80(5)	2751(4)	6718(3)	60(2)
C(221)	1309(4)	8961(3)	-70(3)	45(1)	C(121)	3780(5)	974(4)	6937(3)	57(2)
C(231)	2348(4)	7059(4)	1401(3)	52(1)	C(131)	2790(5)	2885(4)	7450(3)	56(1)
H(4N)	2654(41)	5319(32)	325(28)	40(17)	H(1N)	2336(43)	4729(33)	5473(29)	46(17)

EXPERIMENTAL

Infrared spectra (ir) were recorded from KBr pellets on a Mattson Galaxy Series FTIR 3000 spectrophotometer. Mass spectra were obtained on a Finnigan SSQ 7000 (glc/ms, EI, 70 eV). ^1H and ^{13}C nmr spectra were recorded from $CDCl_3$ solutions on a Varian Gemini 200 (^1H: 199.98 MHz, ^{13}C: 50.29 MHz) spectrometer. The solvent signal was used as internal standard, which was related to TMS with δ 7.24 ppm for ^1H and 77.0 ppm for ^{13}C. Melting points were determined on a Reichert Thermovar hot stage microscope and are uncorrected. Elemental analyses were performed at the "Institut für Physikalische Chemie", University of Vienna, Austria. Reactions were monitored by tlc using Polygram

SIL G/UV_{254} (Macherey-Nagel) plastic backed plates (0.25mm layer thickness) and visualised using an uv lamp. Column chromatography was performed using Merck Kieselgel 60 (70 - 230 mesh).

Methyl 3-(4-pyridazinyl)oxirane-2-carboxylate (**3**)

To an ice cooled solution of sodium methoxide (200 mg, 3.7 mmol) in 5 ml of dry methanol was added within 30 min a solution of 4-pyridazinecarbaldehyde (200 mg, 1.85 mmol) and methyl chloroacetate (402 mg, 3.7 mmol) in 5 ml of dry methanol. The resulting mixture was stirred for 2 h at 0°C and subsequently for 4 days at room temperature. The solution was concentrated to approximatively 4 ml and poured into water (15 ml). The aqueous solution was extracted with dichloromethane and the organic layers were combined, dried over anhydrous sodium sulfate and evaporated in *vacuo*. Purification of the crude product by column chromatography (dichloromethane-methanol, 9:1) afforded 100 mg (30%) of epoxide (**3**) as a 9/1 mixture of the *E* and *Z* isomer. Recrystallization from dichloromethane-ether afforded pure *E* epoxide as pale orange crystals, mp 73-75°C; ^{1}H nmr ($CDCl_3$): 9.13-9.17 (m, 2H, pyridazine H-3, H-6), 7.40 (dd, J_{3-5} = 2.00 Hz and J_{5-6} = 4.90 Hz, 1 H, pyridazine H-5), 4.17 (d, J = 1.70 Hz, 1 H, epoxide H-3), 3.55 (d, J = 1.70 Hz, 1 H, epoxide H-2), 3.86 (s, 3H, CH_3); ir (KBr) : cm^{-1} 1746 (C=O), 1223 (C-O-C); ms: m/z (%) 180 (M^+, 42), 164 (8), 124 (8), 123 (100), 109 (11), 108 (10). Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.15; H, 4.27; N, 15.39.

Ethyl (*E*)-3-(1-oxido-5-pyridazinyl)-2-propenoate (**5a**) and Ethyl (*E*)-3-(1-oxido-4-pyridazinyl)-2-propenoate (**5b**)

To a solution of 150 mg (0.84 mmol) of **4** in 5 ml of dichloromethane was added 790 mg (2.5 mmol) of *m*-CPBA (55 % suspension in water). The mixture was refluxed for 24 h and was then allowed to cool to room temperature. The solution was shaken with a 10 % solution of sodium sulfite, decanted and the organic layer was treated with 5% aqueous sodium hydrogencarbonate, dried over anhydrous sodium sulfate and evaporated *in vacuo*. Column chromatography (ethyl acetate-dichloromethane, 4:1) afforded 65 mg (40%) of **5a** and 49 mg (30%) of **5b** as colorless crystals.

5a: mp 107-109°C; ^{1}H nmr ($CDCl_3$): 8.42 (d, J_{3-4} = 5.57 Hz, 1H, pyridazine H-3), 8.19 (d, J_{4-6} = 1.36 Hz 1H, pyridazine H-6), 7.13 (dd, J_{3-4} = 5.57 Hz, J_{4-6} = 1.36 Hz, 1H, pyridazine H-4), 7.40 (d, B part of an AB system, J = 16.20 Hz, 1H, alkene H-3), 6.60 (d, A part of an AB system, J = 16.20 Hz, 1H, alkene H-

2), 4.27 (q, J = 7.16 Hz, 2H, C<u>H</u>$_2$-CH$_3$), 1.32 (t, J = 7.16 Hz, 3 H, CH$_2$-C<u>H</u>$_3$); ir (KBr): cm^{-1} 1705 (C=O), 1645 (C=C), 1464 (N-O). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.38; H, 5.10; N, 14.45.

5b: mp 142-144°C; ^{1}H nmr ($CDCl_3$): 8.52 (d, J_{3-5} = 3.00 Hz, 1H, pyridazine H-3), 8.08 (d, J_{5-6} = 6.83 Hz, 1H, pyridazine H-6), 7.65 (dd, J_{3-5} = 3.00 Hz, J_{5-6} = 6.83 Hz, 1H, pyridazine H-5), 7.50 (d, B part of an AB system, J = 16.12 Hz, 1H, alkene H-3), 6.46 (d, A part of an AB system, J = 16.12 Hz, 1H, alkene H-2), 4.27 (q, J = 7.16 Hz, 2H, C<u>H</u>$_2$-CH$_3$), 1.32 (t, J = 7.16 Hz, 3H, CH$_2$-C<u>H</u>$_3$); ir (KBr) : cm^{-1} 1711 (C=O), 1635 (C=C), 1467 (N-O). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.65; H, 5.17; N, 14.50.

<u>4-Methoxy-*N*-[(4-pyridazinyl)methylidene]aniline (**6a**) and *N*-[(4-pyridazinyl)methylidene]benzylamine (**6b**)</u>

To a mixture of 600 mg (5.55 mmol) of **2** and sodium sulfate (~ 4 g) in dichloromethane (20 ml) was added at 0°C over a period of 30 min a solution of 5.55 mmol of the appropriate amine in 20 ml of dichloromethane. After 90 min at 0°C the cooling bath was removed and the solution was stirred for 2 h at room temperature. Filtration of sodium sulfate and evaporation of the solvent afforded the crude imines **6a** and **6b**.

Recrystallization of **6a** from dichloromethane-tetrahydrofuran afforded 1.11 g (94%) of pure imine as pale yellow needles, mp 128-129°C; ^{1}H nmr ($CDCl_3$): 9.61(dd, J_{3-6} = 1.20 Hz, J_{3-5} = 2.18 Hz, 1H, pyridazine H-3), 9.31 (dd, J_{3-6} = 1.20 Hz, J_{5-6} = 5.30 Hz, 1H, pyridazine H-6), 7.85 (dd, J_{5-6} = 5.30 Hz, J_{3-5} = 2.18 Hz, 1H, pyridazine H-5), 8.51 (s, 1H, CH=N), 7.28-7.38 (m, BB' part of an AA'BB' system, 2H, phenyl), 6.92-6.99 (m, AA' part of an AA'BB' system, 2H, phenyl), 3.85 (s, 3 H, O-CH$_3$); ir (KBr): cm^{-1} 1620 (C=N). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.10; H, 5.26; N, 19.73.

Recrystallization of **6b** from dichloromethane-tetrahydrofuran afforded 1.01 g (95%) of pure imine as orange crystals, mp 52-53°C; ^{1}H nmr ($CDCl_3$): 9.50 (dd, J_{3-6} = 1.30 Hz, J_{3-5} = 2.24 Hz, 1H, pyridazine H-3), 9.28 (dd, J_{3-6} = 1.30 Hz, J_{5-6} = 5.24 Hz, 1H, pyridazine H-6), 7.76 (dd, J_{3-5} = 2.24 Hz, J_{5-6} = 5.24 Hz, 1H, pyridazine H-5), 8.38 (s, 1H, CH=N), 7.28-7.40 (m, 5H, phenyl-H), 4.90 (s, 2H, CH$_2$); ir (KBr): cm^{-1} 1645 (C=N); ms: m/z (%) 197 (M^+, 20), 170 (20), 112 (10), 92 (10), 91 (100), 65 (30), 51 (16). Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30: Found: C, 72.97; H, 5.63; N, 21.18.

Reaction of Imine (**6a**) with the Lithium Enolate of **9**

To a solution of 111 mg (1.1 mmol) of diisopropylamine in 4 ml of dry tetrahydrofuran was added 0.7 ml (1.1 mmol) of n-butyllithium in n-hexane (1.6M) at -78 °C. The solution was stirred for 10 min followed by slow addition (5 min) of 1 mmol (218 mg) of **9** in 2.0 ml of tetrahydrofuran. The solution was stirred for 50 min at -78° followed by addition of 1 mmol (213 mg) of **6a** in 5 ml of tetrahydrofuran within 10 min. The solution was stirred at -78°C for 4 h and then slowly allowed to warm up to room temperature and further stirred overnight. The reaction was quenched with 25 ml of a saturated solution of aqueous ammonium chloride and the reaction mixture was extracted with ether (2 x 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in *vacuo* to give 300 mg of a dark oil. Purification by column chromatography (eluent: ether) gave 52 mg (12 %) of **7a** as colorless crystals.

Ethyl 2-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenylamino)-3-(4-pyridazinyl)propanoate (**7a**) and (**8a**)

To an ice cold suspension of zinc chloride (70 mg, 0.5 mmol) in dichloromethane (3 ml) was added 106 mg (0.5 mmol) of imine (**6a**) in 2 ml dichloromethane. After stirring for 10 min at this temperature the solution was cooled to -78°C and a solution of silylketene acetal (**10**) (200 mg, 0.6 mmol, ratio *E/Z* = 80/20) in dichloromethane was added dropwise. After 8 h at -78°C the cooling bath was removed and the solution was further stirred overnight. The solution was diluted with 20 ml of dichloromethane, washed with water, saturated aqueous sodium hydrogen carbonate solution and again with water. The organic layer was dried over anhydrous sodium sulfate and evaporated in *vacuo*. Purification of the crude product by column chromatography (eluent: ether) afforded 67 mg (31 %) of **7a** and 57 mg (26 %) of **8a**. Recrystallization from diisopropyl ether afforded colorless crystals.

7a: mp 100-101°C; ^{1}H nmr ($CDCl_3$): 9.22 (dd, 1H, $J_{3\text{-}6}$ = 1,20 Hz, $J_{3\text{-}5}$ = 2.31 Hz, pyridazine H-3), 9.06 (dd, $J_{3\text{-}6}$ = 1,20 Hz, $J_{5\text{-}6}$ =5.25 Hz, 1H, pyridazine H-6,), 7.40 (dd, $J_{3\text{-}5}$ = 2.31 Hz, $J_{5\text{-}6}$ =5.25 Hz, 1H pyridazine H-5), 6.64-6.70 (m, BB' part of an AA'BB' system, 2H, phenyl), 6.39-6.46 (m, AA' part of an AA'BB' system, 2H, phenyl), 4.82 (dd, J = 8.80 Hz, J = 2.50 Hz, 1H, C<u>H</u>-NH), 4.50 (d, J = 8.80 Hz, 1H, C<u>H</u>-CO), 4.43 (d, J = 2.50 Hz, 1H, NH), 4.14 (q, J = 6.53 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.66 (s, 3H, OCH_3), 1.18 (t, J = 6.53 Hz, 3H, C<u>H</u>$_3$CH$_2$), 0.76 (s, 9H, *t*Bu), -0.05 (s, 3H, CH_3Si), -0.329 (s, 3H CH_3Si); ir (Kbr): cm^{-1} 1722 (C=O); ms: m/z (%) 431 (M^+, 6), 215 (18), 214 (100), 161 (6), 75 (12), 73 (12). Anal. Calcd for $C_{22}H_{33}N_3O_4Si$: C, 61.22; H, 7.71; N, 9.74. Found: C, 61.20; H, 7.62; N, 9.66.

8a: mp 124-125°C; ^{1}H nmr ($CDCl_3$): 9.18 (dd, J_{3-6} = 1.20 Hz, J_{3-5} = 2.31 Hz, 1H, pyridazine H-3), 9.06 (dd, J_{3-6} =1.20 Hz, J_{5-6} = 5.25 Hz, 1H, pyridazine H-6), 7.40 (dd, J_{3-5} =2.31 Hz, J_{5-6} = 5.25 Hz, 1H, pyridazine H-5), 6.65-6.75 (m, BB' part of an AA'BB' system, 2H, phenyl), 6.41-6.50 (m, AA' part of an AA'BB' system, 2H, phenyl), 4.70 (dd, J = 8.12 Hz, J = 4.86 Hz, 1H, C<u>H</u>-NH), 4.50 (d, J = 4.86 Hz, 1H, NH), 4.24 (d, J = 8.12 Hz, 1H, C<u>H</u>-CO), 4.04 (q, J = 7.19 Hz, 2H, C<u>H_2</u>CH_3), 3.69 (s, 3H, OCH_3), 1.15 (t, J = 7.19 Hz, 3H, C<u>H_3</u>CH_2), 0.89 (s, 9H, *t*Bu), 0.02 (s, 3H, CH_3Si), -0.02 (s, 3H, CH_3Si); ir (Kbr): cm^{-1} 1753 (C=O); ms: m/z (%) 431(M^+, 6), 215 (16), 214 (100), 161 (8), 75 (16) 73 (9). Anal. Calcd for $C_{22}H_{33}N_3O_4Si$: C, 61.22; H, 7.71; N, 9.74. Found: C, 61.05; H, 7.65; N, 9.67.

<u>Ethyl 2-[(*tert*-butyldimethylsilyl)oxy]-3-(benzylamino)-3-(4-pyridazinyl)propanoate (**7b**) and (**8b**)</u>

The same procedure as described for the preparation of **7a** and **8a** was applied (*E/Z* ratio of silyl ketene acetal (**10**): 20/80) with imine (**6b**) and gave after purification by column chromatography (eluent: ether) 26% of **7b** and 14 % of **8b** (ratio syn/anti: 65/35). **7b** and **8b** were recrystallized from hexane and from hexane-isopropyl ether, respectivly, to afford colorless crystals.

7b: mp 54-55°C, ^{1}H nmr ($CDCl_3$): 9.10-9.18 (m, 2H, pyridazine H-3 and H-6), 7.40-7.45 (m, 1H, pyridazine H-5), 7.10-7.30 (m, 5H, phenyl), 4.21 (d, J = 4.20 Hz, 1H), 4.12 (q, J = 7.14 Hz, 2H, C<u>H_2</u>CH_3), 4.05 (d, J = 4.20 Hz, 1H), 3.74 (d, B part of an AB system, J = 13.50 Hz, 1H, C<u>H_2</u>-C_6H_5), 3.48 (d, A part of an AB system, J = 13.50 Hz, 1H, C<u>H_2</u>-C_6H_5), 1.16 (t, J = 7.14 Hz, 3H, C<u>H_3</u>CH_2), 0.79 (s, 9H, *t*Bu), -0.05 (s, 3H, CH_3Si), -0.245 (s, 3H, CH_3Si); ir (KBr): cm^{-1} 1753 (C=O); ms: m/z (%) 415 (M^+, 2), 199 (10), 198 (66), 91 (100), 57 (40). Anal. Calcd for $C_{22}H_{33}N_3O_3Si$: C, 63.53; H, 7.94; N, 10.10: Found. C, 63.82; H, 7.80; N, 10.15.

8b mp 73-75°C, ^{1}H nmr ($CDCl_3$) 9.08-9.15 (m, 2H, pyridazine H-3 and H-6), 7.40-7.44 (m, 1H, pyridazine H-5), 7.10-7.30 (m, 5H, phenyl), 4.39 (d, J = 5.20 Hz, 1H), 4.06 (q, J = 7.20 Hz, 2H, C<u>H_2</u>CH_3), 3.99 (d, J = 5.20 Hz, 1H), 3.70 (d, B part of an AB system, J = 13.60 Hz, 1H, C<u>H_2</u>-C_6H_5), 3.53 (d, A part of an AB system, J = 13.60 Hz, 1H, C<u>H_2</u>-C_6H_5), 1.13 (t, J = 7.20 Hz, 3H, C<u>H_3</u>CH_2), 0,79 (s, *t*Bu, 9H), -0.05 (s, CH_3Si, 3H), -0.245 (s, CH_3Si, 3H); ir (KBr): cm^{-1} 1749 (C=O); ms: m/z (%) 415 (M^+, 8), 199 (8), 198 (100), 91 (80), 73 (8), 57 (8). Anal. Calcd for $C_{22}H_{33}N_3O_3Si$: C, 63.53; H, 7.94; N, 10.10. Found: C, 63.06; H, 7.81; N, 9.75.

X ray Structure Determination of Compound (**7b**) ($C_{22}H_{33}N_3O_3Si$)

A colorless prism of $C_{22}H_{33}N_3O_3Si$ with dimensions 0.5 x 0.6 x 0.8 mm was used for data collection with a PHILIPS PW1100 four-circle diffractometer and graphite monochromatized Mo Kα radiation. Crystal datas are: $C_{22}H_{33}N_3O_3Si$, M_r = 415.60, orthorhombic, space group *Pcab*, a = 23.202(6) Å, b = 17.2999 (5) Å, c = 12.323 (3) Å, ß = 90°, V = 4946 Å^3 , Z = 8, D_c = 1.116 g.cm^{-3}, μ = 0.120 mm^{-1}, T = 298 °K. Cell dimensions were determined from ±Θ scans of 16 reflections (Θ = 15 - 20°). The intensities of 4409 reflections with Θ<25°, $0 \le h \le 27$, $0 \le k \le 20$, $0 \le l \le 14$, were measured by Θ-2Θ-scans using scan widths of 0.9° + 0.33° x tan(Θ) and a scan speed of 4° min^{-1}. Three standard reflections showed insignificant fluctuations (±0.8%). The data were corrected for *LP* and system instability, but not for absorption. The structure was solved by direct methods using program *XTAL*3.2.[18] Structure refinement on F^2 was carried out with the program *SHELXL*93.[19] Anisotropic temperature factors were applied for all non-hydrogen atoms. Hydrogen atoms were inserted in idealized positions and were refined riding with the atoms to which they were bonded, except for H(8N) which was refined in *x,y,z* without restraints. The isotropic U-values were fixed at 1.2 x U_{eq} (for NH, CH, CH_2) and 1.5 x U_{eq} (for CH_3) of their carrier atoms. A correction for extinction was applied. The $Si(CH_3)_2(C(CH_3)_3)$ group showed a disorder and adopted two different orientations with site occupation factors of 0.545(7) for the 'A' orientation and 0.455(7) for the 'B' orientation. This feature was refined by applying soft distance restraints for 1,2-distances of Si-C = 1.86(3) Å and C-C = 1.54(3) Å, and for 1,3 distances of C_{Si}-C_{Si} = 3.06(10) Å, Si-C_{tBut} = 2.82(10) Å, and C_{tBut}-C_{tBut} = 2.50(10) Å. Both six-membered rings were forced to be flat. The final full-matrix least-squares refinement varied 331 parameters and used all 4314 independent reflections weighted by $w = 1/[\sigma^2(F_O^2) + (0.067P)^2 + 1.11P]$ where $P = (F_O^2 + 2F_C^2)/3$. Final $R1$ = 0.1404, $wR2$ = 0.1361 and S = 1.023 for all data; $R1$ = 0.0627 for the 2065 reflections with $F_O \ge 4\sigma(F_O)$. The final difference Fourier map showed minimum and maximum values of -0.14 and 0.16 e Å^{-3}.

X ray Structure Determination of Compound (**8a**) ($C_{22}H_{33}N_3O_4Si$)

A colorless prism of $C_{22}H_{33}N_3O_4Si$ with dimensions 0.6 x 0.6 x 0.13 mm was used for data collection with a Siemens P4 diffractometer and graphite monochromatized Mo Kα radiation. Crystal datas are: $C_{22}H_{33}N_3O_4Si$, M_r = 431.60, triclinic, space group $P\bar{1}$, a = 11.218(2) Å, b = 14.218 (2) Å, c = 16.020 (4) Å, α =73.04°(1), ß = 89.85°(2), γ = 76.66°(1), V = 2372(1) Å^3 , Z = 4, D_c = 1.208 g.cm^{-3}, μ =

0.130mm^{-1}, T = 213 °K. The intensities of 4539 reflections with 3.1°< Θ<20°, -1 ≤ h ≤ 9, -12 ≤ k ≤12, -14 ≤ l ≤15, were measured by ω-scans using scan widths of 0.75° and a variable scan speed (8.3 to 35° min^{-1}). Three standard reflections every 97 reflections showed insignificant fluctuations. The data were corrected for *LP* and an empirical absorption correction[20] based on a series of ψ-scans was applied. The structure was solved by direct methods and structure refinement on F^2 was carried out with the program *SHELXL*93.[19] Anisotropic temperature factors were applied for all non-hydrogen atoms. Hydrogen atoms were inserted in idealized positions and were refined riding with the atoms to which they were bonded, except for H(1N) and H(4N) which were refined with isotropic temperature factors. The final full-matrix least-squares refinement varied 549 parameters and used all 3722 independent reflections weighted by w = $1/[\sigma^2(F_o^2) + (0.057P)^2 + 1.8947P]$ where $P = (F_o^2 + 2F_c^2)/3$. Final $R1$ = 0.0662, $wR2$ = 0.1183 and S = 1.033 for all data; $R1$ = 0.0461 for the 2857 reflections with $I \geq 2\sigma(I)$. The final difference Fourier map showed minimum and maximum values of -0.311 and 0.363 e Å^{-3}.

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