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ADDITION OF N-BENZYLHYDRAZINE TO SUGAR δ-ENLACTONES

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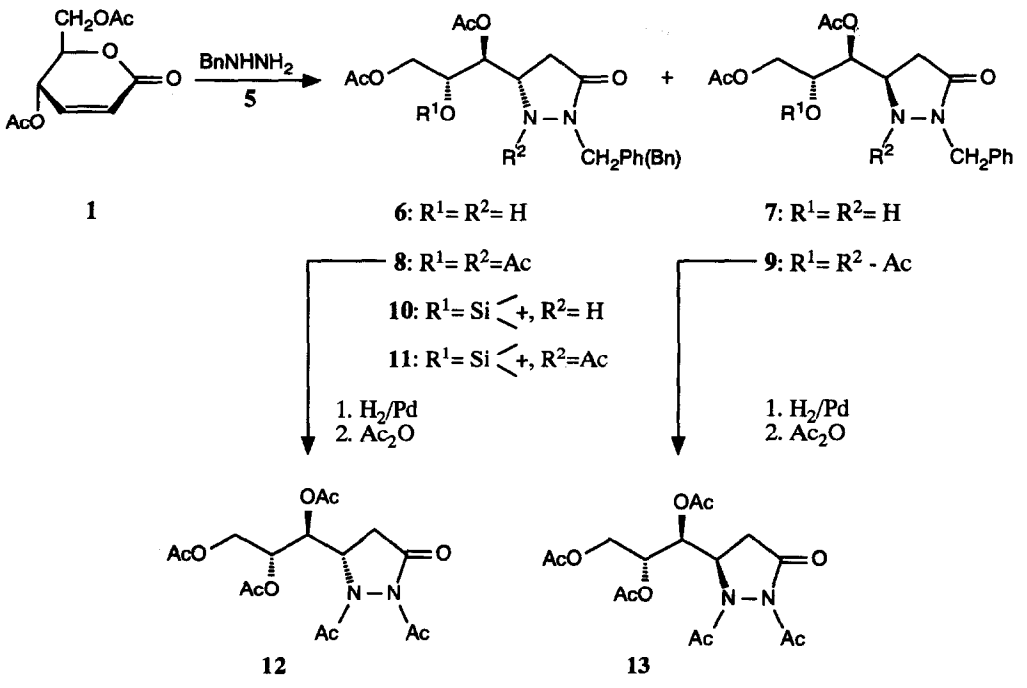
Abstract: The conjugate addition - rearrangement of *N*-benzylhydrazine to sugar δ-enlactone with *erythro* configuration **1** and **2** affords mixtures of respective *ribo* and *arabino* isomers with the former one prevailing. In the case of the *threo* lactone **3** two regioisomers with *xylo* configuration are produced, whereas in the case of **4** only one isomer with the *erythro* configuration is formed. The stereochemical course of these rections was explained.

Owing to their relatively stable conformation, hexopyranoid α,β-unsaturated sugar lactones undergo conjugate addition exclusively *anti* to the terminal substituent (Scheme 1). This axial approach of nucleophiles is well documented in the literature and has been proved for azide anion[1,2], aziridine[3], methoxyl anion[3], alkyl cuprates[4], O-benzylhydroxylamine,[5] and N-benzylhydroxylamine.[6] Recently we have reported on addition of hydrazine to lactones **1-3**, leading to stereospecific formation of pyrazolidin-3-ones.[7] Configuration at the C-5 carbon atom of the pyrazolidin-3-one ring has been assigned on the assumption that hydrazine reacts similarly as other nucleophiles.[7] Owing to the great synthetic and biological value of the cyclic hydrazine derivatives,[8] we decided to investigate addition of *N*-benzylhydrazine (**5**) to lactones **1-4** in order to examine the stereo- and regiochemistry of this reaction.

Addition of *N*-benzylhydrazine (**5**) to the lactone **1** gave after acetylation two products **8** and **9** in a proportion of 3 : 2 respectively. ^{15}N NMR spectra of compounds **8** and **9** showed that both are stereoisomers, with both nitrogen atoms acylated. At room temperature only N-2 nitrogen absorption is visible, whereas (N-1) absorption is absent owing to the slow rate of the amide dynamic process. Temperature elevation to +60°C causes appearance of both signals. Hydrogenolysis of the benzyl substituent of **8** and **9**, followed by acetylation of the nitrogen atom afforded **12** and **13**. Compound **12** was found to be identical with that obtained by the reaction of lactone **1** with hydrazine (Scheme 1).[7]

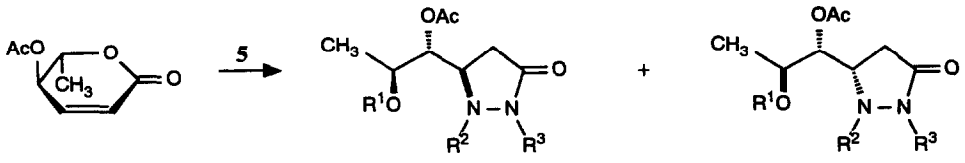
Scheme 1



Addition of *N*-benzylhydrazine to the lactone **2** proceeded in a similar way; the proportion of stereoisomers was, however, more in favor of the *arabino*-pyrazolidin-3-one compound **14** (Scheme 2). Isomers **14** and **15**, and their respective triacetates **16** and **17** could not be separated by column chromatography. ^{15}N NMR spectrum of a mixture of **16** and **17** at room temperature showed only one signal assigned to N-2 being the major isomer (**16**). Absorption at -224.2 ppm testified to the presence of a benzyl group at the *N-2* nitrogen atom. The hydrogenolysis of *N*-benzyl protection in **16** and **17**, followed by acetylation afforded a mixture of isomers **18** and **19**. Compound **18** was found to be identical with that obtained by the reaction between the lactone **2** and hydrazine; consequently it was assigned the L-*ribo* configuration. Silylation and subsequent acetylation of the mixture of **14** and **15** allowed for isolation of the main component **21** by crystallization.

In the case of the D-*glycero* lactone **3**, addition of *N*-benzylhydrazine **5** gave only one product **22** which was characterized as triacetate **23** (Scheme 3). Hydrogenolysis of **23**, followed by acetylation, gave the product **26** identical with that obtained by addition of hydrazine to lactone **3**.

Scheme 2



2 **14**: R^1= R^2= H, R^3= Bn **15**: R^1= R^2= H, R^3= Bn

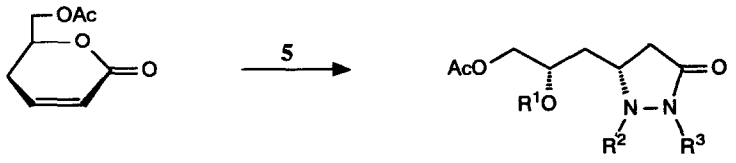
16: R^1= R^2= Ac, R^3= Bn **17**: R^1= R^2= Ac, R^3= Bn

18: R^1= R^2= R^3= Ac **19**: R^1= R^2= R^3= Ac

20: R^1= Si<, R^2= H, R^3= Bn

21: R^1= Si<, R^2= Ac, R^3= Bn

Scheme 3



3

22: R^1= R^2= H, R^3= Bn

23: R^1= R^2= Ac, R^3= Bn

24: R^1= Si<, R^2= H, R^3= Bn

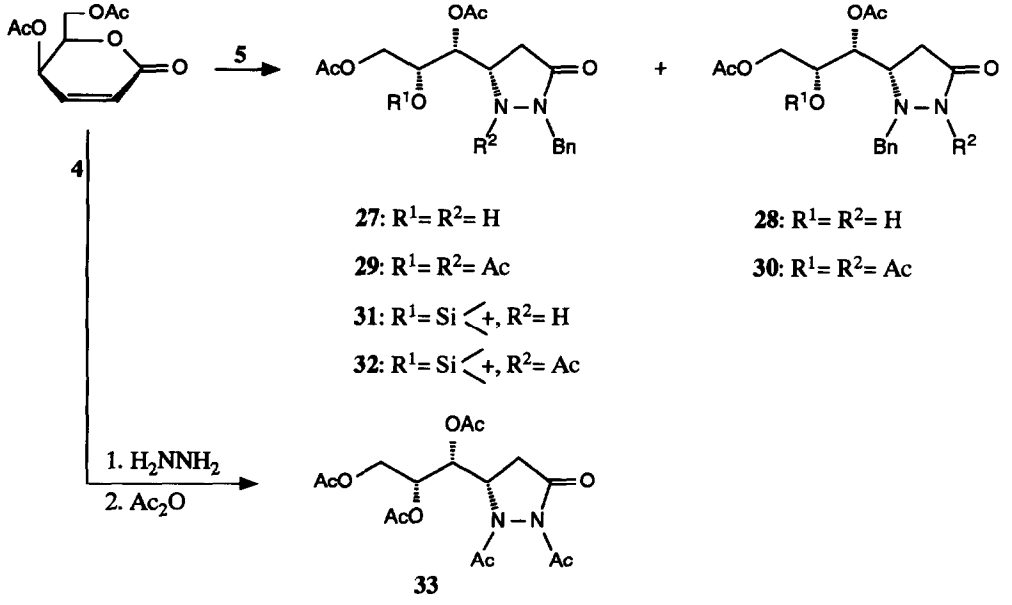
25: R^1= Si<, R^2= Ac, R^3= Bn

26: R^1= R^2= R^3= Ac

The addition of **5** to the D-*threo* lactone **4** afforded two products **27** and **28** in a proportion of 2:3 (Scheme 4). Compounds **27** and **28** were acetylated, yielding the respective triacetates **29** and **30**, which were separated by chromatography. ^{15}N NMR of compounds **29** and **30** showed that they are regioisomers; absorptions at -219.9 and -225.0 ppm, found for the more polar major isomer **29**, pointed to its 2-*N*-benzyl structure, whereas absorptions at -177.9 and -271.7 ppm, found for the other one **30**, indicated to 1-*N*-benzyl substitution. Hydrogenolysis of both regioisomers **29** and **30** and subsequent acetylation afforded the same product **33** from both compounds. Compound **33** was found to be identical with the product obtained from

4 and hydrazine in an addition - acetylation sequence. The structure and configuration of the crystalline compound **30** was proved by X-ray measurements (cf. **Experimental**) thus proving directly or indirectly the regio and stereochemistry of other products obtained.

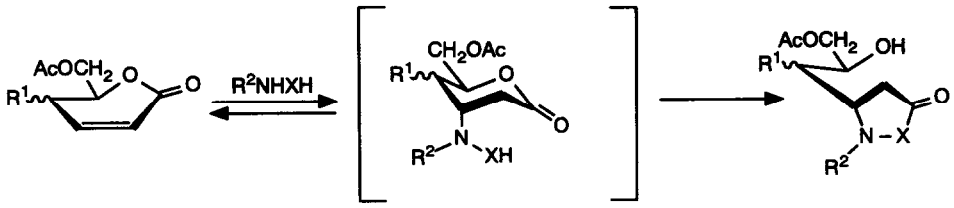
Scheme 4



[15] N NMR spectroscopy proved to be a good tool for recognition of the position of the benzyl group. There is, however, another criterion based on ^{1}H NMR absorption of the 2-*N*-acetyl group (imide acetyl), which in compounds **12**, **13**, **18**, **19**, **26**, **30**, and **33** was found to take place at ~2.5 ppm.

The differences in the behaviour of the conjugate addition of *N*-benzylhydrazine to lactones **1-4** can be explained in terms of the kinetics and thermodynamics of this reaction. Some time ago we have found[2,5] that addition of *O*-benzylhydroxylamine or of the azide anion to lactones **1-4** is reversible; axial approach of the nucleophile has been found to be strongly favored; in a few cases minute amounts of alternative reaction products have been noted in the NMR spectra of post-reaction mixtures. Nucleophiles, such as *N*-benzylhydroxylamine or hydrazine, having two nucleophilic centers undergo *anti* addition, but formation of the Michael adducts has never been observed. Axial location of the hydroxylamine or hydrazine grouping at C-3 induces rapid opening of the six-membered lactone ring by the hydroxy or by the second amino group, to afford the isoxazolidin-5-one or pyrazolidin-3-one skeleton, respectively (Scheme 5).

Scheme 5



R^1= H, OAc

R^2= H, Bn

X= O, NH, NBn

34

In the case of *N*-benzylhydrazine, the primary amino group is more nucleophilic and it is added axially, *anti* to the terminal acetoxymethyl group. The next step is, however, slower than in the case of hydroxylamine or hydrazine addition. Although no Michael adduct is observed, there is a chance that the reversibility of the first step may occur and in consequence a thermodynamic product may appear. In the case of the D-*glycero* lactone **3**, both steps of the addition - rearrangement sequence are relatively fast and therefore only one product **22** is formed. In the case of *erythro* lactones **1** and **2**, owing to the reversibility of the first step, *ribo* **6** and **14**, and *arabino* **7** and **15** adducts are formed, respectively. Owing to the steric hindrance of the *N*-benzyl group, no 1-benzylpyrazolidin-3-ones were found in the mixture. The difference in the proportion of products between addition to *erythro* lactones **1** and **2** can probably be attributed to differences in the conformational behavior of both substrates in the respective transition states. In the case of addition to the *threo* lactone **4** axial 4-acetoxy substituent facilitates the retro-Michael addition, in contrast to lactone **3**. This anchimeric assistance of the acetoxy group causes for lactone **4** lowering the energy barrier and in the consequence allows for the occurrence of the alternative regioisomer. Owing to steric hindrance, the Michael adduct **34** with a terminal *N*-benzylamino group is less reactive towards pyrazolidin-3-one skeleton formation than the regioisomer with a terminal amino group. In consequence, a substantial amount of 1-benzylpyrazolidin-3-one (**28**) is produced.

Contrary to the well recognized stereochemical course of the Michael addition of nucleophiles to α,β-unsaturated δ-lactones,[1-7] which is under kinetic control, conjugate addition - rearrangement of *N*-benzylhydrazine to lactones **1-4** is characterized by the fact that both the kinetic and thermodynamic factors influence the reaction course. The addition of **5** to **3** is noteworthy; it produces only one isomer, having a benzyl group at the *N*-2 nitrogen atom of the five - membered heterocyclic ring. This regiochemistry is

opposite to that found for alkylation and acylation of the pyrazolidin-3-one skeleton.[8]

Experimental

^{1}H NMR spectra were recorded with Bruker AM 500 and Varian Gemini 200 spectrometers. ^{15}N NMR spectra were performed on a Bruker AM 500 spectrometer operating at 50.68 MHz frequency equipped with a standard variable temperature unit, at 303°K, 323°K, and 363°K, in toluene-d_8 solution using nitromethane-d_3 as an external standard O ppm. The technique used was optimized for 2.0 Hz long range INEPT. Typical experimental conditions were; 23 relaxation dealy, 1.08 s acquisition time and 300-2000 scans. IR spectra were obtained on a FT-IR-1600 Perkin - Elmer spectrophotometer. Optical rotations were measured with a JASCO Dip-360 digital polarimeter. Melting points are uncorrected. Column chromatography was performed on Merck silica gel 230-400 mesh, lactones **1-4** were obtained according to known procedures.

Addition of *N*-benzylhydrazine to lactones 1, 2, 3, and 4; general procedure. To a stirred solution of benzylhydrazine hydrochloride (0.4 g, 2.5 mmol) in 96% ethanol (10 ml) sodium hydroxide (0.2 g, 25 mmol) in water (2 ml) was added. To this mixture lactone **1-4** (2.0 mmol) was added. The resulting solution was stirred at room temperature for 3 h. Subsequently the solvent was removed under vacuum and residue was passed through a silica gel column using ethyl acetate as an eluent. The product thus obtained was acetylated with acetic anhydride - pyridine (1:1) mixture (4 ml). After a standard work up the residue was separated on silica gel into pure isomers.

(5S,1'S,2'R) 1-Acetyl-5-(1',2',3'-tri-acetoxy)propyl-2-benzyl-pyrazolidin-3-one (8) from **1**: 51%; syrup; $[\alpha]_D$ -62.8° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1750, 1715, and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.98, 2.02, 2.03, 2.10 (4s, 12H, 4Ac), 2.39 (dd, 1H, *J* 17.1 and 0.8 Hz, H-4), 2.89 (dd, 1H, *J* 17.1 and 9.0 Hz, H-4a), 3.98 (dd, 1H, *J* 12.3 and 3.4 Hz, H-3'), 4.13 (dd, 1H, *J* 12.3 and 7.1 Hz, H-3'a), 4.69, 4.97 (2d, 2H, *J* 14.8 Hz, Benzyl), 4.75 (dd, 1H, *J* 7.2, and 3.6 Hz, H-1'), 4.80 (bt, 1H, *J* 7.2 and 9.0 Hz, H-5), 5.04 (dt, 1H, *J* 3.6, 3.4, and 7.1 Hz, H-2'); ^{15}N NMR (toluene-d_8, 90°C): -221.9 (N-1), -225.7 (N-2).

Anal. Calcd. for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 5.99; N, 6.45. Found: C, 57.86; H, 6.02; N, 6.56.

(5R,1'S,2'R) 1-Acetoxy-5-(1'2'3'-tri-acetoxy)propyl-2-benzyl-pyrazolidin-3-one (9) from **1**: 33%; mp. 74.0-77.0°C; $[\alpha]_D$ +46.0° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1750, 1720, 1695 cm^{-1}; ^{1}H NMR: ($CDCl_3$): 1.88, 1.99, 2.03, 2.11 (4s, 12H, 4Ac), 2.24 (d, 1H, *J* 16.6 Hz, H-4), 2.96 (dd, 1H, *J* 16.6 and 8.8 Hz, H-4a), 3.94 (dd, 1H, *J* 12.6 and 3.9 Hz, H-3'a), 4.14 (dd, 1H, *J* 12.6 and 2.4 Hz, H-3'b), 4.64, 4.89 (2d, 2H, *J* 15.1 Hz, Benzyl), 4.92 (ddd, *J* 8.7, 3.9, and 2.4 Hz, H-2'), 5.03 (m, 1H, H-5), 5.22 (dd, 1H, *J* 8.7 and 3.5 Hz, H-1'); ^{15}N NMR (toluene - d_8, 90°C): -220.6 (N-1), 226.0 (N-2).

Anal. Calcd. for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 5.99; N, 6.45. Found: C, 57.90; H, 6.06; N, 6.41.

(5R,1'R,2'S) 1-Acetyl-5-(1'2'-di-acetoxy)propyl-2-benzyl-pyrazolidin-3-one (16) and **(5S,1'R,2'S) 1-Acetyl-5-(1',2'-di-acetoxy)propyl-2-benzyl-pyrazolidin-3-one (17)** from **2**: spectral and analytical data taken for the mixture: 87%; **16**:**17**= 7:3; IR (CH_2Cl_2): 1740, 1710, 1685 cm^{-1}; ^1H NMR ($CDCl_3$); **16**: 1.14 (d, 3H, *J* 6.6 Hz, CH_3), 1.97, 1.98, 2.11 (3s, 9H, 3Ac), 2.36 (d, 1H, *J* 17.0 Hz, H-4), 2.87 (dd, 1H, *J* 17.0 and 8.7 Hz, H-4a), 4.55 (dd, 1H, *J* 7.7 and 2.8 Hz, H-1'), 4.61, 5.08 (2d, 2H, *J* 14.8 Hz, Benzyl), 4.70 (m, 1H, H-5), 4.71 (dq, 1H, *J* 6.6 and 2.8 Hz, H-2'); ^{15}N NMR (toluene - d_8, 30°C): -224.2 (N-2); **17**: 1.09 (d, 3H, *J* 6.4 Hz, CH_3), 1.88, 1.98, 2.06 (3S, 9H, 3Ac), 2.22 (d, 1H, *J* 16.6 Hz, H-4), 2.98 (dd, 1H, *J* 16.6 and 8.4 Hz, H-4a), 4.70, 4.94 (2d, 2H, *J* 14.9 Hz, Benzyl), 4.84 (dq, 1H, *J* 7.2 and 6.4 Hz, H-2'), 4.97 (m, 2H, H-5,1').

Anal. taken for the mixture of **16**and **17**. Calcd. for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.98; N, 7.44. Found: C, 59.93; H, 6.57; N, 7.37.

(5R,2'S) 1-Acetyl-5-(2',3'-di-acetoxy)propyl-2-benzyl-pyrazolidin-3-one (23) from **3**: 88%; syrup; $[\alpha]_D$ -52.4° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1745, 1722, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): 1.02 (ddd, 1H, *J* 14.5, 8.4, and 5.2 Hz, H-1'), 1.11 (m, 1H, H-1'a), 2.00, 2.02, 2.14 (3s, 9H, 3Ac), 2.18 (d, 1H, *J* 16.7 Hz, H-4), 2.92 (dd, 1H, *J* 16.7 and 8.1 Hz, H-4a), 3.93 (dd, 1H, *J* 12.2 and 5.4 Hz, H-3'), 3.97 (bd, 1H, *J* 12.2 Hz, H-3'a), 4.49, 5.30 (2d, 2H, *J* 14.3 Hz, Benzyl), 4.72 (m, 1H, H-2').

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 60.63; H, 6.38; N, 7.44. Found: C, 60.57; H, 6.37; N, 7.54.

(5S,1'R,2'R) 1-Acetyl-5-(1',2',3'-tri-acetoxy)propyl-2-benzyl-pyrazolidin-3-one (29), from **4**: 52%; syrup; $[\alpha]_D$ -55.4° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1749, 1702, 1648 cm^{-1}; ^1H NMR ($CDCl_3$): 1.86, 1.96, 2.07, 2.08 (4s, 12H, 4Ac), 2.34 (d, 1H, *J* 16.8 Hz, H-4), 3.00 (dd, 1H, *J* 16.8 and 8.8 Hz, H-4a), 4.27 (dd, 1H, *J* 12.4 and 5.2 Hz, H-3'), 4.41 (dd, 1H, *J* 12.4 and 3.7 Hz, H-3'a), 4.61, 5.00 (2d, 2H, *J* 15.0 Hz, Benzyl), 4.91, 5.05 (2bs, 2H, H-5, H-1'), 5.21 (ddd, 1H, *J* 6.4, 5.2, and 3.7 Hz, H-2'). ^{15}N NMR (toluene - d_8, 90°): -219.9 (N-1), -225.7 (N-2).

Anal. Calcd. for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 5.99; N, 6.45. Found: C, 57.86; H, 6.06; N, 6.43.

(5S,1'R,2'R) 2-Acetyl-5-(1',2',3'-tri-acetoxy)propyl-1-benzyl-pyrazolidin-3-one (30), from **4**: 34%; mp. 126-128°C; $[\alpha]_D$ +3.0° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1745, 1713 cm^{-1}; ^1H NMR ($CDCl_3$): 1.96, 2.01, 2.03, 2.48 (4s, 12H, 4Ac), 2.35 (dd, 1H, *J* 17.9 and 0.9 Hz, H-4), 2.80 (dd, 1H, *J* 17.9 and 8.9 Hz, H-4a), 3.49 (ddd, 1H, *J* 8.9, 5.6 and 0.9 Hz, H-5), 3.58 (dd, 1H, *J* 12.2 and 5.5 Hz, H-3'), 3.89, 4.18 (2d, 2H, *J* 12.6 Hz, Benzyl), 4.00 (dd, 1H, *J* 12.2 and 4.4 Hz, H-3'a), 4.95 (dd, 1H, *J* 5.6 and 5.0 Hz, H-1'), 5.23 (q, 1H, *J* 5.6, 5.5, and 4.4 Hz; H-2'). ^{15}N NMR (toluene-d_8, 90°C): -177.9 (N-2), -271.7 (N-1).

Anal. Calcd. for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 5.99; N, 6.45. Found: C, 57.97; H, 5.98; N, 6.55.

2'-*O*-Silylated pyrazolidin-3-ones 10, 20, 24, and 31. General procedure. Initially purified adducts **6** and **7**, **14** and **15**, **22**, **27** and **28** (0.4 mmol); see procedure above was silylated with t-butyldimethylsilyl

chloride (0.075 g, 0.5 mmol) in DMF (1 ml) in the presence of imidazole (0.034 mg, 0.5 mmol) at room temperature for 3 h. Subsequently the mixture was poured into water and extracted with ethyl ether. The extract was washed with brine, dried, evaporated and purified on a silica gel column using hexane - ethyl acetate 1:1 $^{v}/_{v}$ mixture as an eluent to isolate silylated main component only **10**, **20**, **24**, and **31**. Compounds **10**, **20**, **24**, and **31** were characterized after acetylation of the nitrogen atom as respective peracetates **11**, **21**, **25**, and **32**.

11: syrup; $[\alpha]_D$ -37.6° (*c* 1, CH_2Cl_2): IR (CCl_4): 1750, 1720, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.04, 0.04, 0.88 (3s, 15H, t-BuMe_2Si), 1.93, 2.02, 2.17 (3s, 9H, 3Ac), 2.56 (dd, 1H, *J* 16.8 and 1.0 Hz, H-4), 2.87 (dd, 1H, *J* 16.8 and 8.9 Hz, H-4a), 3.21 (m, 1H, H-2'), 3.85-3.92 (m, 2H, H-3', 3'a), 4.72, 5.03 (2d, 2xH, *J* 14.7, and Benzyl), 4.71 (dd, 1H, *J* 5.6 and 2.7 Hz, H-1'), 4.83 (dd, 1H, *J* 8.9 and 5.7 Hz, H-5).

Anal. Calcd. for $C_{25}H_{38}N_2O_7Si$: C, 59.29; H, 7.50; N, 5.53. Found: C, 59.49; H, 7.70; N, 5.66.

21: syrup; $[\alpha]_D$ +34.0° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1735, 1705, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.10, 0.87 (2s, 15H, t-BuMe_2Si), 0.84 (d, 1H, CH_3), 1.88, 2.17(2s, 6H, 2Ac), 2.62 (dd, 1H, *J* 16.8 and 1.1 Hz, H-4), 2.87 (dd, 1H, *J* 16.8 and 9.0 Hz, H-4a), 3.79 (dq, 1H, *J* 6.6 and 3.7 Hz, H-2'), 4.61 (t, 1H, *J* 4.4 and 3.7 Hz, H-1'), 4.78, 5.03 (2d, 2H, *J* 14.6 Hz, Benzyl), 4.79 (bs, 1H, H-5).

Anal. Calcd. for $C_{23}H_{36}N_2O_5Si$: C, 61.6; H, 8.09; N, 6.25. Found: C, 61.75; H, 7.78; N, 6.41.

25: syrup; $[\alpha]_D$ -39.4° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 1745, 1720, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.01, 0.04, 0.85 (3s, 15H, t-BuMe_2Si), 0.85 (m, 1H, H-2'), 1.11 (ddd, 1H, *J* 14.1, 9.0, and 4.0 Hz, H-2'a), 2.02, 2.10 (2s, 6H, 2Ac), 2.22 (d, 1H, *J* 16.3 Hz, H-4), 2.88 (dd, 1H, *J* 16.3 and 8.2 Hz, H-4a), 3.50 (dd, 1H, *J* 11.2 and 5.1 Hz, H-3'), 3.64 (m, 1H, H-2'), 3.78 (dd, 1H, *J* 11.2 and 6.4 Hz, H-3'a), 4.44 (bs, 1H, H-5), 4.62, 5.31 (2d, 2H, *J* 14.2 Hz, Benzyl).

Anal. Calcd. for $C_{23}H_{36}N_2O_5Si$: C, 61.60; H, 8.03; N, 6.25. Found: C, 61.36; H, 8.13; N, 6.25.

32: syrup; $[\alpha]_D$ -30.0° (*c* 1, CH_2Cl_2), IR (CH_2Cl_2): 1748, 1711, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.06, 0.09, 0.88 (3s, 15H, t-BuMe_2Si), 1.84, 2.03, 2.08 (3s, 9H, 3Ac), 2.76 (d, 1H, *J* 16.6 Hz, H-4), 2.91 (dd, 1H, *J* 16.6 and 8.6 Hz, H-4a), 3.90 (dd, 1H, *J* 11.1 and 6.7 Hz, H-3'), 3.96 (m, 1H, H-2'), 4.08 (dd, 1H, *J* 11.1 and 3.6 Hz, H-3'a), 4.34, 4.62 (2bs, 2H, H-5, 1'), 4.76, 5.04 (2d, 2H, J 14.3 Hz, Benzyl). MS m/z M^+ Calcd. for $C_{25}H_{38}N_2O_7Si$: 506.24482. Found 506.24421.

Hydrogenolysis of compounds 8, 9, 16 and 17, 23, 29 and 30. General procedure.

Pyrazolidin-3-ones **8**, **9**, **16** and **17**, **23**, **29**, and **30** (0.5 mmol) were hydrogenated in a boiling methanol (7 ml) over 10% Pd/C (0.1 g) with ammonium formate (0.15 g, 2.5 mmol) during 0.5 h. The progress of reaction was followed with tlc (ethyl acetate). After disappearance of the substrate, the reaction mixture was filtered through Celite, concentrated and acetylated with acetic anhydride - pyridine mixture. After standard work up the crude product was purified by chromatography.

12: obtained from **8**, spectral and analitical data reported in Ref.7.

13: obtained from **9**, syrup; $[\alpha]_D$ -61.4° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1750, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): 2.01, 2.03, 2.04, 2.17, 2.53 (5s, 15H, 5Ac), 2.48 (dd, 1H, *J* 17.6 and 0.7 Hz, H-4), 3.04 (dd, 1H, *J* 17.6 and 8.8 Hz, H-4a), 4.19 (dd, 1H, *J* 12.8 and 3.7 Hz, H-3'), 4.28 (dd, 1H, *J* 12.8 and 2.6 Hz, H-3'a), 5.19 (ddd, 1H, *J* 8.6, 3.7, and 2.6 Hz, H-2'), 5.28 (ddd, 1H, *J* 8.8, 2.7, and 0.7 Hz, H-5), 5.34 (dd, 1H, *J* 8.6 and 2.7 Hz, H-1').

Anal. Calcd. for $C_{16}H_{22}N_2O_9$: C, 49.74; H, 5.89; N, 7.25. Found: C, 50.02; H, 5.89; N, 6.84.

18 and **19** were obtained as a mixture from a mixture of **16** and **17**. Spectral and analytical data of **18** were reported in Ref. 7.

19: ^1H NMR ($CDCl_3$) selected data taken from the mixture: 1.21 (d, 3H, *J* 6.1 Hz, CH_3), 2.42 (dd, 1H, *J* 17.6 and 0.7 Hz, H-4), 3.05 (dd, 1H, *J* 17.6 and 8.9 Hz, H-4a), 5.03-5.13 (m, 2H, H-5,2'), 5.26 (bd, 1H, *J*–8 Hz, H-1').

26: obtained from **23**, spectral and analytical data reported in Ref. 7.

33: obtained independently from **29** and **30**; mp. 145-147°; $[\alpha]_D$ +24.8° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1746, 1693 cm^{-1}; ^1H NMR ($CDCl_3$): 2.03, 2.04, 2.08, 2.08, 2.53 (5s, 15H, 5Ac), 2.50 (d, 1H, *J* 17.5 Hz, H-4), 3.04 (dd, 1H, *J* 17.5 and 8.7 Hz, H-4a), 4.33 (dd, 1H, *J* 12.7 and 4.2 Hz, H-3'), 4.53 (dd, 1H, *J* 12.7 and 3.1 Hz, H-3'a), 5.20 (m, 1H, H-5), 5.27 (ddd, 1H, *J* 7.2, 4.2, and 3.1 Hz, H-2'), 5.31 (dd, 1H, *J* 7.2 and 3.7 Hz,
H-1').

Anal. Calcd. for $C_{16}H_{22}N_2O_9$: C, 49.74; H, 5.69; N, 7.25. Found: C, 49.86; H, 5.80; N, 7.07.

Compound **33** was obtained also from lactone **4** and hydrazine according to the general procedure described in Ref. 7.

X-Ray structural determinations of compound 30.

A well-shaped colourless crystal of **30** obtained from an AcOEt/hexane solution (dimensions 0.24 X 0.17 X 0.15 mm) was chosen for X-ray diffractometric measurements on a CAD-4 (Enraf-Nonius) four-circle automated diffractometer with graphite-monochromated CuK_α radiation. The cell dimensions were refined on 25 angle settings and the intensities were collected by an $\omega/2\Theta$ technique in the range up to $2\Theta_{max}$ = 153. Of total 7858 measured intensities 7035 were unique and of $I > 2\sigma_I$. The Lorentz and polarisation but no absorption correction were applied to the data.

Crystal data

$C_{21}H_{26}N_2O_8$, M_r = 434.45, orthorhombic space group $P2_12_12_1$ (No. 19), Z = 12, F(000) = 2760; a = 12.705(1), b = 17.884(1), c = 30.518(3) Å, V = 6933.8 $Å^3$; D_x = 1.26 g cm^{-1} ; μ (Cu K_α) = 7.23 cm^{-1}.

The structure was solved by direct methods program SHELXS-86[10]. The positional and individual

thermal (initially isotropic then anisotropic) parameters were refined by a least-squares full-matrix method program SHELXL-93.[11] The position of hydrogen atoms were calculated. After the convergence was reached, the empirical, spherical absorption correction was calculated by program DIFABS,[12] and applied to all observed reflections. The correction factors were (minimum, maximum, average) 0.629, 1.417, 1.010, respectively. The final refinement step involved all atomic parameters including those of hydrogen (with isotropic temperature factors) and converged at R = 0.0645, R_W = 0.0555 (statistical weights).

The final residual electron density maximum was below 0.21 e/Å. The refined positional parameters for the non-H atoms of **30**, are shown in Table 1.

Fig. 1. The arbitrarily oriented molecule of **30** with the crystallographic labelling of atoms.

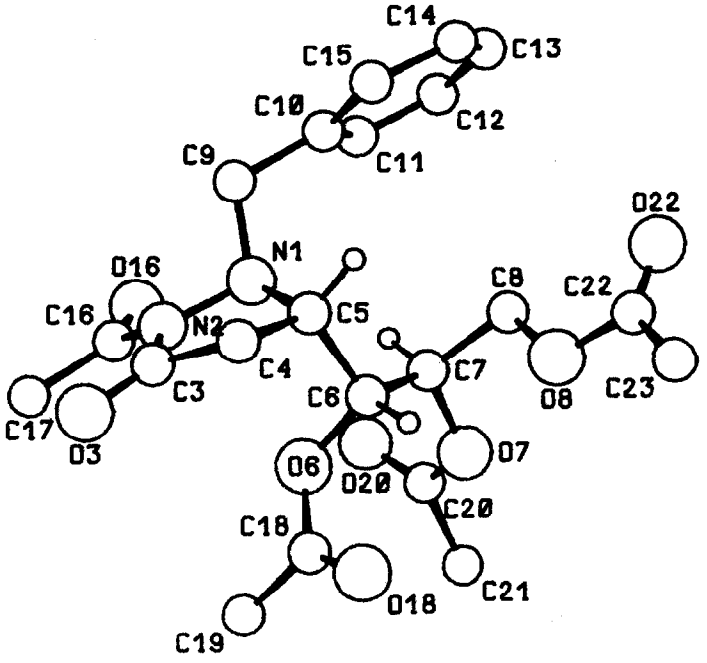


Table 1. Fractional atomic coordinates (10^4) for non-hydrogen atoms of compound **30**.

	Molecule 1			Molecule 2			Molecule 3		
	x/a	y/b	z/c	x/a	y/b	z/c	x/a	y/b	z/c
N(1)	7760(2)	7372(1)	-45.3(6)	2648(2)	7663(1)	3428.3(6)	7663(2)	7350(1)	3268.6(6)
N(2)	7641(2)	7779(1)	-447.6(6)	2485(2)	7251(1)	3829.2(7)	7523(2)	7806(1)	2883.2(6)
C(3)	8490(2)	8266(2)	-524.0(9)	3354(3)	6805(2)	3939(1)	8379(2)	8283(2)	2809.2(9)
C(4)	9243(2)	8176(2)	-156(1)	4153(2)	6907(2)	3588(1)	9159(2)	8141(2)	3166(1)
C(5)	8589(2)	7800(1)	198.0(9)	3540(2)	7263(1)	3211.4(9)	8504(2)	7744(1)	3516.2(9)
C(6)	8088(2)	8363(1)	505.4(8)	3130(2)	6681(1)	2888.3(8)	8024(2)	8303(1)	3839.6(8)
C(7)	7369(2)	8001(1)	847.7(8)	2444(2)	7024(1)	2531.9(8)	7234(2)	7955(1)	4155.3(8)
C(8)	7978(3)	7582(1)	1194.9(9)	3071(3)	7427(2)	2187.0(9)	7720(3)	7437(2)	4489(1)
C(9)	8071(3)	6590(1)	-145.7(9)	2897(2)	8449(1)	3541.4(8)	7969(2)	6589(1)	3123.0(9)
C(10)	8119(2)	6141(1)	272.0(9)	3015(2)	8910(1)	3132.3(9)	8092(2)	6072(1)	3512(1)
C(11)	7201(3)	5950(2)	489(1)	2141(3)	9051(2)	2866(1)	7211(3)	5859(2)	3757(1)
C(12)	7241(4)	5557(2)	882(1)	2260(4)	9468(2)	2483(1)	7341(4)	5389(2)	4115(1)
C(13)	8192(5)	5349(2)	1052(1)	3233(4)	9745(2)	2372(1)	8318(5)	5132(2)	4224(2)
C(14)	9115(4)	5533(2)	842(2)	4092(4)	9617(2)	2635(2)	9181(4)	5335(3)	3980(2)
C(15)	9071(3)	5927(2)	445(1)	3973(3)	9201(2)	3017(1)	9062(3)	5804(2)	3627(1)
C(16)	6673(2)	7742(2)	-664.2(9)	1481(2)	7263(2)	4010.4(8)	6538(2)	7808(2)	2683.6(9)
C(17)	6524(3)	8237(2)	-1054(1)	1273(3)	6757(2)	4395(1)	6371(3)	8343(2)	2310(1)
C(18)	7648(2)	9606(1)	273.6(8)	2747(2)	5417(1)	3090.5(9)	7720(2)	9582(1)	3621.3(8)
C(19)	6881(3)	10043(1)	9(1)	1970(3)	4946(2)	3335(1)	6981(3)	10053(2)	3363(1)
C(20)	5781(2)	8681(2)	936(1)	872(2)	6326(2)	2433.0(9)	5745(2)	8721(2)	4292(1)
C(21)	5303(3)	9314(2)	1176(1)	402(3)	5682(2)	2188(1)	5352(3)	9357(2)	4559(1)
C(22)	9422(3)	7812(2)	1667(1)	4482(4)	7165(3)	1717(1)	7057(9)	6581(3)	5020(2)
C(23)	10240(3)	8355(3)	1791(1)	5285(4)	6600(4)	1598(2)	6119(10)	6185(4)	5180(2)
O(3)	8564(2)	8695(1)	-832.4(7)	3411(2)	6407(2)	4256.3(9)	8451(2)	8738(1)	2516.8(8)
O(6)	7446(1)	8867(1)	247.0(5)	2498(1)	6147(1)	3129.5(6)	7445(1)	8854(1)	3590.4(5)
O(7)	6778(1)	8571(1)	1069.4(5)	1868(1)	6441(1)	2307.1(6)	6732(1)	8542(1)	4400.1(5)
O(8)	8769(2)	8084(1)	1367.6(7)	3830(2)	6904(1)	2018.1(7)	6843(3)	7035(1)	4687.6(8)
O(16)	6010(2)	7308(1)	-533.1(8)	821(2)	7682(1)	3865.0(7)	5871(2)	7371(1)	2807.2(7)
O(18)	8364(2)	9858(1)	480.9(8)	3485(2)	5192(1)	2891(1)	8457(2)	9795(1)	3827.2(9)
O(20)	5376(2)	8309(2)	659.5(9)	444(2)	6688(2)	2707.5(8)	5276(2)	8433(2)	4004(1)
O(22)	9344(4)	7199(2)	1802(1)	4444(5)	7779(2)	1580(1)	7927(8)	6526(3)	5154(2)

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