SYNTHESIS OF PYRAZOLIDIN-3-ONES FROM α,β-UNSATURATED SUGAR LACTONES AND HYDRAZINE

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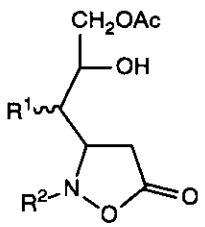
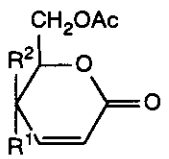
Abstract - Conjugate addition - cyclization of hydrazine to δ-lactones (**2**, **3**, and **6**) provides the respective pyrazolidin-3-ones as single products. The addition proceeds *anti* to the terminal carbon atom of the sugar lactone.

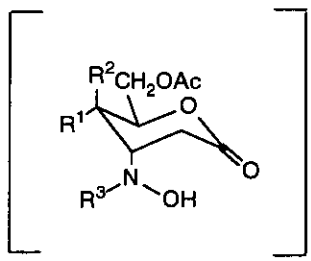
Recently we have described direct stereospecific formation of isoxazolidin-5-ones (**1**) *via* conjugate addition - cyclization involving *N*-substituted hydroxylamines and α,β-unsaturated δ-lactones (**2-4**).[1-3]



R^1= H, OAc
R^2=Me, Bn, $CH_2C_6H_4OCH_3$
1



2: R^1= R^2= H
3: R^1= OAc, R^2= H
4: R^1= H, R^2= OAc



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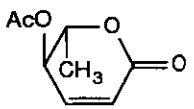
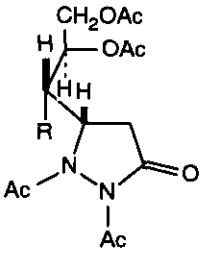


6

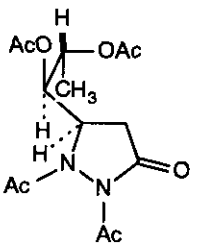
The hydroxylamine enters the lactone molecule (**2-4**) exclusively *anti* to the terminal acetoxymethyl substituent, but formation of the Michael adduct (**5**) has never been observed. Axial location of the hydroxylamine group induces easy opening of the six - membered lactone ring by the hydroxyl group to afford a isoxazolidin-5-one skeleton.[1,2] Although formation of pyrazolidin-3-ones from α,β-unsaturated esters and hydrazine is a known process,[4] the results of *N*-substituted hydroxylamine addition have prompted us to investigate hydrazine addition to sugar δ-enlactones in order to find a stereocontrolled entry to optically pure 5-substituted

pyrazolidin-3-ones. Very recently conjugate addition - cyclization of hydrazine to achiral 3-ethyl-5,6-dihydro-2*H*-pyron has been reported.[5]

Pyrazolidin-3-ones and other cyclic hydrazine derivatives represent a group of compounds of a special synthetic,[5-7] biological,[8] and physical value.[9] Transformation of pyrazolidin-3-ones into β-lactams[6] well fits into our research program.[1-3]



7: R= H
8: R= OAc



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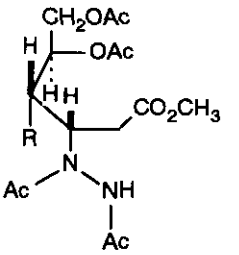
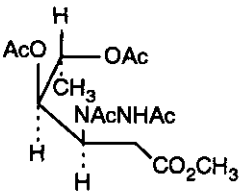


10: R= H
11: R= OAc



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For the present work the lactones (**2**, **3**, and **6**) of a D-glycero, D-erythro, and L-erythro configuration, respectively were selected. Hydrazine in ethanol solution was added at room temperature. In all cases there was only one product resulting from conjugate addition of hydrazine, followed by immediate opening of the lactone ring by the *N*-amino residue and formation of the pyrazolidin-3-one skeleton. Owing to the risk of acetyl group migration, leading to mixtures of products, the resulting pyrazolidin-3-ones were acetylated and characterized as respective peracetates (**7**-**9**). The D-erythro (**7**), D-ribo (**8**), and L-ribo configuration (**9**), respectively, were assigned on the assumption that hydrazine entered the lactone rings *anti* with respect to the terminal acetoxymethyl or methyl substituent.[1,2] This axial approach of nucleophiles to six - membered α,β-unsaturated

carbonyl compounds is well documected in the literature.[1,2,10-13] In the case of unsaturated δ-lactones it was proved for azide anion,[11] aziridine,[12] methoxyl anion,[12] and alkyl cuprates addition.[13] Introduction of acetyl groups at both nitrogen atoms caused weakening of the pyrazolidin-3-one ring. Methanolysis of compounds (**7-9**), without any catalyst, afforded the respective methyl esters of 2,3-dideoxy-3-hydrazinoaldonic acids (**10-12**) in a good yield. This opening of the five-membered pyrazolidinone ring, complementary to the known hydrogenolytic procedure,[14] offers an entry to 3-hydrazino-3-deoxy sugars.

EXPERIMENTAL

^{1}H Nmr spectra were recorded with Bruker AM 500 and Varian Gemini 200 spectrometers. 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 (**2**, **3**, and **6**) were obtained according to known procedures.[15]

Addition of hydrazine to lactones 2, 3, and 6; general procedure. To a solution of a lactone (0.2 mmol) in ethanol (2 ml), 55% hydrazine in water (0.4 g; 6.9 mmol) was added. The mixture was stirred at room temperature for 3 h. Subsequently the solvent was evaporated and the crude product was acetylated with an excess of acetic anhydride - pyridine mixture. The resulting solution was poured into water and extracted with methylene chloride (3 x 3 ml). The extract was washed, dried over magnesium sulfate and evaporated. The crude residue was purified on a silica gel column using hexane - ethyl acetate (1:1 $^v/_v$) as an eluent and gave the respective pyrazolidin-3-one (**7-9**).

(3*R*, 2'*S*)-1,2-Di-*N*-acetyl-5-(2',3'-diacetoxypropyl)pyrazolidin-3-one (**7**); from **2**; 69%; syrup; $[\alpha]_D$ +46.5° (c 1, CH_2Cl_2); ir (CH_2Cl_2): 1740, 1690 cm^{-1}; ^{1}H nmr ($CDCl_3$): 1.78, 1.99 (2m, 2H, H-1'a, 1'b), 2.07 (s, 9H, 3Ac), 2.49 (d, 1H, *J* 17.7 Hz, H-4a), 2.57 (s, 3H, Ac), 3.05 (dd, 1H, *J* 17.7, 8.3 Hz, H-4b), 4.15 (dd, 1H, *J* 12.2, 5.3 Hz, H-3'a), 4.32 (dd, 1H, *J* 12.2, 3.4 Hz, H-3'b), 4.95 (bq, 1H, Σ*J* 21.6 Hz, H-5), 5.09 (m, 1H, H-2'); ms

(m/z): $(M+1)^+$, 329. Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.2; H, 6.1; N, 8.5. Found: C, 51.1; H, 6.5; N, 8.7.

(3*S*, 1'*S*, 2'*R*)-1,2-Di-*N*-acetyl-5-(1',2',3'-triacetoxypropyl)pyrazolidin-3-one (8); from **3**; 75%; syrup; $[\alpha]_D$ +32.2° (c 1, CH_2Cl_2); ir (CH_2Cl_2): 1750, 1695 cm^{-1}; ^1H nmr ($CDCl_3$): 2.03, 2.06, 2.07, 2.10 (4s, 12H, 4Ac), 2.54 (s, 3H, Ac), 2.76 (dd, 1H, *J* 18.0, 1.2 Hz, H-4a), 3.02 (dd, 1H, *J* 18.0, 8.9 Hz, H-4b), 4.21 (dd, 1H, *J* 12.4, 5.4 Hz, H-3'a), 4.33 (dd, 1H, *J* 12.4, 3.1 Hz, H-3'b), 5.1-5.3 (m, 3H, H-5, H-1', H-2'); ms (m/z): $(M+1)^+$, 387. Anal. Calcd for $C_{16}H_{22}N_2O_9$: C, 49.7; H, 5.7; N, 7.3. Found: C, 49.9; H, 6.0; N, 7.0.

(3*R*, 1'*R*, 2'*S*)-1,2-Di-*N*-acetyl-5-(1'2'-diacetoxypropyl)pyrazolidin-3-one (9); from **6**; 80%; mp 86-88 °C; $[\alpha]_D$ -32.0° (c 1, CH_2Cl_2); ir (CH_2Cl_2): 1740, 1690 cm^{-1}; ^1H nmr ($CDCl_3$): 1.31 (d, 3H, *J* 6.4 Hz, CH_3), 2.03, 2.05, 2.06 (3s, 9H, 3Ac), 2.55 (s, 3H, Ac), 2.75 (dd, 1H; *J* 18.0, 1.0 Hz, H-4a), 3.00 (dd, 1H, *J* 18.0, 7.9 Hz, H-4b), 5.0-5.2 (m, 3H, H-5, H-1', H-2'); ms (m/z): $(M+1)^+$, 329. Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.2; H, 6.1; N, 8.5. Found: C, 51.2; H, 6.1: N, 8.6.

Methyl 5,6-Di-*O*-acetyl-2-(*N*,*N*'-diacetyl)hydrazino-2,3,4-trideoxy-D-erythrohexaldonate (10). Compound **7** (0.033 g, 0.1 mmol) was dissolved in methanol (5 ml) and left overnight. Subsequently the solvent was evaporated and the residue was purified to afford **10** (0.035 g, 98%); syrup; $[\alpha]_D$ +65.2° (c 1, CH_2Cl_2); ir (CH_2Cl_2): 1735, 1710, 1675 cm^{-1}; ^1H nmr ($CDCl_3$): 1.82 (m, 1H, H-4), 1.97 (m, 1H, H-4'), 2.07, 2.10, 2.12 (4s, 12H, 4Ac), 2.29 (dd, 1H, *J* 16.7, 8.9 Hz, H-2), 2.80 (dd, 1H, *J* 16.7, 5.2 Hz, H-2'), 3.67 (s, 3H, OCH_3), 4.20 (dd, 1H, *J* 12.2, 3.1 Hz, H-6), 4.28 (dd, 1H, *J* 12.2, 6.4 Hz, H-6'), 4.58 (m, 1H, H-5), 4.95 (m, 1H, H-3), 8.72 (s, 1H, NH); ms (m/z): $(M+1)^+$, 361. Anal. Calcd for $C_{15}H_{24}N_2O_8$: C, 50.0; H, 6.7; N, 7.8. Found: C, 49.6; H, 6.8; N, 7.6.

Methyl 4,5,6-Tri-*O*-acetyl-2-(*N*,*N*'-diacetyl)hydrazino-2,3-dideoxy-D-ribohexaldonate (11). Compound **11** was obtained according to the above procedure; 98%; mp 150-151 °C; $[\alpha]_D$ +11.6° (c 1, CH_2Cl_2); ir (CH_2Cl_2):

1745, 1715, 1685 cm^{-1}; ^1H nmr ($CDCl_3$): 2.32 (dd, 1H, *J* 16.5, 6.9 Hz, H-4a), 2.69 (dd, 1H, *J* 16.5, 5.4 Hz, H-4b), 3.68 (s, 3H, OCH_3), 4.24-4.34 (bm, 2H, CH_2OAc); ms (m/z): $(M+1)^+$, 419. Anal. Calcd for $C_{17}H_{26}N_2O_{10}$: C, 48.8; H, 6.3; N, 6.7. Found: C, 48.6; H, 6.2; N, 6.9.

Methyl 4,5-Di-*O*-acetyl-2-(*N*,*N*'-diacetyl)hydrazino-2,3,6-trideoxy-L-ribohexaldonate (**12**). Compound **12** was obtained according to the above procedure: 98%; mp 118-119 °C; $[\alpha]_D$ -38.4° (c 1, CH_2Cl_2); ir (CH_2Cl_2): 1745, 1715, 1680 cm^{-1}; ^1H nmr ($CDCl_3$): 1.28 (d, 1H, *J* 6.7 Hz, CH_3), 2.00, 2.06, 2.07, 2.08 (4s, 12H, 4Ac), 2.33 (m, 1H, H-2), 2.63 (m, 1H, H-2'), 3.68 (s, 3H, OCH_3), 4.74 (q, 1H, *J* 6.7 Hz, H-5), 5.28 (bs, 2H, H-3, 4); ms (m/z): $(M+1)^+$, 361. Anal. Calcd for $C_{15}H_{24}N_2O_8$: C, 50.0; H, 6.7; N, 7.8. Found: C, 50.0; H, 6.9; N, 7.9.

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