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Baker's yeast reduction of 4-hetero-2-(2-nitroethyl)cyclohexanones

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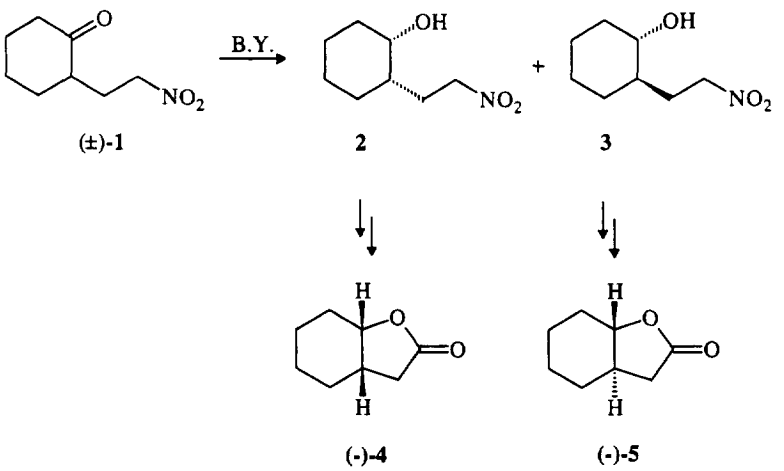
Abstract: Baker's yeast reduction of 3-(2-nitroethyl)-tetrahydro-4H-pyran-4-one **10** and 3-(2-nitroethyl)-tetrahydro-4H-thiopyran-4-one **11** gave the corresponding optically active *cis* alcohols with good diastereo- and enantioselectivity. The unreacted optically active ketones were also isolated. © 1997 Elsevier Science Ltd

Baker's yeast reduction of prochiral cyclic and acyclic ketones has been established as a reliable method for the synthesis of alcohols with high enantiomeric excess.[1] *Inter alia*, it has been reported that baker's yeast reduces linear α-, β- and γ-nitroketones to the corresponding optically active nitroalcohols,[2] which are useful chiral building blocks for asymmetric synthesis.[3]

We investigated the baker's yeast reduction of 2-(2-nitroethyl)cycloalkanones[4] with the aim of obtaining enantiomerically pure precursors of γ-lactones.[4] In fact bioreduction of 2-(2-nitroethyl)cyclohexanone (±)-**1**[4a] furnished the corresponding *cis* and *trans* nitroalcohols **2** and **3** with a good chemical yield as well as a high degree of diastereo- and enantioselectivity (Scheme 1).[4a] Protection of the hydroxy group of the optically active nitroalcohols by DHP (Dihydropyran), followed by oxidation of the nitromethylenic group in basic medium,[5] gave the expected γ-lactones (−)-**4** and (−)-**5** after deprotection and cyclization.



Scheme 1.

We were interested in extending our work to cyclic ketones containing a heteroatom in the ring in order to verify the influence of the heteroatom on the bioreduction. The substrates chosen were 4-hetero-2-(2-nitroethyl)cyclohexanones (±)-**10** and (±)-**11**, in which the heteroatom was oxygen and sulfur respectively (Scheme 2).

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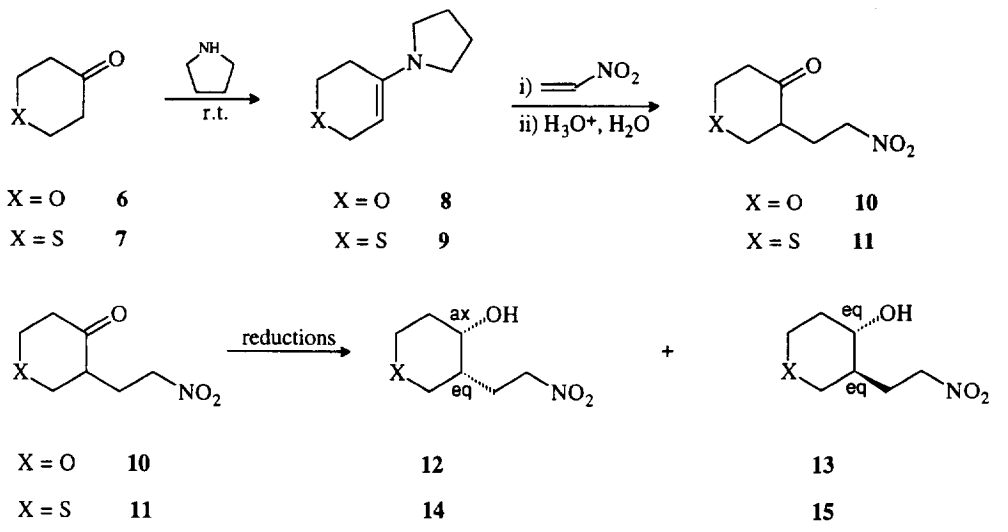

Scheme 2.

Results and discussion

Ketones (±)-**10** and (±)-**11** were prepared by nitroethylation of the corresponding pyrrolidino enamines **8**[6a] and **9**[6b] derived from 4-heterocyclohexanone **6** and **7** respectively, followed by hydrolysis of the crude reaction mixtures under mild acidic conditions (Scheme 2).

Bioreductions were performed with commercial baker's yeast under the conditions used by Nakamura *et al.*[7] Racemic nitroalcohols were obtained by $NaBH_4$ reductions of the nitroketones **10** and **11** in ethanol, at room temperature, and they were used for a comparison with the products of the biotransformation.

Bioreduction of 3-(2-nitroethyl)-tetrahydro-4H-pyran-4-one (±)-**10** (48% of conversion) gave the *cis* derivative (+)-**12** as the only diastereoisomer, while bioreduction of compound (±)-**11** gave a mixture of *cis* and *trans* isomers (+)-**14** and **15** (58% of conversion) in the ratio of 85:15.[8] The results are summarized in the Table 1 which also lists the results obtained with sodium borohydride and those obtained for the carbocyclic derivative (±)-**1**, for a comparison. It is interesting to underline that both heterocyclic systems were bioreduced more rapidly than their cyclohexanone analogue (8–10 days *vs.* 15 days) and that the diastereoselectivity of the tetrahydropyrane derivative was very high (100%) whereas that of the thiopyrane derivative was very similar to that of the cyclohexanol system (*cis/trans* ratio: 85/15 *vs.* 80/20).

It is also important to note that in the case of the bioreduction of (±)-**10** the reaction was stopped at a low degree of conversion (48%) in order to obtain the compound (+)-**12** as a pure diastereoisomer. If the reaction was allowed to proceed further, **13** was also formed, albeit in small percentage.

On the contrary, in the bioreduction of (±)-**1**, both diastereoisomers **2** and **3** were formed since the very beginning of the reaction.[4a]

The stereochemistry of the alcohols was deduced by ^{1}H-NMR analysis of the respective carbinol proton signals. Thus the *cis* isomers (+)-**12** and (+)-**14** showed a doublet of triplets at 4.01 and 3.89 ppm respectively, the vicinal coupling constants being 3.2, 3.2 and 6.3 Hz for the former compound and 2.9, 2.9 and 5.8 Hz for the latter. These indicated the equatorial orientation of the carbinol protons and hence the axial orientation of the hydroxy groups.[9] Also the carbinol proton signals of the *trans* isomers **13** and **15** were doublets of triplets, resonating at 3.37 and 3.35 ppm respectively. However the values of their vicinal coupling constants (2.4, 11.7, 11.7 Hz for **13** and 3.9, 9.3, 9.3 Hz for **15**) clearly proved the equatorial orientation of the hydroxy group in both derivatives.

Table 1. Baker's yeast and $NaBH_4$ reduction of (±)-**1**, (±)-**10** and (±)-**11**

Ketones	Alcohols	$NaBH_4$ (total yield, %)	$NaBH_4$ (%)	B.Y. (conversion, %)	B.Y. (%)	e.e., %
	2		40[a]		80[b]	94[c]
1		80		80[b]		
	3		60[a]		20[b]	94[c]
	12		35[a]		>99[b]	>99[d]
10		44		48[b]		
	13		65[a]		<1[b]	-
	14		60[a]		85[a]	70[d]
11		33		58[a]		
	15		40[a]		15[a]	>99[d]

a) Determined by ^{1}H-NMR analysis; b) Determined by HRGC analysis; c) Determined by ^{1}H-NMR of the Mosher's ester; d) Determined by HRGC of its trimethylsilyl derivative.

The absolute configuration of the alcohols (+)-**12**, (+)-**14** and **15**,[8] was determined by means of an analysis of their CD spectra.

The unreacted ketones (−)-**1**, (−)-**10** and (−)-**11**, in fact, isolated from their respective bioreduction mixture, showed an e.e. of 90%,[4a] 88% and 77% respectively. Their CD curves are reported in Figure 1 and they all show a positive band around 285 nm for the $n \rightarrow \pi^*$ transition. Since a positive Cotton effect is related to the R configuration of C-2 in 2-alkylcyclohexanones,[10] in accordance with the octant rule,[11] it is likely that the configuration of the stereocentre in the three ketones are the same. This is R for (−)-**1** and (−)-**11** and S for (−)-**10**, as a consequence of a different priority sequence [(−)-**1**: C=O>$CH_2CH_2NO_2$>CH_2CH_2; (−)-**10**: C=O>CH_2–O>$CH_2CH_2NO_2$; (−)-**11**: CH_2–S>C=O>$CH_2CH_2NO_2$].

The ketone (−)-**11** showed a further band at 236 nm with positive Cotton effect, which was attributed to the sulfur atom band.[12] The same band, although of opposite sign, was also present in the spectrum of the alcohol (+)-**14**. The opposite Cotton effect observed for (−)-**11** and (+)-**14** was interpreted as due to the opposite configuration of the stereocenters bearing the nitroethyl chain.

Since the enantiomeric excess of the unreacted ketones S-(−)-**10** and R-(−)-**11** was high, it seems reasonable to assign the opposite configurations to the same stereocenters in the resulting *cis* alcohols (+)-**12** and (+)-**14** which were the major products. Their absolute configuration is therefore 3R,4S and 3S,4S.

The octant rule was stated for cyclohexanone derivatives. To be sure that it could also be used for 4-heterocyclohexanones, the absolute configuration of the alcohols (+)-**12** and (+)-**14** was determined by means of other methods.

First of all, a comparison was made between the CD curves of their 3,5-dinitrobenzoates (+)-**16** and (+)-**17** with that of an analogous derivative of known absolute configuration, namely the compound (+)-**18**[13] derived from the alcohol **2**. As shown in Figure 2 the curves were superimposable. Since the configuration of **2** is 1S,2S,[4a] the *cis* alcohols (+)-**12** and (+)-**14** are 3R,4S- and 3S,4S-isomers.

The absolute configuration of the alcohol (+)-**12** was further confirmed by a method proposed by M. Trujillo *et al.*[14] for the determination of the absolute configuration of cyclic and acyclic secondary alcohols. The tetra-O-benzoyl-β-glucosylation of a secondary alcohol induces dramatic shifts in ^{1}H-NMR peaks resonances of the aglycon part. The differences between the proton chemical shifts of the

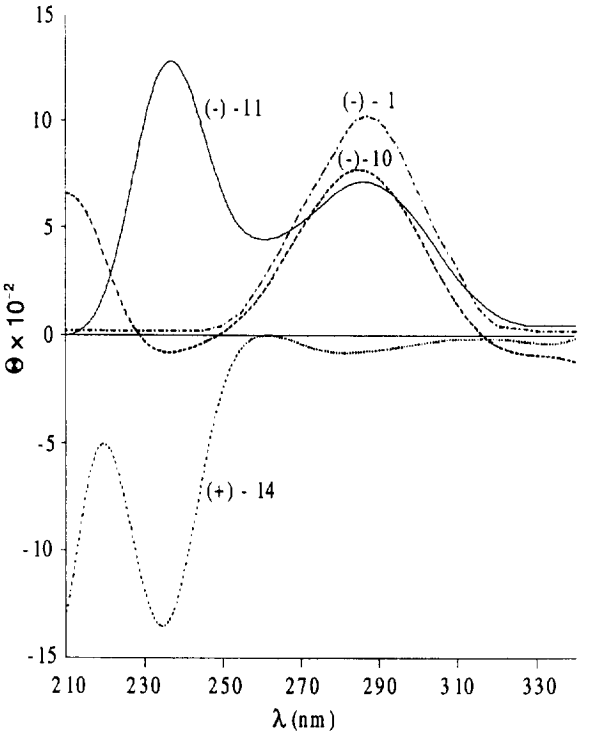

Figure 1. CD Spectra of the ketones.

D-glucosylated derivative and the free alcohol ($\Delta\delta=\delta_D-\delta_{ROH}$) can be correlated with the absolute configuration of the chiral alcohol.

Protons *anti* to the endocyclic glucopyranoside oxygen (O-5) are shielded due to the diamagnetic effect of the benzoyl group at C-2 and thus exibit a negative $\Delta\delta$, whereas protons *syn* to that oxygen atom show a positive $\Delta\delta$, due to their proximity to the heteroatom.

The β-D-glucopyranoside tetrabenzoate (+)-**21** was synthesized and fully characterized (Figure 3). The differences in chemical shift found for its protons, when compared with those of the free alcohol (+)-**12**, confirmed the configurational assignments made above. In fact, the protons *anti* to the O-5 showed negative chemical shift differences whereas those *syn* to the endocyclic glucopyranoside oxygen showed positive chemical shift differences. Furthermore, the chemical shift difference of the carbinyl proton is negative ($\Delta\delta=-0.24$). This is also consistent with the S configuration assigned to it.

Finally, the absolute configuration of the *trans* alcohol **15** was determined by comparing the CD curve of its 3,5-dinitrobenzoate (+)-**19** with that of (+)-**20**,[15] derived from the *trans* alcohol **3** (Figure 4) whose absolute configuration is known to be 1S,2R.[4a] Also in this case, the CD spectra are superimposable. Therefore the absolute configuration of the alcohol **15** is 3R,4S.

In conclusion, when compared with the reactivity of the carbocyclic analog **1**, both heterocyclic substrates **10** and **11** have been found to be bioreduced faster and with higher diastereoselectivity. Also enantioselectivity was higher, with the exception of the *cis* alcohol **14**, whose optically purity was moderate. The oxygen atom in the six-membered ring is responsable for the excellent diastereoselectivity observed in the bioreduction. We think this is due to the possibility for the oxygen atom to form a hydrogen bond with the enzyme which would stabilize the reactive conformation of the ketone.

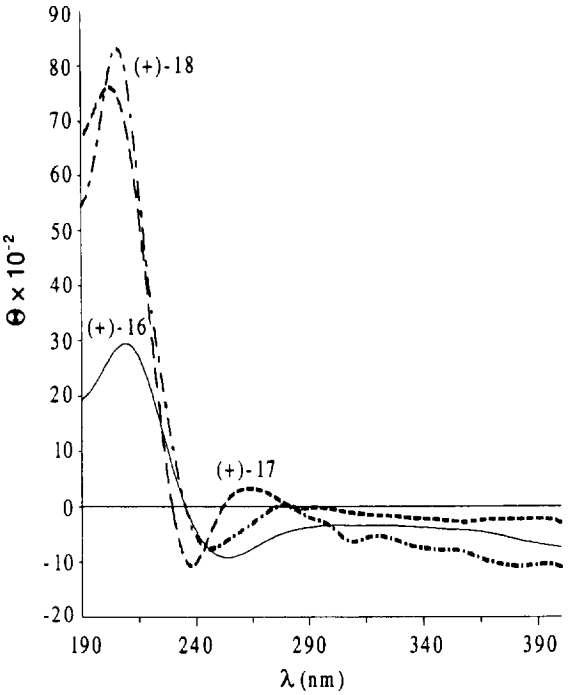

Figure 2. CD Spectra of the *cis* benzoates.

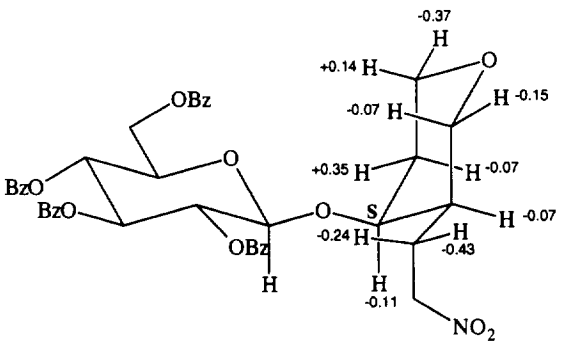

Figure 3. β-D-Glucopyranoside tetrabenzoate (+)-**21** with the Δδ values (ppm) for each proton.

Experimental section

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$, unless otherwise stated, on a Jasco FT/IR 200 spectrophotometer. ^{1}H-NMR spectra were run on a Jeol EX-400 (400 MHz) spectrometer, using deuteriochloroform as solvent and tetramethylsilane as internal standard. ^{13}C-NMR spectra were recorded on a Jeol EX-400 (100.5 MHz) instrument. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. CD spectra were obtained on a Jasco J-700A spectropolarimeter (0.1-cm cell) in methanol (unless otherwise stated); UV spectra were recorded on a Perkin–Elmer Lambda 2 and a Jasco V-550 spectrophotometers (1 cm cell) in methanol (unless otherwise stated); GLC analysis were obtained on a Carlo Erba GC 8000 instrument, the capillary column being OV 1701 (25 m × 0.32 mm) (carrier gas He, 40KPa, condition are indicated for each compound) and a Chiraldex^{TM} type G-TA, trifluoroacetyl γ-cyclodextrin (40 m × 0.25 mm) (carrier gas He, 180KPa); mass spectra were run by the electron-impact mode (70 eV)

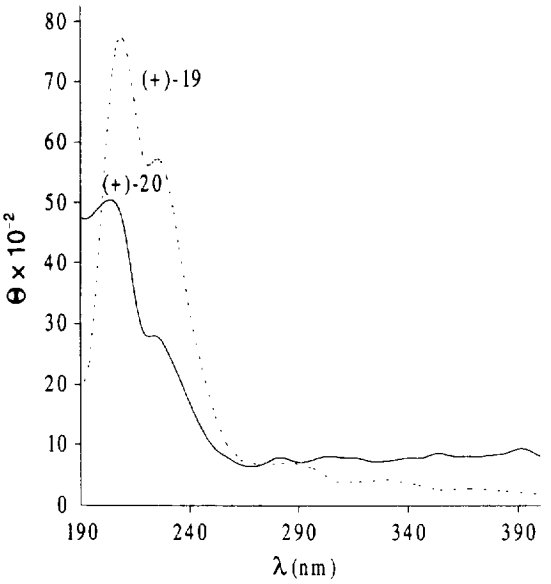

Figure 4. CD Spectra of the *trans* benzoates.

on a Hewlett Packard 5971 A GC-MS instrument and a VG 7070 (70 eV). TLC's were performed on Whatman K6F silica gel plates (eluant: light petroleum/ethyl acetate). Flash Chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). Light petroleum refers to the fraction with b.p. 40–70°C and ether to diethyl ether. Tetrahydro-4H-pyran-4-one, tetrahydro-4H-thiopyran-4-one, 2,3,4,6-tetra-O-benzoyl-α-glucopyranosyl bromide and AgOTf were purchased from Aldrich.

3,6-Dihydro-4-(1-pyrrolidinyl)-2H-pyran **8**[6a]

2.5 ml (30 mmol) of pyrrolidine was added to 1.8 ml (20 mmol) of tetrahydro-4H-pyran-4-one without solvent. The mixture was stirred at 0°C. After 90 min the enamine was completely formed. After elimination of the excess of the base under the vacuum, the resulting oil was used as obtained. IR (film): 1645 cm^{-1}; ^{1}H-NMR, δ, ppm: 4.23 (2H, m, O–CH_2–C=), 4.18 (1H, m, =C–H), 3.97 (2H, t, J 5.9, O–CH_2), 3.24 (4H, m, N(CH_2)$_2$), 2.29 (2H, m, O–CH_2–CH_2), 1.86 (4H, m, $NCH_2(CH_2)_2$); ^{13}C-NMR, δ, ppm: 140.4 (s), 90.6 (d), 65.7 (t), 64.3 (t), 46.8 (2t), 27.6 (t), 24.4 (2t).

3,6-Dihydro-4-(1-pyrrolidinyl)-2H-thiopyran **9**[6]

2.2 ml (26 mmol) of pyrrolidine was added to 2.0 g (17.2 mmol) of tetrahydro-4H-thiopyran-4-one in 5 ml of benzene. After stirring for 90 min the enamine was completly formed. After elimination of the excess of the base under the vacuum, the resulting oil was used as obtained. IR (film): 1635 cm^{-1}; ^{1}H-NMR, δ, ppm: 4.37 (1H, m, =C–H), 3.19 (2H, m, S–CH_2–C=), 2.96 (4H, m, N(CH_2)$_2$), 2.74 (2H, m, S–CH_2), 2.40 (2H, m, S–CH_2–CH_2), 1.78 (4H, m, $NCH_2(CH_2)_2$); ^{13}C-NMR, δ, ppm: 143.7 (s), 90.3 (d), 46.9 (2t), 28.4 (t), 25.6 (t), 25.4 (2t), 24.4 (t).

3-(2-Nitroethyl)-tetrahydro-4H-pyran-4-one ***10***

A solution of 1.44 g (20 mmol) of nitroethylene in 8 ml of ether was added to a stirred solution of 4.1 g (20 mmol) of the crude 3,6-dihydro-4-(1-pyrrolidinyl)-2H-pyran in 8 ml of ether, at −40°C. After 12 h at −18°C, the solvent was evaporated and the crude was dissolved in methanol. The solution was acidified with 10% HCl to pH 2. After 2 h, methanol was removed in vacuo, the acqueous phase was extracted with chloroform and the combined organic layers were dried and evaporated. The ketone was obtained in 56% yield (after purification by flash-chromatography). Anal. found C 48.3, H 6.19, N

8.37%. $C_7H_{11}NO_4$ requires: C 48.55, H 6.40, N 8.10%; m.p. (from ether/light-petroleum): 49–50°C; Retention time 21.3 min (OV 1701) (2 min 100°C, 3°C/min, 150°C); IR (nujol): 1715 cm^{-1} (C=O), 1550 (NO_2), 1100 (C–O–C); ^{1}H-NMR, δ, ppm: 4.52 (2H, m, CH_2NO_2), 4.28 (1H, m, H-6eq), 4.23 (1H, dd, J_1 6.6, J_2 10.7, H-2eq), 3.69 (1H, dt, J_1=J_2 11.7, J_3 2.4, H-6ax), 3.38 (1H, t, J 10.7, H-2ax), 2.70 (2H, m, H-3+H-5ax), 2.41 (1H, dt, J_1=J_2 2.4, J_3 14.2, H-5eq), 2.32 (1H, m, $CH_2CH_2NO_2$), 1.86 (1H, dquint, J_1=J_2=J_3 7.3, J_4 3.9, $CH_2CH_2NO_2$); ^{13}C-NMR, δ, ppm: 206.9 (s), 73.2 (t), 72.3 (t), 68.7 (t), 48.1 (d), 42.6 (t), 23.0 (t); MS, m/z: 173 (M^+; 1.3), 127 ([M−NO_2]$^+$, 4), 125 ([M−H_2NO_2]$^+$, 11), 101 (51), 97 (29), 73 (21), 71 (11), 69 (34), 68 (37), 55 (100), 54 (94).

(−)-(3S)-3-(2-Nitroethyl)-tetrahydro-4H-pyran-4-one ***10***

e.e. 88% (by chiral HRGC); $[\alpha]_D^{25}$=−19.3 (c 0.57, CH_3OH), $[\Theta]_{285}$=+774; UV, λ_{max} (ε, $M^{-1}cm^{-1}$): 294.0 (31).

3-(2-Nitroethyl)-tetrahydro-4H-thiopyran-4-one ***11***

A solution of 1.24 g (17.2 mmol) of nitroethylene in 5 ml of ether was added to a stirred solution of 3.8 g (17.2 mmol) of the crude of 3,6-dihydro-4-(1-pyrrolidinyl)-2H-thiopyran in 5 ml of ether, at −40°C. The ketone was obtained in 60% yield (after purification by flash-chromatography). Retention time 13.8 min (OV 1701) (2 min 150°C, 3°C/min, 200°C); oil; IR (film): 1710 cm^{-1} (C=O), 1550 (NO_2); ^{1}H-NMR, δ, ppm: 4.44 (2H, m, CH_2NO_2), 2.93 (3H, m), 2.81 (1H, m), 2.70 (3H, m), 2.42 (1H, m), 1.98 (1H, m); ^{13}C-NMR, δ, ppm: 208.7 (s), 73.2 (t), 49.8 (d), 44.4 (t), 36.0 (t), 30.9 (t), 27.2 (t); MS, m/z: 189 (M^+; 6), 159 (29), 143 ([M−NO_2]$^+$, 6), 141 ([M−H_2NO_2]$^+$, 15), 140 (23), 122 (27), 109 (12), 101 (11), 97 (19), 89 (21), 88 (78), 87 (16), 86 (17), 85 (33), 79 (12), 73 (10), 69 (12), 68 (11), 61 (19), 60 (75), 59 (43), 58 (25), 55 (100), 54 (42), 53 (25).

(−)-(3R)-3-(2-Nitroethyl)-tetrahydro-4H-thiopyran-4-one ***11***

e.e. 77% (by chiral HRGC); $[\alpha]_D^{25}$=−11.6 (c 0.38, CH_3OH); $[\Theta]_{286}$=+716, $[\Theta]_{236}$=+1278; UV, λ_{max} (ε, $M^{-1}cm^{-1}$): 294.0 (43), 239.2 (390).

General procedure for the reduction with $NaBH_4$

Sodium borohydride (5 mmol) was added to a stirred solution of the ketone (10 mmol) in 6 ml of ethanol. After 2 h at room temperature, water was added and the acqueous phase was extracted with ether. The organic phase was washed with saturated NaCl and dried.

General procedure for the reduction with baker's yeast[7]

100 g of baker's yeast in 200 ml of water was preincubated for 30 min at 50°C, added to 10 mmol of the ketone and the mixture stirred at room temperature under N_2. The course of the reduction was checked every 2–3 days by HRGC or ^{1}H-NMR. At the end of the reaction, brine was added and the broth was continuosly extracted for 48h with ether. The organic phase was dried and evaporated.

Reduction of 3-(2-nitroethyl)-tetrahydro-4H-pyran-4-one ***10***

Reduction with $NaBH_4$ of **10** gave the *cis* and *trans* alcohols **12** and **13** (32% overall yield) in ratio 35:65 respectively which could not be separated by flash-chromatography. Reduction with baker's yeast of **10** gave after 8 days the alcohol *cis* (+)-**12** (conversion 48%) in admixture with the unreacted ketone (−)-**10**. The *cis* alcohol was separated in 22% yield from the unreacted ketone (22%) by flash-chromatography.

cis-*(+)-(3R,4S)-4-Hydroxy-3-(2-nitroethyl)-tetrahydro-4H-pyran* ***12***

Retention time 31.2 min (OV 1701) (2 min at 100°C, 3°C/min, 150°C); IR (neat): 3400 (OH), 1550, 1360 (NO_2), 1100 (C–O–C); ^{1}H-NMR, δ, ppm: 4.50 (2H, m, CH_2NO_2), 4.01 (1H, dt, J_1=J_2 3.2, J_3 6.3, H-4), 3.83 (1H, ddd, J_1 3.4, J_2 8.8, J_3 12.2, H-6eq), 3.61 (2H, m, H-6ax+H-2ax), 3.53 (1H, dd, J_1 3.6, J_2 11.2, H-2eq), 3.01 (1H, bs, OH), 2.17 (1H, sext., J 7.3, $CH_2CH_2NO_2$), 1.98 (1H, sext.,

J 7.3, $CH_2CH_2NO_2$), 1.81 (2H, m, H-3+H-5ax), 1.69 (1H, m, H-5eq); ^{13}C-NMR, δ, ppm: 73.6 (t, C-β), 67.2 (t, C-2), 66.0 (d, C-4), 63.6 (t, C-6), 37.8 (d, C-3), 32.6 (t, C-5), 24.4 (t, C-α); MS, m/z: 173 ([M−H_2]$^+$; 0.4), 127 ([M−H_2NO_2]$^+$, 8), 101 (28), 99 (11), 97 (11), 83 (17), 81 (32), 79 (19), 73 (15), 71 (43), 70 (29), 69 (39), 68 (12), 67 (18), 61 (10), 57 (61), 56 (14), 55 (100), 54 (57), 53 (38); e.e. >99% (by chiral HRGC of its trimethylsilyl derivative); $[\alpha]_D^{25}$=+2.8 (c 0.14, CH_3OH).

trans-*4-Hydroxy-3-(2-nitroethyl)-tetrahydro-4H-pyran* ***13***

Retention time 30.5 min (OV 1701) (2 min at 100°C, 3°C/min, 150°C); ^{1}H-NMR, δ, ppm: 4.58 (2H, m, CH_2NO_2), 3.93 (1H, m), 3.86 (1H, dd, J_1 3.9, J_2 12.2), 3.37 (1H, dt, J_1=J_2 11.7, J_3 2.4, H-4), 3.04 (1H, dd, J_1 10.5, J_2 11.7); ^{13}C-NMR, δ, ppm: 74.0 (t), 72.2 (d), 69.8 (t), 66.3 (t), 41.5 (d), 35.3 (t), 27.2 (t). Although also the NMR spectra were run on the mixture, the peaks are given separately for the two alcohols.

Reduction of 3-(2-nitroethyl)-tetrahydro-4H-thiopyran-4-one ***11***

Reduction with $NaBH_4$ of **11** gave the *cis* and *trans* alcohols **14** and **15** (30% overall yield) in ratio 60:40 respectively which could not be separated by flash-chromatography.

Reduction with baker's yeast, after 10 days, afforded the alcohols *cis* and *trans* in 85% and 15% respectively, with a conversion of 58%, in admixture with the unreacted ketone. The mixture of the two alcohols was separated from the unreacted ketone in 33% yield by flash-chromatography.

cis-*(+)-(3S,4S)-4-Hydroxy-3-(2-nitroethyl)-tetrahydro-4H-thiopyran* ***14***

In admixture with 8% of the *trans* isomer (after purification by flash-chromatography). Retention time 19.8 min (OV 1701) (2 min 150°C, 3°C/min, 200°C); IR (film): 3400 cm^{-1} (OH), 1550 (NO_2); ^{1}H-NMR, δ, ppm: 4.47 (2H, m, CH_2NO_2), 3.89 (1H, dt, J_1=J_2 2.9, J_3 5.8, H-4), 2.88 (1H, ddd, J_1 3.0, J_2 9.7, J_3 12.7, H-6ax), 2.76 (1H, dd, J_1 9.3, J_2 13.2, H-2ax), 2.39 (2H, m, H-2eq+H-6eq), 2.26 (1H, m, $CH_2CH_2NO_2$), 2.14 (1H, m, $CH_2CH_2NO_2$), 1.97 (3H, m, H-3+2H-5), 1.70 (1H, bs, OH); ^{13}C-NMR, δ, ppm: 73.5 (t, C-β), 68.2 (d, C-4), 38.8 (d, C-3), 33.7 (t, C-5), 30.3 (t, C-α), 28.3 (t, C-2), 23.5 (t, C-6); MS, m/z: 191 (M$^+$; 36), 159 ([M−S]$^+$; 10), 158 ([M−HS]$^+$, 11), 157 ([M−H_2S]$^+$; 54), 143 ([M−H_2NO_2]$^+$, 19), 139 ([M−H_2S−H_2O]$^+$; 21), 127 (14), 116 (18), 112 (18), 101 (20), 100 (23), 99 (100), 98 (48), 97 (28), 93 (28), 81 (38), 72 (30), 68 (47), 61 (46), 57 (48), 55 (78); e.e. 70% (by chiral HRGC of its trimethylsilyl derivative); $[\alpha]_D^{25}$=+5.9 (c 0.37, CH_3OH); $[\Theta]_{234}$=−1350; UV, λ_{max} (ε, M^{-1}cm^{-1}): 247.5 (27).

trans-*(3R,4S)-4-Hydroxy-3-(2-nitroethyl)-tetrahydro-4H-thiopyran* ***15***[8]

Retention time 19.4 min (OV 1701) (2 min 150°C, 3°C/min, 200°C); ^{1}H-NMR, δ, ppm: 4.49 (2H, m, CH_2NO_2), 3.35 (1H, dt, J_1=J_2 9.3, J_3 3.9, H-4), 2.66 (2H, m); ^{13}C-NMR, δ, ppm: 74.1 (t), 73.4 (d), 42.6 (d), 36.5 (t), 31.6 (t), 28.2 (t), 26.9 (t), e.e. >99% (by chiral HRGC of its trimethylsilyl derivative).

General procedure for the synthesis of the 3,5-dinitrobenzoates

1 g of a solution of 3,5-dinitrobenzoylchloride in 5 ml of benzene was added to 0.5 ml of the optically active alcohol in 1 ml of anhydrous pyridine, under reflux for 15 min. After cooling water was added and the mixture was extracted with ether. The products were purified by flash-chromatography.

cis-*(+)-(3R,4S)-4-(3,5-Dinitrobenzoyloxy)-3-(2-nitroethyl)-tetrahydro-4H-pyran* ***16***

m.p. (from ether/light-petroleum): 121–122°C; Anal. found: C 45.8, H 4.23, N 11.18%. $C_{14}H_{15}N_3O_9$ requires: C 45.53, H 4.09, N 11.38%; IR (nujol): 1730, 1712 cm^{-1} (C=O), 1630 (Ar), 1546 (NO_2); ^{1}H-NMR, δ, ppm: 9.27 (1H, t, J 2.0, Ar-H), 9.16 (2H, d, J 2.0, Ar-H), 5.48 (1H, dt, J_1=J_2 5.6, J_3 2.9, H-4), 4.49 (2H, m, CH_2NO_2), 3.92 (1H, quintet, J 5.6, H-6), 3.77 (3H, m, 2H-2+H-6), 2.17 (3H, m, H-3+$CH_2CH_2NO_2$), 2.02 (2H, q, 2H-5); ^{13}C-NMR, δ, ppm: 161.8 (s), 148.8 (s), 133.5 (s), 129.3 (d), 122.7 (d), 73.0 (t), 72.5 (d), 67.4 (t), 64.4 (t), 36.5 (d), 29.1 (t), 24.0 (t);

$[\alpha]_D^{25}$=+29.0 (c 0.08, CH_3CN), $[\Theta]_{211}$=+3975, $[\Theta]_{232}$=0, $[\Theta]_{247}$=−1229 (CH_3CN); UV (CH_3CN), λ_{max} (ϵ, $M^{-1}cm^{-1}$): 228.2 (20400), 207.3 (30900).

cis-*(+)-(3S,4S)-4-(3,5-Dinitrobenzoyloxy)-3-(2-nitroethyl)-tetrahydro-4H-thiopyran* ***17***

m.p. (from ether/light-petroleum): 110–111°C; Anal. found C 43.50, H 3.88, N 10.60%. $C_{14}H_{15}N_3O_8S$ requires: C 43.64, H 3.92, N 10.70%; IR (nujol): 1720 cm^{-1} (C=O), 1630 (Ar), 1550 (NO_2); ^{1}H-NMR, δ, ppm: 9.26 (1H, t, J 2.0, Ar-H), 9.14 (2H, d, J 2.0, Ar-H), 5.38 (1H, dt, J_1=J_2 2.4, J_3 7.3, H-4), 4.49 (2H, m, CH_2NO_2), 2.86 (2H, m), 2.73 (1H, m), 2.63 (1H, m), 2.28 (4H, m), 2.13 (1H, m); ^{13}C-NMR, δ, ppm: 162.0 (s), 149.1 (s), 133.8 (s), 129.6 (d), 123.0 (d), 74.5 (d), 73.2 (t), 37.5 (d), 30.5 (t), 29.5 (t), 27.7 (t), 24.8 (t); $[\alpha]_D^{25}$=+37.3 (c 0.11, CH_3CN), $[\Theta]_{202}$=+7685, $[\Theta]_{230}$=0, $[\Theta]_{236}$=−1225 (CH_3CN); UV (CH_3CN), λ_{max} (ϵ, $M^{-1}cm^{-1}$): 228.0 (21400), 207.0 (33100).

trans-*(+)-(3R,4S)-4-(3,5-Dinitrobenzoyloxy)-3-(2-nitroethyl)-tetrahydro-4H-thiopyran* ***19***

m.p. (from ether/light petroleum): 137–138°C; Anal. found C 43.37, H 3.74, N 10.61%. $C_{14}H_{15}N_3O_8S$ requires: C 43.64, H 3.92, N 10.70%; IR (nujol): 1720 cm^{-1} (C=O), 1630 (Ar), 1550 (NO_2); ^{1}H-NMR, δ, ppm: 9.25 (1H, t, J 2.0, Ar-H), 9.16 (2H, d, J 2.0, Ar-H), 5.02 (1H, dt, J_1=J_2 8.3, J_3 3.9, H-4), 4.49 (2H, m, CH_2–NO_2), 2.96 (1H, m), 2.84 (1H, m), 2.76 (1H, m), 2.54 (1H, dd, J_1 8.8, J_2 14.2), 2.41 (2H, m), 2.22 (1H, m), 2.08 (2H, m); ^{13}C-NMR, δ, ppm: 162.1 (s), 149.0 (s), 133.8 (s), 129.7 (d), 123.0 (d), 77.0 (d), 73.2 (t), 39.1 (d), 31.7 (t), 30.8 (t), 28.8 (t), 26.4 (t); $[\alpha]_D^{25}$=+76.4 (c 0.14, CH_3CN), $[\Theta]_{208}$=+7778, $[\Theta]_{226}$=+5680 (CH_3CN); UV (CH_3CN), λ_{max} (ϵ, $M^{-1}cm^{-1}$): 226 (21500), 207 (32700).

General procedure for the synthesis of trimethylsilyl derivatives of alcohols

0.09 mmol of $(CH_3)_3SiCl$ and 0.09 mmol of Et_3N were added to a stirred solution of 0.06 mmol of alcohol in 2 ml of anhydrous THF at room temperature. After 12 h THF was evaporated and water was added. The aqueous phase was extracted with ether and the combined organic layers were washed first with 10% HCl and than with saturated $NaHCO_3$. The quantitative derivatized alcohol was than analyzed by chiral HRGC.

General procedure for the synthesis of β-O-glucopyranosides[14]

To a solution of 2,3,4,6-tetra-O-benzoyl-α-glucopyranosyl bromide in dry CH_2Cl_2 (10 ml/mmol) under Ar and at room temperature were added 0.5 equiv of the chiral alcohol and 0.5 equiv of 1,1,3,3-tetramethylurea. The reaction mixture was cooled at 0°C in an ice bath, and 1 equiv of the promoter AgOTf was than added. The reaction was stopped after 30 min with a few drops of water. After filtration through a bad of Celite the product was purified by flash-chromatography.

cis-*(+)-(3R,4S)-3-(2-Nitroethyl)-tetrahydro-4H-pyran-4-yl-β-D-glucopyranoside tetrabenzoate* ***21***

m.p. (from ether/light-petroleum): 160–161°C; Anal. found: C 65.40, H 5.28, N 1.70. $C_{41}H_{39}NO_{13}$ requires. C 65.33, H 5.22, N 1.86; IR (nujol): 1735, 1720 (C=O), 1600 (Ph), 1550 (NO_2), 1120, 1110, 1090, 1070 cm^{-1}; ^{1}H-NMR, δ, ppm: 7.98 (2H, d, J 7.9), 7.93 (2H, d, J 7.6), 7.90 (2H, d, J 8.8), 7.80 (2H, d, J 7.0), 7.58–7.25 (12H, m), 5.91 (1H, t, J 9.8, H-3′), 5.61 (1H, t, J 9.8, H-4′), 5.56 (1H, dd, J_1 9.8, J_2 7.9, H-2′), 4.91 (1H, d, J 7.9, H-1′), 4.61 (1H, dd, J_1 3.0, J_2 12.2, H-6′), 4.49 (1H, dd, J_1 6.2, J_2 12.2, H-6′), 4.16 (1H, m, H-5′), 3.99 (1H, m, CH_2NO_2), 3.90 (2H, m, CH_2NO_2+H-4), 3.75 (1H, m, H-6ax), 3.46 (3H, m, H-6eq+2H-2), 2.04 (1H, m, H-5eq), 1.74 (4H, m, H-5ax+H-3+C$H_2$$CH_2NO_2$); ^{13}C-NMR, δ, ppm: 171.2 (s), 165.7 (s), 165.5 (s), 165.1 (s), 164.8 (s), 133.4–128.1 (d), 101.5 (d, C-1′), 77.0 (d, C-4), 72.7 (t, C-β), 72.6 (d, C-3′), 72.1 (d, C-5′), 71.8 (d, C-2′), 69.6 (d, C-4′), 66.9 (t, C-2), 63.4 (t, C-6), 62.8 (t, C-6′), 36.9 (d, C-3), 31.0 (t, C-5), 24.4 (t, C-α); $[\alpha]_D^{25}$=+26.3 (c 0.52, CH_3CN); $[\Theta]_{235}$=+26490, $[\Theta]_{213}$=+3490 (CH_3CN).

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