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BEHAVIOUR OF THE GEM-CYANO-ETHOXYCARBONYL CYCLOHEXANE, THIOPYRAN AND PYRAN DERIVATIVES WITH SODIUM BOROHYDRIDE AND LITHIUM ALUMINIUM HYDRIDE.

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Abstract:

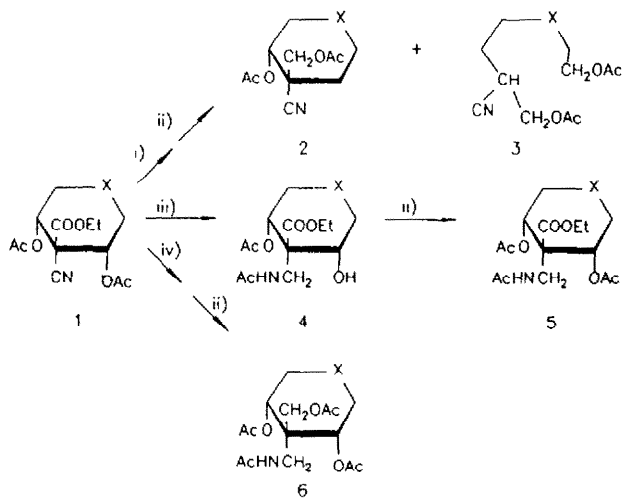
Treatment of the gem-cyano ethoxycarbonyl compounds **1a-c** with $NaBH_4$ in 2-propanol or PEG-400 produced reduction of the ethoxycarbonyl group and simultaneous reductive deacetoxylation. Similar treatment of **7** with $NaBH_4$-$CoCl_2$ produced selective reduction of the cyano group to aminomethyl group and rearrangement O→N of an acetyl group to aminomethyl group. Treatment of **1a-c** and **7** with $LiAlH_4$ gave, after acetylation, the gem-aminomethyl-hydroxymethyl compounds **6a-c** and **11** respectively. Compounds **4a-b**, **5a-b** and **6a-b** show a prefered conformations with both acetoxy groups in an equatorial disposition. However compounds **4c**, **5c** and **6c** prefer the conformation with both acetoxy groups in an axial disposition.

The reactions of 1,5-dialdehydes with active methylene compounds have been studied[1]. We have reported[1] on the reaction of glutaraldehyde, thiodiglycolaldehyde, diglycolaldehyde and α-(S) (3-ethoxycarbonyl-2-methyl-fur-5-yl)diglycolaldehyde with ethyl cyanoacetate and in all cases cyclohexan, thiopyran ad pyran derivatives were isolated by integration of the methylene carbon atom to form a cyclic product.

It is well known that the esters and nitriles are essentially inert toward reduction by sodium borohydride[2] although in some instances a few exceptions are reported. In fact, cyano esters[3] can be converted into the corresponding cyano alcohols. On the other hand, nitriles are reduced to primary amines by $CoCl_2$- $NaBH_4$ system[4]. In this report we study the behaviour of cyano esters **1a-c** and **7** toward $NaBH_4$, $CoCl_2$-$NaBH_4$ and $LiAlH_4$.

Treatment of meso derivatives **1a-c** with $NaBH_4$, using 2-propanol as solvent, gave as result **2a-c** (major) and **3a-b** (minor) after acetylation of the crude product mixture. The yields are summarized in Table 7. The major products **2a-c** were formed by reduction of the ethoxycarbonyl group and reductive removal of the acetoxy group. Similar reductive eliminations have been reported[5] in O-mesyl and O-acetyl nitrosugar derivatives. The formation of the minor compounds **3a-b** could be explained tentatively by the following sequence of reactions (see scheme 3).

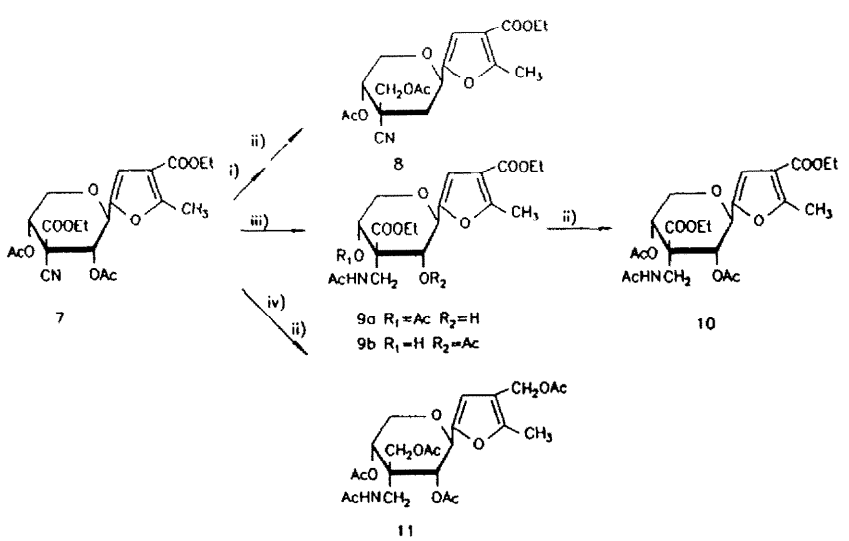
SCHEME 1



a: X = CH_2
b: X = S
c: X = O

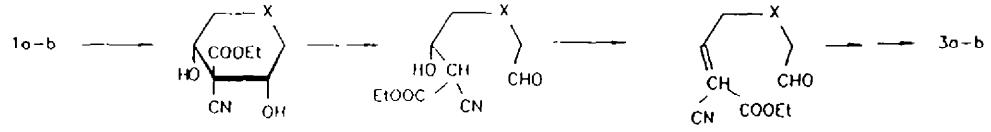
Reagents: i) $NaBH_4$, 2-propanol or PEG-400. ii) Ac_2O-Py. iii) $NaBH_4$, $CoCl_2$, MeOH. iv) $LiAlH_4$-THF or Et_2O

SCHEME 2



Reagents: i) $NaBH_4$, 2-propanol or PEG-400. ii) Ac_2O-py. iii) $NaBH_4$, $CoCl_2$, MeOH. iv) $LiAlH_4$, Et_2O.

SCHEME 3



The formation of the compounds **3a-b** in this conditions support the reversibility of this kind of cyclization reactions [1d,1h]. When the treatment of **1a-c** with sodium borohydride was carried out using polyethylene glycol 400 as solvent, in order to enhance its reducing power[6], only **2a-c** were isolated after acetylation (see Table 6). The reduction of **7** with $NaBH_4$ in 2-propanol as well as polyethylene glycol 400 gave product **8** after acetylation (see Table 6). In this case neither reductive deacetoxylation at C-4 nor ring opening products were detected.

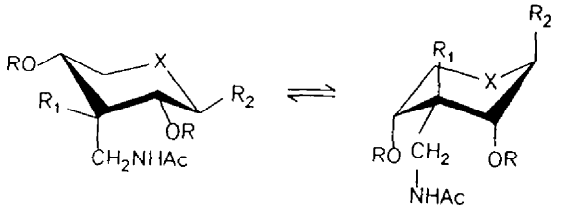
Selective reduction of **1a-c** and **7** with $NaBH_4$-$CoCl_2$ [4] afforded **4a-c** and **9a-b** respectively. In this reactions an acetyl group has migrated to the aminomethyl group[7]. Conventional acetylation of **4a-c** and **9a,b** with acetic anhydride-pyridine gave **5a-c** and **10** respectively. The yields of both steps are summarized in Table 7. Reductive deacetoxylations were not observed in this reactions.

Reduction of **1a-c** and **7** with lithium aluminium hydride, followed by acetylation with acetic anhydride-pyridine afforded the corresponding peracetylated derivatives **6a-c** and **11**, respectively. The yield are summarized in Table 8. Reductive deacetoxylations were not observed in these reactions.

The structure of all products were established on the basis of elemental analysis or mass spectra and spectroscopic data (see Tables 1-4).

Compounds **4c**, **5c** and **6c** had $[^3J_{2a,3} + {}^3J_{2c,3}]$ values between 3.5- 7.0 Hz (see Table 1) reflecting a diaxial orientation of the acetoxy (or hydroxy) groups in agreement with the supposed prefered conformation **13**.

SCHEME 4



12 **13**

R = H, OAc; R_1 = COOEt or CH_2OAc; R_2 = H, furan.

Table 1. ^{1}H-NMR for **2a-c, 4a-c, 5a-c** and **6a-c**[a]

Comp	H-3	H-5	H-2,2', 6,6'	CH_2N	CH_2O	COOEt	Others
2a[b]	4.69 (dd) (11.3, 4.3)[c]	2.15-1.40 (m, 8H)[a]	-------	-------	4.14 = Δ_{AB}	-------	2.08, 2.07 (2 CH_3CO)
2b	4.87 (dd) (10.7, 4.0)	2.91-2.81 (m)	2.75-2.65 (m 1H) 2.50-2.39(m,2H), 2.05-1.95 (m,1H)	-------	4.14 = Δ_{AB} (J_{AB} = 11.1)	-------	2.05, 2.04 (2 CH_3CO)
2c	4.83 (dd) (10.1, 4.8)	3.95 (dd) (11.5, 5.1)	3.96-3.90 (m, H-6eq), 3.68 (dp-t) ($J_{5a',6a} = J_{6,6'} \approx$ 12, $J_{5e,6a} \approx$ 2.3 Hz, H-6a),3.46 (dd, J 11.5, 10.1, H-2a)	--------	4.19 (s)	-------	2.1-2.06 (m, 1H, H-5e) 1.90 (dp-t, $J_{5,5'} \approx J_{5a,6a} \approx$ 12 Hz, $J_{5a,6e} \approx$ 4.6 Hz) 2.10, 2.11 (2s, 2 CH_3CO)
4a[b]	5.12 (dd) (9.8, 4.2)	4.11 (dd) (7.2, 3.6)	1.84-1.33 (m)[c]	3.80-3.75 (m)	-------	4.17 (q) 1.23 (t) (7.1) (7.1)	6.50(bs, 1H, NH) 2.95 (ba, 1H, OH) 2.01, 1.94 (2s, CH_3CO)
4b	5.43 (dd) (6.5, 3.0)	4.35-4.25 (m)	2.85-2.63 (m)	3.71 (d AB syst) (14.3, 6.5)	------	4.28-4.08 1.27(t) (m) (7.1)	6.05 (bs, 1H, NH) 3.28 (d, J 10.8, OH) 2.10, 1.93 (2s, 2CH_3C)
4c	5.30 (bs)		←4.05-3.28(m)→		------	4.15(q) 1.24(t) (7.1) (7.1)	6.03 (bs, NH) 2.10, 1.88 (2s, 2CH_3CO)
5a[b]	5.20 (pt) ($J_1 + J_2$ = 13.85)		1.85-1.68(m)[c] 1.52-1.37 (m)	3.78 (d) (6.2)	-------	4.11 (q) 1.19 (t) (7.12) (7.12)	6.22 (t, J 5.6, NH) 1.96, 1.91 (2s, 2 CH_3CO)
5b	5.33 (dd) (10.85, 4.05)		2.93(dd) (13.6,10.85) 2.49(dd) (13.7,4.0)	3.80 (d) (6.3)	-------	4.10 (q) 1.15 (t) (7.12) (7.12)	6.31 (t, J 6.3 Hz,1H, NH) 1.92, 1.89 (2s, 2 CH_3CO)
5c	5.39 (bs)		3.96 (dd) (13.4,2.3) 3.58 (dd) (12.8,1.2)	3.53 (d) (6.5)	-------	4.22 (q) 1.30 (t) (7.1) (7.1)	5.92 (t, J 6.5 Hz, NH) 2.16, 1.92 (2s, 2 CH_3CO)
6a[b]	4.89(dd) (10.6, 4.2)		1.90-1.32 (m)[c]	3.69 (d) (5.8)	4.06 (s)	-------	6.35 (t, J 6.0 Hz, NH) 2.07, 2.04, 2.02 (3s, 3CH_3CO)
6b	5.09 (dd) (11.1, 4.2)		2.79 (dd) (13.4.11.1) 2.52(dd) (13.6,4.1)	3.66 (d) (6.0)	4.06 (s)	------	6.00 (bt, J 5.6, NH) 2.03, 2.00, 1.93 (3s, 4CH_3CO)
6c	4.85 (p-t) ($J_1 + J_2$ = 7.0)		3.75 (m, 4H)	3.50 (d) (6.5)	4.14 (s)	------	5.93 (t, J 6.2, NH) 2.13, 2.08, 1.91 (3s, 4 CH_3CO)

a) Multiplicities. d = doublet; t = triplet, s = singlet; q = quartet; dd = double doublet; bs = broad singlet; p-t = pseudo-triplet; m = multiplet.

b) For simplicity it use the same numbering that for tetrahydropyran and tetrahydrothiopyrane derivatives (series b and c).

c) Includes X = CH_2

Table 2. ^{13}C-NMR for **2a-c, 4a-c, 5a-c** and **6a-c**

Comp	C-5	C-3	C-2	C-6	C-4	Others
2a	32.0	71.8	23.5	28.7	44.5	170.1, 170.0 (2 CO), 118.8 (CN), 65.1 (CH_2OAc) 21.0, 20.6 (2 CH_3CO), 21.7 (C-1)
2b	35.3	70.8	24.1	28.6	44.3	169.8, 169.4 (2 CO), 117.6 (CN), 64.4 (CH_2OAc) 20.7, 20.4 (2 CH_3CO)
2c	32.1	67.2	65.8	64.5	43.0	170.0, 169.6 (2 CO), 117.8 (CN), 64.0 (CH_2OAc) 20.7, 20.6 (2 CH_3CO)
4a	73.4	72.0	29.0	26.4	55.4	173.0, 171.0, 169.8 (3 CO), 61.6 (CH_3CH_2), 37.0 (CH_2N) 23.4, 21.1 (CH_3CO), 18.6 (C-1), 14.0 (CH_3CH_2)
4b	70.5	69.1	31.6	28.1	53.9	171.5, 170.7, 169.8 (3 CO), 62.0 (CH_2CH_3), 39.1 (CH_2H) 23.3, 21.1 (2 CH_3CO), 14.1 (CH_3CH_2)
4c	69.1	66.9	70.5	67.9	51.4	171.0, 170.7, 170.2 (3 CO), 62.1 (CH_2CH_3), 40.3 (CH_2N) 23.1, 21.1 (2 CH_3CO), 14.0 (CH_3CH_2)
5a	73.4		25.9		54.5	172.2, 169.7, 169.5 (3 CO), 61.7 (CH_2CH_3), 36.4 (CH_2CN) 23.4, 20.9 (2 CH_3CO), 18.5 (C-1), 14.0 (CH_3CH_2)
5b	74.1		25.3		54.8	171.4, 169.6, 168.9 (3 CO), 61.9 (CH_2CH_3), 35.1 (CH_2N) 23.4, 20.7 (2 CH_3CO), 13.9 (CH_3CH_2)
5c	67.8		67.9		50.8	170.8, 170.3, 170.1 (3 CO), 62.7 (CH_3CH_2), 39.6 (CH_2CN) 23.4, 21.2 (2 CH_3CO), 14.1 (CH_3CH_2)
6a	71.8		26.0		44.5	170.9, 170.7, 169.7 (4 CO), 60.8 (CH_2OAc), 36.9 (CH_2N) 23.3, 21.2, 20.9 (4 CH_3CO), 19.2 (C-1)
6b	72.1		25.4		44.6	170.7, 170.0, 169.1 (4 CO), 60.0 (CH_2OAc), 35.9 (CH_2N) 23.4, 20.9, 20.7 (4 CH_3CO)
6c	67.5		65.7		42.4	170.9, 170.4, 170.2 (4 CO), 61.2 (CH_2OAc), 36.6 (CH_2N) 23.5, 21.1, 20.8 (4 CH_3CO)

Table 3. ^{1}H-NMR for **8-11**.

Comp	H-1	H-2	H-4	H-5,5'	H-furan	Me-furan	Others
8	4.73 (dd) (11.6, 2.1)	2.34 (dd) (14.0, 2.1), 2.17 (dd) (14.0, 11.6)	4.94 (dd) (10.4, 5.0)	4.11 (dd) (11.5, 5.0) 3.70 (dd) (11.5, 10.6)	6.59 (s)	2.55 (s)	4.26 (q, 2H, J 7.1 Hz, CH_2CH_3), Δ_{AB} = 4.23 (J_{AB} ≈ 12 Hz, CH_2OAc) 2.13, 2.12 (2s, 6H, 2Ac), 1.31 (t, 3H, J 7.1 Hz, CH_3CH_2)
9a	4.62 (d) (9.7)	4.49 (d)[a] (9.6)	5.37 (dd) (9.9, 5.3)	4.29-3.62 (m)	6.71 (s)	2.56 (s)	3.02 (bs, OH) 2.06, 1.94 (2s, CH_3CO for 8a)
9b	4.47 (d)[a] (9.7)	5.47 (d) (9.7)	4.52-4.43 (m)	-------	6.56 (s)	2.52 (s)	1.45-1.32 (4t, 7H, $4CH_3CH_2$) 1.96, 1.91 (2s, 2 CH_3CO for 8b)
10	4.69 (d) (9.28)	5.66 (d) (9.25)	5.54 (dd) (9.0, 5.2)	4.05 (dd) (11.7, 5.3) 3.86 (dd) (4.0, 11.7)	6.60 (s)	2.51 (s)	6.14 (t, 6H, 1H, NH), 4.92 (q, J 7.1Hz, CH_2-fur), 4.14 (dq, J 7.0 and 3.0 Hz, 2H, CH_2O), 3.97 (dd, J 6.2, 2.1Hz, CH_2N), 1.94, 2.08, 1.87 (3s, CH_3CO), 1.29, 1.24 (2t, J 7.15 Hz, CH_3CH_2)
11	4.56 (10.0)	5.37 (d) (10.0)	5.19 (dd) (10.3, 5.3)	3.97 (dd) (11.3, 5.3) 3.69 (dd) (11.3, 10.4)	6.27 (s)	2.23 (s)	5.96 (t, J 6.1 Hz, NH), 4.78 (s, 2H, CH_2OAc-fur), 3.85 (t, J 6.3 Hz, CH_2N), Δ_{AB} = 3.98 (J_{AB} 11.8, CH_2OAc), 2.07, 2.06, 1.98, 1.94, 1.88 (5CH_3CO)

Table 4. ^{13}C-NMR for **8-11**

	8	**10**	**11**
C-1	69.3*	69.6*	69.1*
C-2	35.3	70.4*	70.4*
C-3	43.2	53.0	44.3
C-4	66.7*	70.5*	68.1*
C-5	64.4	64.7	63.7
C-1'	149.3	147.5	147.7
C-2'	109.1	110.6	111.2
C-3'	114.4	114.2	115.4
C-4'	159.6	159.9	151.7
CH3-fur	14.4	14.4	11.6
Others	169.9, 169.6, 163.7 (3 x COO), 117.6 (CN), 65.8 (CH_2OAc) 60.3 (CH_2CH_3) 13.8 (CH_3CH_2)	171.0, 169.8, 169.2, 168.4, 163.7 (5 CO), 62.4, 60.2 (2 x CH_2CH_3), 35.7 (CH_2N), 23.5, 20.7, 20.5 (3 x CH_3CO), 13.9, 13.8 (2 x CH_3CH_2)	170.9, 170.8, 170.0, 169.2, 168.3 (5 CO), 60.8, 57.7 (2 x CH_2OAc) 35.5 (CH_2N), 23.5, 20.9, 20.8, 20.5 (5 x CH_3CO)

*) This signals can be interchangeable

Table 5. Relative steric energies[a], overlap populations[b], calculated and experimental values for $^3J_{H-H}$ for compounds **4a-c**, **5a-c**, **6a-c**, **9a-b** and **10**[c].

Compounds		**4a**[c]	**4b**	**4c**	**5a**[c]	**5b**	**5c**	**6a**[c]	**6b**	**6c**	**9a**[c]	**9b**	**10**
ΔH	12	28.8	23.7	27.3	28.0	28.1	32.1	25.7	26.2	29.8	45.3	44.6	49.8
	13	29.8	25.1	27.5	27.8	28.2	30.9	26.7	27.1	29.7	47.8	46.2	50.3
%population	12	79.0	68.5	43.1	46.6	37.1	12.4	90.2	86.3	51.9	98.6	95.8	81.6
	13	21.0	31.5	56.9	53.4	62.9	87.6	9.8	13.7	48.1	1.4	4.2	18.4
$^3J_{H-H}$ averaged	J2a,3	9.4	9.2	6.0	7.2	7.0	3.6	10.6	10.6	6.7	-----	-----	-----
	J2e,3	4.7	2.9	2.9	3.3	2.4	1.7	4.4	3.4	4.1	-----	-----	-----
	J5,6a	10.7	9.3	6.1	7.0	7.1	3.6	10.6	10.6	6.7	-----	-----	-----
	J5,6e	4.2	3.5	3.0	3.5	2.4	1.7	4.3	3.4	3.3	-----	-----	-----
	J1,2	-----	-----	-----	-----	-----	-----	-----	-----	-----	9.5	9.3	8.2
	J4,5a	-----	-----	-----	-----	-----	-----	-----	-----	-----	10.5	10.4	8.2
	J4,5be	-----	-----	-----	-----	-----	-----	-----	-----	-----	5.4	4.8	4.5
$^3J_{H-H}$ experimental	J2a,3	7.2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
	J2e,3	3.6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
	J5,6a	9.8	6.5	-----	J+J=	10.8	2.3	10.6	11.1	J+J=	-----	-----	-----
	J5,6e	4.2	3.0	-----	13.8	4.0	1.2	4.2	4.2	7.0	-----	-----	-----
	J1,2	-----	-----	-----	-----	-----	-----	-----	-----	-----	9.7	9.7	9.2
	J4,5a	-----	-----	-----	-----	-----	-----	-----	-----	-----	9.9	-----	9.0
	J4,5e	-----	-----	-----	-----	-----	-----	-----	-----	-----	5.3	-----	5.2

a) Steric energies relative to the most stable conformer of each in Kcal-mol^{-1}.

b) Sum of the equilibrium populations of conformer **12** and **13** in %.

c) For simplicity the same numbering is used that for tetrahydropyran and tetrahydrothiopyran derivatives **4b-c**, **5b-c** and **6b-c**.

Two attractive "gauche effect"[8] between the oxygen of the ring and acetoxy groups and a repulsive interaction syn-diaxial among acetoxy groups exist in this conformation

Compounds **4a-b, 5a-b** and **6a-b** had $[^3J_{2a,3} + {}^3J_{2e,3}] = 10.8$ Hz (see Table 1) in agreement with the prefered conformation **12**. Cyclohexane derivatives **4a, 5a, 6a** show a repulsive syn-diaxial interaction in the conformation **13** , absent in the conformation **12**.. In contrast, thiopyrans derivatives **4b, 5b** and **6b** show an "gauche repulsive effect"[9] in the conformation **13** which is absent in the conformation **12**.

Compounds **8-11** showed $J_{1,2}$ values of 9.2-11.6 Hz according to an equatorial disposition of furan group in a $^4C_1$(D) conformation. The signal for H-4 were double doublet ($^3J_{4,5a}$ 9.0- 10.4 Hz, $^3J_{4,5e}$ 5.0-5.3 Hz), in agreement with the equatorial disposition of acetoxy group in a $^4C_1$(D) conformation.

Molecular mechanics calculations for compounds **4a-c, 5a-c, 6a-c, 9a-b** and **10** have been performed. The results are summarized in Tables 5 and 6. Table 5 shows the steric energy of the most stable conformation in both **12** and **13** conformers, percentage in the conformational mixture, averaged theoretical coupling constants and experimental coupling constants. The theoretical coupling constants obtained from the molecular mechanics geometries are in good agreement with those obtained from NMR spectra (see Table 5).

THEORETICAL CALCULATIONS

The Allinger Molecular mechanic methodology[10] has been used for the theoretical calculations. The Osawa and Jaime[11] MM2 program version is used as follows.

The input data have been developed using molecular model and with the aid of the Q.C.P.E. nº 488 Program, obtaining initial aproached geometries which are optimized with MM2 program until minimum energetic geometries are obtained. The optimization of these energetic minima is performed by taking the adecuate conformational mixture of the group attached to the tetrahydropyran rings, using the tree option of the Osawa program[11].

A collection of conformers of minimum energies and their corresponding cartesian coordinates can be obtained.

The average H-H coupling constants and the relative populations are calculated through Q.C.M.P. nº 0.25 program, which is set up in the use of the generalized Karplus equations[12], mixing the above minimum energies cartesian coordinated.

EXPERIMENTAL

Melting points were determinated with a Reichter hotplate microscope and were uncorrected. Solutions

were dried over Na_2SO_4 or $MgSO_4$ before concentration under disminished pressure. I.R. spectra were recorded with Pelkin Elmer 983G spectrophotometer, using KBr disks for solids. NMR spectra were obtained with Bruker AM-300 spectrometer (solutions in $CDCl_3$, internal Me_4Si). Optical rotations were measured with a Perkin Elmer 141 polarimeter. Elemental analysis were performed with a Pekin-Elmer analyzer 240C. M.S. spectras were performed with a Hewlet-Packard 5988A spectrometer. T.l.c. were performed on silica gel 60 (Merck), with detection by charring with sulphuric acid, and columns chromatography were performed on silica gel 60 (Scharlau).

Treatment of 1a-c and 7 with $NaBH_4$. Sodium borohydride (500 mg) for 30 min was portionwise added to a magnetically stirred solution of the substrates (1 mmol) at 40° C After addition was completed the reaction was stirred for an additional time at room temperature, and the pH of the mixture was adjusted to ca. 6 by adding acetic acid and the salts were removed by filtration. The filtered solution was evaporated in vacuo and the new residue was acetylated by conventional method (acetic anhydride-pyridine, 1.5:1.5 mL). The acetylated products were fractionated in a column chromatography (ether-hexane, 1:2). The following amounts and conditions were used:

Table 6. (Solvent A = 2-propanol; B = PEG-400)

Substrate (mg)	Solvent (A o B) (mL)	Time (h)	Products (mg, %)
1a (500)	A (25)	6	**2a** (310, 77) + **3a** (25, 6)
1b (630)	B (30)	3	**2b** (230, 45)
1b (1000)	A (40)	7	2b (230, 28.2) + 3b (330, 40)
1c (600)	B (30)	3	2c (210, 44)
1c (340)	A (25)	8	2c (180, 66)
7 (680)	A (25)	6	**8** (150, 25.3)
7 (610)	B (30)	3	**8** (283, 53)

t-2-Acetoxy-r-1-acetoxymethyl-1-cyanocyclohexane (2a) and 1,7-diacethoxy-2-cyano- heptane (3a) . Column chromatography gave first **2a**. Mp 56-60° C. IR 2244, 1742, 1639, 1234, 1044 and 934 cm^{-1}. NMR data see Tables 1 and 2. Anal. calc. for $C_{12}H_{17}NO_4$: C, 60.25; H, 7.11; N, 5.86. Found C, 59.90; H, 7.34; N, 5.99.

Eluted second was **3a** as a colourless syrup. IR 2245, 1742, 1463, 1366, 1238 and 1046 cm^{-1}. ^{1}H-NMR δ 4.14 (1H, dd, J = 11.1 and 5.6 Hz, H-1), 4.07 (1H, dd, J = 11.1 and 7.3 Hz, H-1'), 3.99 (2H, t, J = 6.5 Hz, H-7,7'), 2.90-2.78 (1H, m, H-2), 2.04 and 1.97 (6H, 2s, 2 x CH_3COO), 1.70-1.30 (8H, m, H-3,3', 4,4', 5,5', 6,6'). ^{13}C-NMR δ 170.9 and 170.2 (2 x COO), 119.5 (CN), 64.0 and 63.0 (C-1, C-7), 31.4 (C-2), 28.6, 28.2, 26.4 and 25.4 (C-3,4,5 and 6), 20.8 and 20.5 (2 x CH_3COO). MS m/z: 242($M^{+\cdot}$ + 1) and 198($M^{+\cdot}$-C_2H_3O).

t-3-Acetoxy-r-4-acetoxymethyl-4-cyanotetrahydrothiopyran (2b) and 1,7-diacetoxy-2-cyano-5-thioheptane (3b). Column chromatography gave first **2b**. Mp 65-66° C. IR 2241, 1742, 1228, 1030 and 979 cm^{-1}. NMR data see Tables 1 and 2. Anal. Calc. for $C_{11}H_{15}NO_4S$: C, 51.36; H, 5.84; N, 5.44. Found: C, 51.33; H, 5.58; N, 5.31.

Eluted second was **3b** as a colourless syrup. IR 2246, 1740, 1366, 1238 and 1046 cm^{-1}. ^{1}H-NMR δ 4.25-4.10 (4H, m, H-1,1', 7,7'), 3.19-3.08 (1H, m, H-2), 2.85-2.60 (4H, m, H-4,4', 6,6'), 2.08 and 2.03 (6H, 2s, 2 x CH_3COO), 2.02-1.75 (2H, m, H-3,3'). ^{13}C-NMR δ 170.5, 170.1 (2 x COO), 118.9 (CN), 63.1, 62.5 (C-1 and C-7), 30.3 (C-3), 30.2 (C-2), 29.1, 28.6 (C-4, C-6), 20.7 and 20.4 (2 x CH_3COO). MS m/z: 259 ($M^{+\cdot}$), 216($M^{+\cdot}$-C_2H_3O) and 199($M^{+\cdot}$- $C_2H_4O_2$), 43.

t-3-Acetoxy-r-4-acetoxymethyl-4-cyanotetrahydropyran (2c). Column chromatography gave **2c** ,as a colourless syrup. IR 2252, 1749, 1372, 1225, 1051 and 757 cm^{-1}. NMR data see Tables 1 and 2. MS M/z: 242($M^{+\cdot}$ + 1), 198($M^{+\cdot}$-C_2H_3O), 168 and 43.

5-(3-Acetoxymethyl-4-O-acetyl-3-C-cyano-2,3-dideoxy-β-D-*threo*-pentopyranosyl)-3-ethoxycarbonyl-2-methylfuran (8). Column chromatography gave **8** as a colourless syrup. $[\alpha]_{25}^{D}$ + 20° (c 0.8, chloroform). IR 2982, 2339, 1751, 1712, 1617, 1582, 1430, 1371, 1061 and 757 cm^{-1}. NMR data see Tables 3 and 4. MS m/z: 393($M^{+\cdot}$) and 348($M^{+\cdot}$-C_2H_5O).

Treatment of 1a-c and 7 with $NaBH_4$ in PEG-400. Sodium borohydride (0.6 g, 15 mmol) was portionwise added for 30 min to a solution of the sustrate (5 mmol) in PEG-400 (30 mL). Under stirring, the solution was kept at room temperature for 3 h. Diluted HCl (10%) was dopwise added to the reaction mixture and the product was extracted with ethyl acetate (3 x 25 mL). After removing the solvent, the crude product was acetylated by convencional method (acetic anhydride-pyridine, 1.5:1, 5 mL) and the new crude product was purified by column chromatography (ether-hexane 1:2).

Treatment of 1a-c and 7 with $NaBH_4$-Cl_2Co. To a methanolic solution (120 mL) of the corresponding nitrile, cobaltous chloride was added and then, sodium borohydride portionwise for 30 min. under stirring at room temperature. The stirring was kept for an additional time until completion of the reaction. A aqueous solution of HCl 5% (100 mL) was added and methanol was removed in vacuo. The reaction was made alkaline by addition of aqueous NH_4OH, an then extracted with ethyl acetate (4 x 75 mL). The solvent was removed under diminished pressure to give a syrup which was purified by column chromatography. The following amounts and conditions were used:

Table 7.

Starting compounds (g, mmol)	$NaBH_4$:$CoCl_2$ (g)	Time (h)	Products (g, %)
1a (10.3, 3.37)	2.4:2.25	6	**4a** (0.94, 98)
1b (14, 4.44)	3.2:3.2	25	**4b** (1.0, 71)
1c (1.0, 3.34)	2.4:2.4	1.5	**4c** (0.84, 83)
7 (0.45, 1.00)	0.8:0.8	1.5	**9a + 9b** (0.39, 86)

1-Acetamidomethyl-t-2-acetoxy-r-1-ethoxycarbonyl-t-6-hydroxy-6cyclohexane (4a): Column chromatography (ether:methanol 5:1) gave **4a**. Mp 117-118° C (from ether). IR 3407, 3332, 2937, 2861, 1730, 1647, 1536, 1475, 1446, 1384, 1367, 1295, 1278, 1239, 1206, 1170, 1140, 1112, 1090, 1063, 1028, 969, 924, 683 and 626 cm^{-1}. NMR data see Tables 1 and 2. MS m/z: 302($M^{+\cdot}$ + 1) and 242($M^{+\cdot}$-$C_2H_4O_2$). Anal. calc. for $C_{14}H_{23}NO_6$: C, 55.81; H, 7.64; N, 4.65. Found: C, 55.78; H, 7.84; N, 4.75.

4-Acetamidomethyl-t-3-acetoxy-r-4-ethoxycarbonyl-t-5-hydroxy- tetrahydrothiopyran (4b). Column chromatography (etyl acetate-methanol 5:1) gave **4b**. M.p. 184-185° C (from ethyl acetate). IR 3405, 3311, 1727, 1647, 1535, 1462, 1291, 1229, 1092, 973 and 691 cm^{-1}. NMR data see Tables 1 and 2. Anal. Calc. for $C_{13}H_{21}NO_6S$: C, 48.90; H, 6.58; N, 4.39. Found: C, 49.21; H, 6.76; N, 4.46.

4-Acetamidomethyl-t-3-acetoxy-r-4-ethoxycarbonyl-t-5-hydroxy-tetrahydropyran(4c). Column chromatography (ethyl acetate-methanol 20:1) gave **4c**. Mp 80-85° C. IR 3317, 3088, 1727, 1660, 1545, 1442, 1370, 1296, 1228, 1278, 1144 and 1141 cm^{-1}. NMR data see Tables 1 and 2. Anal. Calc. for $C_{13}H_{21}NO_7$: C, 51.49; H, 6.93; N, 4.62%. Found: C, 51.84; H, 7.11; N, 4.71.

5-(3-C-Acetamidomethyl-2-O-acetyl-3-deoxy-3-ethoxycarbonyl-β-D-*xylo*pentopyrano- syl) (9a) and 5-(3-C-acetamidomethyl-5-O-acetyl-3-deoxy-3-ethoxycarbonyl-β-D-*xylo*pentopyranosyl)-3-ethoxycarbonyl-2 -methylfuran (9b). Column chromatography (ether) gave **9a + 9b**. (Ratio 2:1 based on the ^{1}H-NMR data.). IR 3399, 1727, 1667, 1618, 1581, 1528, 1228, 1024, 1035, 981, 906, 857, 805, 779, 736 and 700 cm^{-1}. ^{1}H-NMR see Table 3. Anal. calc. for $C_{21}H_{29}NO_{10}$: C, 55.38; H, 6.37; N, 3.08. Found: C, 55.03; H, 6.26; N, 3.08.

Acetylation of 4a-c and 9a + 9b. Coventional treatment of these compounds with acetic anhydride-pyridine (1.5:1. 5 mL) and catalytic amounts (1%) of dimethylaminopyridine gave a crude that was purified by column chromatography (ether-hexane 3:1) . The yields were in the range 94-100%.

1-Acetamidomethyl-t-2,t-6,diacetoxy-r-1-ethoxycarbonylcyclohexane (5a). Mp 94-95° C (from ethanol). IR 3555, 3365, 1746, 1651, 1547, 1441, 1239, 1159, 1028, 974, 921, 864 and 693 cm^{-1}. NMR data (see Tables 1 and 2). Anal. cal. for $C_{16}H_{25}NO_7$: C, 55.98; H, 7.29; N, 4.08. Found: C, 56.27; H, 7.53; N, 3.84.

4-Acetamidomethyl-t-3,t-5-diacetoxy-r-4-ethoxycarbonyltetrahydrothiopyran (5b). Mp 101-102° C (from hexane-ether). IR 3350, 1708, 1682, 1539, 1265, 1227, 1024, 951 and 695 cm^{-1}. RMN data see Tables 1 and 2. Anal. calc. for $C_{15}H_{23}NO_7$: C, 49.86; H, 6.37; N, 3.98. Found: C, 50.05; H, 6.52; N, 3.88.

4-Acetamidomethyl-t-3, t-5-diacetoxy-r-4-ethoxycarbonyltetrahydropyran (5c). Mp 130-132° C (from chloroform-hexane). IR 3353, 1722, 1680, 1542, 1265, 1236, 1190, 1142, 1094, 1045, 972, 864, 815, 778 and 698. NMR data see tables 1 and 2. Anal. cal. for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.67; N, 4.06. Found: C, 52.06; H, 6.58; N, 4.02.

5-(3-C-acetamidomethyl-2,4-di-O-acetyl-3-deoxy-3-ethoxycarbonyl- β-D-*xylo*-pentopyranosyl)-3-ethoxycarbonyl-2-methylfuran (10). Mp 145-146° C (from ether). $[\alpha]_D^{25}$ = -11.3° (c 1,

chloroform). IR 3402, 1717, 1528, 1433, 1227, 1074, 905, 849 and 779 cm^{-1}. NMR data see tables 3 and 4. M.S. m/z: 498($M^{+\cdot}$ + 1), 452($M^{\cdot}$ + 1-C_2H_6O), 365 ($M^{+\cdot}$-C_3H_6NO-$C_2H_4O_2$), 306($M^{+\cdot}$-C_3H_4NO-$2C_2H_4O_2$). Anal. calc. for $C_{23}H_{31}NO_{11}$: C, 55.53; H, 6.24; N, 2.82. Found: C, 55.79; H, 6.35; N, 2.78.

Treatment of 1a-c and 7 with $AlLiH_4$. Lithium aluminium hydride is suspended in anhydrous ether or THF in a 100 mL two-necked flask equipped with a dropping funnel and an efficient reflux condenser protected from moisture by a calcium chloride tube. A solution of the sustrate in some solvent is introduced for 30 minutes from the dropping funnel, while the reaction is magnetically stirred. After addition was completed, reflux was maintained for an additional time (see below). The reaction mixture was then cooled and aqueous NaOH 2N (3 mL) was added. The salts formed were removed by filtration. The filtered was evaporated in vacuo and the residue was conventionally acetylated with the mixture Ac_2O-Py giving a crude product from which the reaction products were isolated by crystallization or by column chromatography. The following amounts and condition were used:

Table 8.

Substrate (mg)	Solvent (mL)	$LiAlH_4$ (mg) (Solvent, mL)	Time (h)	Product (mg, %)
1a (340)	THF (10)	(200) (20)	1	**6a** (350, 80)
1b (630)	THF (20)	(304) (20)	2	**6b** (510, 71)
1c (500)	Ether (80)	(350) (20)	2	**6c** (200, 35)
7 (400)	Ether (80)	(250) (10)	3	**11** (260, 61)

1-Acetamidomethyl-t-2,t-6-diacetoxy-r-1-acetoxymethylcyclohexane (6a). Crystallization of the crude product from ether gave **6a**. Mp 145-146° C. IR 3300, 1737, 1639, 1561, 1236 and 1033 cm^{-1}. NMR data see Tables 1 and 2. Anal. calc. for $C_{16}H_{25}NO_2$: C, 55.98; H, 7.29; N, 4.08. Found: C, 56.03; H, 7.55; N, 4.05.

4-Acetamidomethyl-t-3,t-5-diacetoxy-r-4-acetoxymethyl-tetrahydrothiopyran (6b). Crystallization of the crude product from ether- methanol gave **6b**. Mp 164-165° C. IR 3301, 1737, 1638, 1557, 1224, 1019 and 969 cm^{-1}. NMR data see Tables 1 and 2. Anal. cal. for $C_{15}H_{23}NO_7S$: C, 49.86; H, 6.37; N, 3.88. Found: C, 49.82; H, 6.47; N, 3.74.

4-Acetamidomethyl-t-3,t-5-diacetoxy-r-4-acetoxymethyltetrahydropyran (6c). Crystallization of the crude product from ether gave **6c**. Mp 140-141° C. IR 3291, 1747, 1637, 1559, 1220 and 1023 cm^{-1}. NMR data see Tables 1 and 2. Anal. cal. for $C_{15}H_{23}NO_8$: C, 52.13; H, 6.70; N, 4.06. Found: C, 52.22; H, 6.73; N, 4.07.

5-(3-C-Acetamidomethyl-3-acetoxymethyl-2,4-di-O-acetyl-3-deoxy-β-D-*xylo*-pentopyranosyl)-3-acetoxy methyl-2-methylfuran (11). Column chromatography (ether-hexane, 1:3) of the crude product gave **11** as a colourless syrup. $[\alpha]_D^{25}$ = -8° (c 1, chloroform). IR: 3397, 1742, 1667, 1529, 1236, 1033 and 756 cm^{-1}. NMR data see Tables 3 and 4. MS (m/z): 438 ($M^{+\cdot}$-$C_2H_4O_2$).

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REFERENCES

1. a) .López Aparicio, F.J.; Zorrilla Benítez, F.; Santoyo González, F. *An. Quim.*, **1985**, *81C*, 178. b) López Aparicio, F.J.; Santoyo González, F.; Domínguez Martínez, J.A. *Carbohydr. Res.*, **1986**, *147*, 237. c) López Aparicio, F.; Santoyo González, F.; García Mendoza, P.; Hernandez Mateo, F. and Domínguez Martínez, J.A., *An. Quim.* **1987**, *83C*, 148. e) López Aparicio, F.J.; Santoyo González, F and García Mendoza, P. *J. Chem. Res., 1987, (S)* 84, *(M)* 831. f) Santoyo González, F.; Hernández Mateo, F. and López Aparicio F.J. *ibid*, **1989**, *(S)* 168, *(M)* 1375. g) Santoyo González, F.; Hernandez Mateo, F.; García Mendoza, P.; López Aparicio F.J. and López Herrera, F.J. *ibid*, 1989, *(S)* 166, *(M)* 1354.

2. Brown H.C. and Krishnamurthy S. *Tetrahedron*, **1979**, *35*, 567

3. a) Berlinguest L. *Can. J. Chem.* **1955**, *33*, 1119; b) Cavill G.W.K. and Whitfiel F.B. *Proc. Chem. Soc.* **1962**, 380; c) Meschino J.A. and Bond C.H., *J. Org. Chem.***1963**, *28*, 3129; d) Soai K., Oyamada H.; Takase M. and Ookawa A. *Bull. Chem. Soc. Jpn.***1984**, *57*, 1948; e) Makarevic J. and Skaric V., *J. Chem. Res.* **1989**,*(S)* 212; *(M)* 1643.

4. a) Ganem B. and Osby J.O. *Chem. Rev.* **1986**, *86*, 763-780 and references cited therein; b) Seyden-Penne J. «*Reductions par les Alumino- et Borohydrures in Synthèse Organique*», Tec. et Doc., París, **1988**, 112-116.

5. a) Baer H.H.; Hanna H.R.; *Can. J. Chem.* **1980**, *58*, 1751; b) Aamlid K.H.; Hough L.; Richardson A.C. and Hendiy D. *Carbohydr. Res.* **1987**, *164*, 373; c) Yoshikawa M.; Ikeda Y.; Yakeraka K.; Torihara M. and Kitagama I., *Chem. Lett.*, **1984**, 2097.

6. Santaniello E.; Ferraboschi P. and Sozzani P., *J. Org. Chem.* **1981**, *46*, 4584.

7. a) Phillips A.P. and Baltzly R., J. *Am. Chem. Soc.* **1947**, *69*, 200; b) Sugihara J.M. *Advances in Carbohydr. Chem.*, 1953, *8*, 5- 7, c) M. Caswell, R.K.; Chaturvedi; S.M. Lane;. Zrilichovsky and G.L. Schmir. *J. Org. Chem.*, **1981**, *46*, 1585; d) M.J. Lyapova; I.G. Pojarlieff and B.J. Kurtev. *J. Chem. Res.*, **1981**, *(S)* 351.

8. Wolfe S. *Acc. Chem. Res.*, **1972**, 102.

9. a) Zefirov N.S.; Rogozina S.V.; Kurkotava E.H.; Goucharev A.V. and Belov N.V. *J. Chem. Soc. Chem. Comm.*, **1974**, 260. b) Zefirov N.S. and Rogozina S.V.; *Tetrahedron*, **1974**, *30*, 2345. c) Zefirov N.S.; Gurvich L.G.; Sashkov A.S.; Krimer M.Z. and Vorobleva E.A. *Tetrahedron* **1976**, *32*, 1211. d) Elliel E.L. and Juaristi E.J. *J. Am. Chem. Soc.* **1978**, *100*, 6114.

10. Burkert U.; Allinger N.L., «*Molecular Mechanics*», American Chemical Society, Washington D.C. **1982.**

11. Jaime C.; Osawa E., *Tetrahedron* **1983**, *39*, 2769.

12. Haasnoot C.A.; Lenuw A.A.M.; Altona C., *Tetrahedron*, **1980**, *36*, 2783.