Pergamon

Tetrahedron Vol. 51, No. 6, pp. 1775-1788, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01056-0

Baker's Yeast Reduction of Prochiral γ-Nitroketones: Enantioselective Synthesis of (*S*)-4-Nitroalcohols

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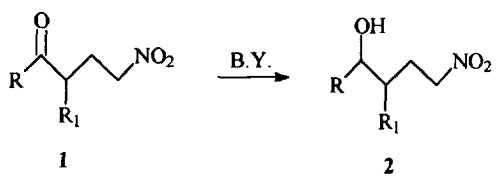
Abstract: The baker's yeast reduction of seven different prochiral nitroketones **1a-g** occurred on the *re* face of the carbonyl group, thus affording the (*S*)-nitroalcohols **2a-g**, with different level of enantioselectivity (e.e. 15-99%). The best results (e.e. = 99%) were achieved when the substituent R is markedly different from the nitroalkyl group [e.g. **1a** (R = Me) and **1e** (R = *o*-MeO-C_6H_4)]. The e.e. and the configuration of the bioproducts were assigned by NMR study of the corresponding Mosher esters and in one case (**2d**) by means of chemical correlation. The syntheses of optically active lactone **7** and pyrrolidine **11** starting from **2d** are also described.

Enantiomerically pure nitroalcohols with a primary nitro group are potentially important building blocks in synthesis of enantiomerically pure compounds as they can be converted into useful chiral compounds, either by exploiting the acidity of the protons at the position α to the nitro group for new C-C bond formation, or by converting the nitro group into carbonyl, amino, hydrogen or other functionalities.[1] Therefore, several studies on microbial reduction of aliphatic δ- and γ-nitroketones (i.e. 4-nitro-2-butanone,[2-4] 5-nitro-2-pentanone,[2] 5-nitro-3-pentanone,[4] and 6-nitro-3-hexanone[2,4]) to the corresponding (*S*)-nitroalcohols have been recently carried out.

Our interest in the use of chiral nitroalcohols as useful precursors for the synthesis of chiral heterocycles[5] led us to extend the baker's yeast reduction to the differently substituted aliphatic and aromatic prochiral γ-nitroketones **1b-g** (Scheme 1). In particular, the bioreduction of aryl substituted nitroketones **1d-g** would be of great interest because it represents the first example of enantioselective reduction of this type of substrate. In order to highlight the utility of the produced chiral nitroalcohols for the synthesis of chiral

Scheme 1



1 **2**

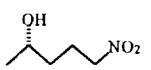
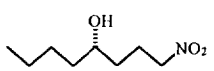
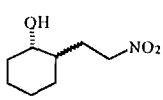
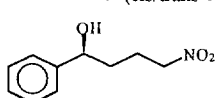
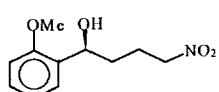
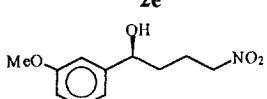
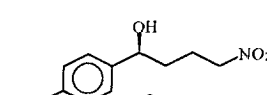
a: R = CH_3 , R_1 = H
b: R = *n*-C_4H_9 , R_1 = H
c: R - R_1 = -$(CH_2)_4$ -
d: R = C_6H_5 , R_1 = H
e: R = *o*-MeO-C_6H_4 , R_1 = H
f: R = *m*-MeO-C_6H_4 , R_1 = H
g: R = *p*-MeO-C_6H_4 , R_1 = H

heterocycles through manipulation of the nitro group, we report the enantioselective synthesis of (*S*)-(-)-5-phenyl-4,5-dihydrofuran-2-(3*H*)-one and (*R*)-2-phenylpyrrolidine starting from compound **2d**.

Results and Discussion

The nitroketones **1a-g** were prepared by slow addition of the corresponding vinyl ketones (for **1a,b**)[6] or Mannich's bases (for **1c-g**)[7] to nitromethane, with benzyl trimethylammonium hydroxide as catalytic base, in yields ranging from 44 to 52 %. Racemic nitroalcohols were obtained by $NaBH_4$ reduction of the nitroketones **1a-g** and were used for comparison with the products of the enzymatic reduction. The bioreductions of the nitroketones **1a-g** were carried out by adding the pure compounds to a fermenting suspension of baker's yeast in an aqueous solution of glucose heated at 30-35°C.[8] The reactions were monitored by GC and the end of the reaction indicated by the slowing down of conversion of nitroketone. The experimental conditions and results are summarised in Table 1.

Table 1. Baker's Yeast Reduction of Nitroketones **1a-g** to Nitroalcohols **2a-g**.

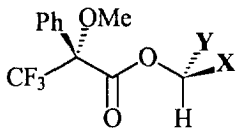
Nitroketone	Nitroalcohol	Time (d)	Conv.[a] (%)	Yield (%)	Config.	E.e. (%)	$[\alpha]_D$[b] (°)
1a	 **2a**	4	89	74	*S*	99	+18.5
1b	 **2b**	2 5	67 91	57 26	*S* *S*	27 15	+2 +1.3
1c	 **2c** (cis/trans 60/40)	3	52	45	(1*S*,2*S*) (1*S*,2*R*)	78 99	
1d	 **2d**	7	89	59	*S*	78	-40.7
1e	 **2e**	7	64	63	*S*	99	-28.1
1f	 **2f**	7	67	31	*S*	76	-24.2
1g	 **2g**	7	82	54	*S*	76	-32.0

[a] Conversion evaluated by GC on the crude mixture. [b] In $CHCl_3$ at 25 °C.

Although the microbial reduction of **1a** has already been described, [2-4] we compare here the results obtained by us[5] in the same conditions used for the reduction of the other nitroketones **1b-g**. The reduction of nitroketone **1c** with baker's yeast has been reported when our work was drawing to a conclusion, but it was carried out in anaerobic conditions and without nutrients.[9]

The enantiomeric excesses of the produced chiral nitroalcohols **2a-g** were determined by comparison of the NMR spectra of their (*R*)-(+)-MPTA (Mosher acid) derivatives **3a-g** with those of the racemic nitroalcohols.[10] The configurational assignment of the nitroalcohols **2a-g** was established by ^{1}H-NMR study of the Mosher esters **3a-g** and in one case (**2d**) also by means of chemical correlations. In all cases the absolute configuration of the newly created stereocentre resulted to be (*S*). In Table 2 the most significant chemical shifts of Mosher esters **3a-g** of the racemic mixture are reported. [The diastereoisomers (*S,R*)- and (*R,R*)-**3a-g**, in the following discussion, are simply referred to as (*S*)- and (*R*)-**3a-g**, indicating only the configuration of the carbinolic stereocentre at the alcohol moiety, the configuration of the acid being always *R*].

Table 2. Most significant ^{1}H-NMR data (ppm) of the Mosher esters **3a-g**.[a,b]



3a-g

(*S*)-**3a**	**X** = -$(CH_2)_3NO_2$	**Y** = -CH_3
(*S*)-**3b**	**X** = -$(CH_2)_3NO_2$	**Y** = -$(CH_2)_3CH_3$
(1*S*,2*S*)-**3c** and (1*S*,2*R*)-**3c**	**X-Y** = -$CH(CH_2CH_2NO_2)$-$(CH_2)_4$-	
(*S*)-**3d**	**X** = Ph	**Y** = -$(CH_2)_3$-NO_2
(*S*)-**3f**	**X** = *o*-MeO-C_6H_5	**Y** = -$(CH_2)_3$-NO_2
(*S*)-**3f**	**X** = *m*-MeO-C_6H_5	**Y** = -$(CH_2)_3$-NO_2
(*S*)-**3g**	**X** = *p*-MeO-C_6H_5	**Y** = -$(CH_2)_3$-NO_2

	3a		**3b**		**3c** [c]		**3d**		**3e**		**3f**		**3g**	
	S	*R*	*S*	*R*	*S,S* *S,R*	*R,R* *R,S*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*
-CH_2-NO_2	4.24	4.34	4.23	4.34			4.34	4.26	4.32	4.24	4.32	4.25	4.32	4.24
-OMe	3.56	3.50	3.54	3.51	3.57	3.49	3.51	3.43	3.53	3.49	3.52	3.45	3.47	3.40

[a] The reported absolute configuration refers to the alcohol moiety. The configuration of the acid moiety is always *R*. [b] The values refer to the ^{1}H-NMR spectra of the Mosher esters of the racemic nitroalcohols prepared by chemical reduction of the corresponding ketones. [c] The complex pattern of the signals in the 4-4.4 ppm region does not allow the assignment of the CH_2NO_2 signals.

On the basis of the model of Mosher ester shown in Table 2, it has been established[10] that the phenyl group of the acid moiety has a shielding effect on the facing X group. Therefore, the lower value of ^{1}H-NMR chemical shift of CH_2-NO_2 for ester derivatives **3** is associated with the (*S*)-enantiomer for nitroalcohols **2a-c**, and to the (*R*)-enantiomer for nitroalcohols **2d-g**. Furthermore, the lower value of chemical shift of the MeO-group of the acid moiety for esters **3d-g** is related with the (*R*)-enantiomer. These assignments are consistent with the configurations previously assigned to compounds **2a** and **2c** by chemical correlations.[2,3,9]

The bioreduction of 1-nitro-4-octanone **1b** produced with low enantioselectivity a mixture of

enantiomers of nitroalcohol **2b**, the major having the (*S*) configuration. The enantiomeric excess of (*S*)-(+)-**2b** was slighty decreased (27% to 15%) as conversion proceeded.

In the bioreduction of 2-(2-nitroethyl)cyclohexanone (**1c**), when the reaction was stopped at a conversion of 52%, a partial kinetic resolution was observed, the two enantiomers (*R*)-**1c** and (*S*)-**1c** being reduced at a slightly different rate, affording a 60/40 mixture of the two diastereoisomers (1*S*,2*S*)- and (1*S*,2*R*)-2-(2-nitroethyl)cyclohexanol (respectively *cis*-**2c** and *trans*-**2c**). Several attempts to separate the mixture by chromatography failed. The stereochemical assignment of *cis*- and *trans*-**2c** is made on the relative ^{1}H-NMR chemical shifts of the carbinolic protons. In the *cis*-isomer the proton at C-1 is equatorial and resonates at 3.87 ppm, whereas in the *trans*-isomer is axial and resonates at lower c.s. (3.22 ppm).[11] The enantiomeric excess was determined with accuracy on the mixture of the two diastereoisomers (1*S*,2*S*)-**2c** and (1*S*,2*R*)-**2c** by recording the ^{13}C-NMR spectra of the Mosher esters **3c**. It was possible to discriminate the four signals of the methoxy groups [δ 73.1 and 73.2 ppm, for the (1*S*,2*S*)/(1*S*,2*R*) pair, and δ 79.3 and 79.4 ppm for (1*R*,2*S*)/(1*R*,2*R*) pair], allowing us to give the values of 99% and 78% respectively for the enantiomeric excesses of (1*S*,2*R*)-**2c** and of (1*S*,2*S*)-**2c**.

It is noteworthy that the reduction with baker's yeast of **1c** goes in the same direction when the biotransformation is carried out in anaerobic conditions and without nutrients,[9] even though a better kinetic resolution is achieved [the (1*S*,2*S*)/(1*S*,2*R*) ratio is 4 to 1]. Furthermore, good enantiomeric excesses (94%) for both the two isomers are obtained, whereas in our conditions only for (1*S*,2*R*)-**2c** this is achieved.

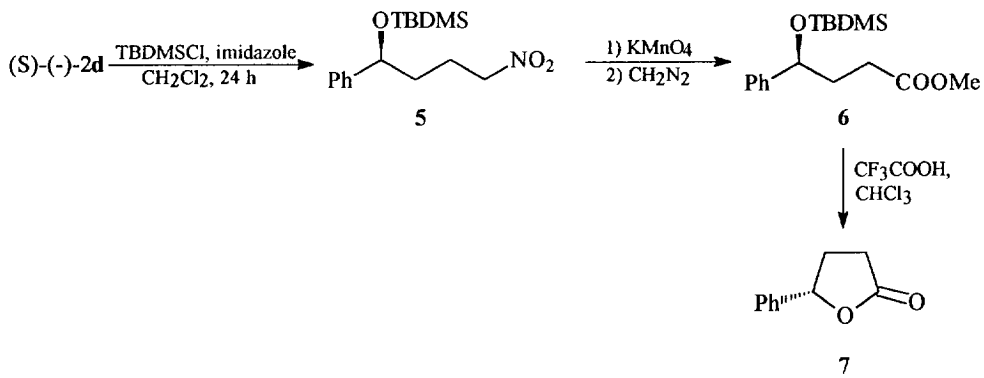
When nitroketones **1d-g** were submitted to baker's yeast reduction, (*S*)-(-)-**2d-g** were obtained with enantiomeric excesses ranging between 76% and 99%. The reaction times for the bioreduction of these aromatic nitroketones were longer if compared to those required by nitoketones **1a-c**, and at least 7 days were necessary to reach an acceptable conversion. Looking at the e.e. of nitroalcohols **2d-g**, it appears that the substitution on the phenyl ring strongly affects the differentiation between the *re* and *si* faces of the prochiral nitroketone only if the methoxy group is in *ortho* position. In fact, there is no appreciable difference among the e.e.'s of unsubstituted nitroalcohol **2d** and *meta*- and *para*-methoxy substituted **2f-g**.

The results of our bioreductions seem to be in agreement with the reduction of γ-nitro ketones **2a-g** by baker's yeast on the *re* face of the prochiral carbonyl group, according the Prelog's rule.[12] It is remarkable that the nitro group has a polar effect which is recognized by the enzyme. In fact the bioreduction of similar aliphatic ketones whitout the nitro group occurred with poor enantioselectivity.[13] Our results show that in aliphatic nitroketones **1a-c** the large group is represented by the nitroalkyl chain, and the alcohol with absolute *S* configuration is obtained as the major enantiomer. The low e.e. of **2b** could be a consequence of the poor differentiation between the large and small group of the nitroketone **1b**. In the bioreduction of aromatic nitroketones **1d-g** a clear inversion of priority between aryl and nitro group occurred, being the aryl group recognized as *the larger*[12] one by the enzyme. Furthermore, for the biotransformation of **1e**, a favourable interaction with the *o*-MeO group in the active site of the enzyme involved in the reduction should take place in order to explain the increased enantioselectivety.

The trasformation of nitroalcohol **2d** into optically active compounds, for instance lactone **7** (Scheme 2) and pyrrolidine **11** (Scheme 3), with known absolute configuration, was at this point carried out in order to confirm the previously assigned configurations and to show the synthetic versatility of these chiral nitroalcohols.

The procedure for the synthesis of optically active (*S*)-(-)-5-phenyl-4,5-dihydrofuran-2-(3*H*)-one 7 required the protection of the hydroxy group as TBDMS ether,[14] followed by the oxidation[15] of the CH_2-NO_2 group to give 4-(dimethyl-*t*-butylsilyloxy)-4-phenylbutanoic acid, then transformed into the corresponding methyl ester **6** ($[\alpha]_D$ -44.7°; *c* 0.694, $CHCl_3$). Finally, lactone **7** was quantitatively obtained by treating **6** with an excess of CF_3COOH in chloroform. The optical rotation of **7** ($[\alpha]_D$ -27.6°; c 0.680, $CHCl_3$) if compared to the value reported for the (*S*) enantiomer with 95% e.e. ($[\alpha]_D$ -32.5°; c 4.3, $CHCl_3$), [14] is in agreement with both the value of e.e. calculated by NMR (78%) and the (*S*) absolute configuration of nitroalcohol **2d**.

Scheme 2.

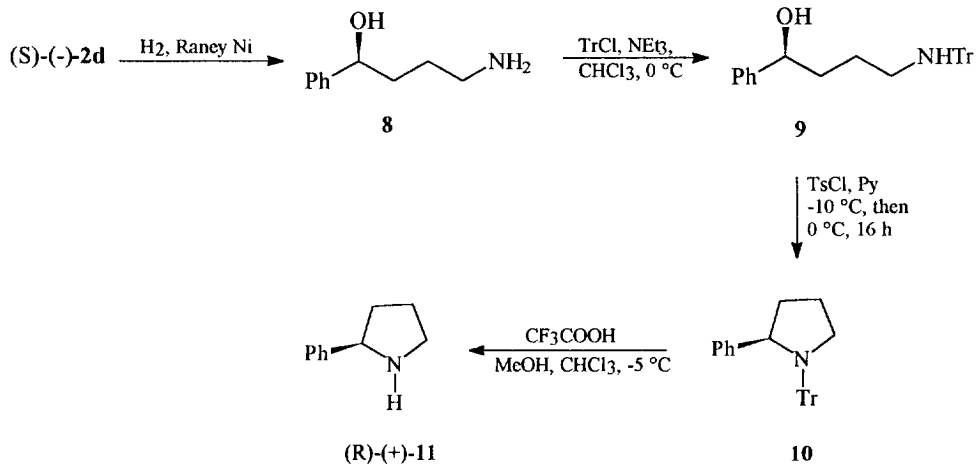


In Scheme 3 the synthesis of optically active (*R*)-(+)-2-phenylpyrrolidine is reported. This was accomplished, after catalytic reduction of (*S*)-(-)-**2d** to the corresponding aminoalcohol **8** (88% yield), by protecting selectively the amino group with triphenylchloromethane (trityl chloride) at 0° C in chloroform and in presence of NEt_3 to give **9**. This was then converted into *N*-trityl 2-phenylpyrrolidine (90% yield) **10** by treating with an excess of TsCl in pyridine at low temperature (from -10° to 0° C). No traces of the *O*-tosyl derivative were observed by proton NMR in the crude reaction mixture, and therefore no heating of this mixture was necessary for the ring closure. In an analogue experiment for the synthesis of substituted aziridines[16] a THF solution of the *O*-tosyl *N*-trityl intermediate was refluxed for 24 h in order to achieve the ring closure.

Both **9** and **10** were not purified because of the *N*-trityl bond cleavage on silica gel and therefore they were used and characterized as crude reaction mixtures.

Finally, the deprotection of the N atom was carried out by treating **10** with CF_3COOH in MeOH-$CHCl_3$ at -5° C, affording (*R*)-(+)-**11** with an overall yield of 26%. The value of the optical rotation ($[\alpha]_D$ +24.6°; *c* 0.837, MeOH) compared to that of the optically pure (*R*)-2-phenylpyrrolidine ($[\alpha]_D$ +32.5°; *c* 2.19, MeOH)[17a,b] indicates an e.e. value of 76 % for **11**. Considering the e.e. (78%) and the (*S*) absolute configuration of nitroalcohol **2d**, the ring closure has therefore taken place with complete inversion of configuration.

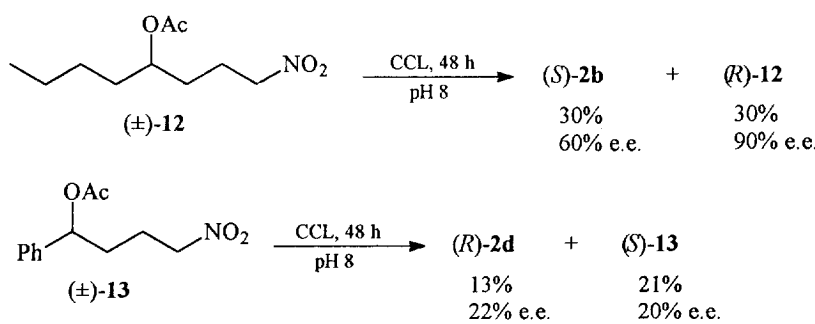
Scheme 3.



A possible alternative strategy for the preparation of optically active nitroalcohols could be the resolution of the racemic mixture of the corresponding acetates with an hydrolytic enzyme. Therefore we applied the same methodology already described for resolution of the enantiomers of 5-nitro-2-pentanol[4] to compounds **2b** and **2d** as acetates (Scheme 4). In particular we chose **2b** because the results of the reduction with baker's yeast were the less satisfactory.

Thus (±)-*O*-acetyl 1-nitro-4-octanol (**12**) was submitted to enzymatic hydrolysis with *Candida cylindracea* lipase (CCL) in phosphate buffer (pH = 8) and isopropanol for 48 h. Chromatography of the reaction mixture afforded (*S*)-**2b** (30%, 60% e.e. by ^{1}H-NMR of Mosher ester) and (*R*)-**12** (30%, 90% e.e. by chiral HRGC). When (±)-*O*-acetyl 1-phenyl-4-nitrobutanol (**13**) was submitted in the same conditions to the enzymatic hydrolysis the (*R*)-nitroalcohol and the (*S*)-*O*-acetyl derivative were recovered in very low yield (13 and 21%, respectively) and e.e. (22 and 20%, respectively). Therefore this does not appear as a route to obtain synthetically useful (*R*)-**2d**, whereas the hydrolysis of (*R*)-**12** would afford (*R*)-**2b** with a value of e.e. (90%) acceptable for synthetic purposes.

Scheme 4.



In conclusion, the microbial reduction of γ-nitroketones, by using baker's yeast, is an excellent way to obtain optically pure secondary γ-nitroalcohols, provided the substituent R is markedly different from the nitroalkyl group. These compounds have been proved to be very useful chiral precursors for the synthesis of different types of heterocyclic rings exploiting both the nitro and the hydroxy functionalities.

Experimental

Melting points were determined with a Büchi 510 apparatus. IR spectra were recorded with a Perkin Elmer 881 spectrophotometer. ^{1}H- and ^{13}C-NMR were recorded in $CDCl_3$ on a Varian Gemini at 200 MHz. MS spectra were obtained at 70 eV with a Carlo Erba QMD 1000 spectrometer and an Hewlett Packard A-5790-5970 GC-MS instrument. Elemental analysis were performed with a Perkin Elmer 240 C and gas-chromatographic analysis with a Hewlett Packard 5890 A instrument, equipped with a HP1 capillary column (100% methylsilicone, 0.53 mm i.d.). The R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}). Chromatografic purifications were performed by flash column chromatography on silica gel. Baker's yeast (*Saccharomyces cerevisiae*, Type II), and *Candida cylindracea* lipase (CCL) were purchased from Sigma. 1-Hepten-3-one was obtained from β-chloroethyl-butylketone prepared by treating pentanoyl chloride with ethylene and $AlCl_3$ following the procedure described by Lloid et al.[18] for the synthesis of methyl 7-chloro-5-oxoheptanoate. Nitroketone **1c** was prepared as reported.[7] Mannich bases for the synthesis of **1d-g** were prepared by the usual procedure[19] starting from the corresponding acetophenones. Reduction of nitroketones **1a-g** to the racemic nitroalcohols **2a-g** was carried out by using $NaBH_4$ in a MeOH-H_2O solution at 0-5 °C.[20] The Mosher esters of alcohols **2a-g** were prepared by the usual procedure.[21]

1-Nitro-4-octanone (1b). 1-Hepten-3-one (6 g, 53.57 mmol) was added dropwise in 30 min to a refluxing solution of CH_3NO_2 (29.2 g, 478.7 mmol), anhydrous Et_2O (5 ml) and benzyl trimethylammonium hydroxide (Triton B) (0.5 ml, 35% MeOH solution) under nitrogen with magnetic stirring. After 8 h, the solution was cooled to r.t., washed with 50 ml of water, then with 50 ml of brine and dried over Na_2SO_4. After evaporation, the residual oil was distilled under vacuum (110-112°C/0.7 mbar) affording **1b** (4.6 g, 50% yield).

1b. Colourless oil. ^{1}H-NMR δ 0.88 (t, *J* 7.5 Hz, 3H), 1.28 (m, 2H), 1.54 (m, 2H), 2.25 (m, 2H), 2.39 (t, *J* 7.3 Hz, 2H), 2.55 (t, *J* 6.6 Hz, 2H), 4.41 (t, *J* 6.6 Hz, 2H); ^{13}C-NMR δ 13.7 (q), 21.1 (t), 22.2 (t), 25.8 (t), 38.2 (t), 42.5 (t), 74.6 (t), 209.0 (s); MS *m/z* (rel. intensity) 116 (32), 88 (41), 85 (100), 84 (23), 83 (38), 73 (19), 69 (30), 60 (38), 57 (100), 56 (39), 55 (96); IR (neat) 1711, 1550 cm^{-1}. (Anal. Found: C, 55.45; H, 8.95; N, 8.31. Calc for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09)

4-Nitro-1-phenyl-1-butanone (1d). 1-Phenyl-3-(N,N-dimethylamino)-1-propanone (24.78 g, 140 mmoles) was added dropwise under nitrogen in 40' to a stirred refluxing solution of nitromethane (73.2 g, 1.2 mol) and Triton B (7.7 ml, 35% MeOH solution). After 3 h of reflux the solution was left 12 h at r.t., then washed with water and brine, and dried overnight over Na_2SO_4. After addition of 37% HCl (7 drops) the solution was concentrated and distilled by Kugelröhr (145-150 °C/0.1 mbar), affording a yellow oil (12.5 g, 46%) which solidified on cooling. Recrystallization from MeOH afforded **1d** (6.5 g, 24%).

1d. Colourless solid, m.p. 63-64 °C; ^{1}H-NMR δ 2.44 (m, 2H), 3.14 (t, *J* 6.8 Hz, 2H), 4.53 (t, *J* 6.6 Hz, 2H), 7.46 (m, 3H), 7.94 (m, 2H); ^{13}C-NMR δ 21.4 (t), 34.5 (t), 74.7 (t), 127.9 (d, 2C), 128.7 (d, 2C),

133.5 (d), 136.3 (s), 197.9 (s); MS *m/z* (rel. intensity) 193 (M^+, 0.2), 163 (5), 146 (5), 105 (100), 77 (96); IR ($CDCl_3$) 1681 (C=O), 1547 (NO_2) cm^{-1}. (Anal. Found: C, 62.18; H, 5.75; N, 6.98. Calc. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.27).

1-(2'-Methoxyphenyl)-4-nitro-1-butanone (1e). 1-(2'-Methoxyphenyl)-3-(N,N-dimethylamino)-1-propanone (2.45 g, 11.8 mmol) was treated as above with nitromethane (6.12 g, 0.1 mol) and Triton B (0.64 ml). Usual work-up and chromatography gave **1e** (1.37 g, 52 %).

1e. Colourless oil. R_f (EtOAc/light petroleum, 1:2.5) 0.43; ^{1}H-NMR δ 2.39 (m, 2H), 3.12 (t, *J* 6.8 Hz, 2H), 3.89 (s, 3H), 4.49 (t, *J* 6.7 Hz, 2H), 6.98 (m, 2H), 7.47 (ddd, *J* 8.4, 7.3, 1.8 Hz, 1H), 7.71 (dd, *J* 7.7, 1.8 Hz, 1H); ^{13}C-NMR δ 29.7 (t), 39.8 (t), 55.4 (q), 74.9 (t), 111.6 (d), 120.7 (d), 127.0 (s), 130.4 (d), 134.0 (d), 158.8 (s), 200.1 (s); MS *m/z* (rel. intensity) 223 (M^+, 17), 177 (30), 135 (100); IR (neat) 1670 (C=O), 1547 (NO_2) cm^{-1}. (Anal. Found: C, 58.97; H, 5.91; N, 6.44. Calc. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27).

1-(3'-Methoxyphenyl)-4-nitro-1-butanone (1f). 1-(3'-Methoxyphenyl)-3-(N,N-dimethylamino)-1-propanone (11.97 g, 57.7 mmol) was treated as above with nitromethane (47.6 g, 0.778 mol) and Triton B (1.04 ml). Usual work-up, bulb to bulb distillation (170 °C/0.07 mbar) and recrystallization (MeOH) gave **1f** (5.66 g, 44 %) as white solid.

1f. M.p 47-48 °C ; ^{1}H-NMR δ 2.46 (m, 2H), 3.14 (t, *J* 7.0 Hz, 2H), 3.86 (s, 3H), 4.54 (t, *J* 6.8 Hz, 2H), 7.14 (m, 1H), 7.33-7.58 (m, 3H); ^{13}C-NMR δ 22.7 (t), 35.8 (t), 56.6 (q), 75.8 (t), 113.4 (d), 121.0 (d), 121.7 (d), 130.9 (d), 138.8 (s), 161.0 (s), 198.9 (s); MS *m/z* (rel. intensity) 223 (M^+, 52), 135 (100); IR (neat) 1685 (C=O), 1551 (NO_2) cm^{-1}. (Anal. Found: C, 59.07; H, 5.98; N, 5.95. Calc. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27).

1-(4'-Methoxyphenyl)-4-nitro-1-butanone (1g). 1-(4'-Methoxyphenyl)-3-(N,N-dimethylamino)-1-propanone (10 g, 48.2 mmol) was treated as above with nitromethane (36.7 g, 0.6 mol) and Triton B (0.87 ml). Usual work-up, bulb to bulb distillation (165 °C/0.14 mbar) and recrystallization (MeOH) gave **1g** (7.42 g, 69 %) as white solid.

1g. M.p 67-68 °C ; ^{1}H-NMR δ 2.44 (m, 2H), 3.10 (t, *J* 6.8 Hz, 2H), 3.88 (s, 3H), 4.54 (t, *J* 6.8 Hz, 2H), 6.94 (m, 2H), 7.93 (m, 2H); ^{13}C-NMR δ 22.8 (t), 35.3 (t), 56.7 (q), 76.0 (t), 115.0 (d, 2C), 130.8 (s), 131.4 (d, 2C), 164.9 (s), 187.8 (s); MS *m/z* (rel. intensity) 223 (M^+, 33), 135 (100); IR (neat) 1673 (C=O), 1598, 1549 cm^{-1}. (Anal. Found: C, 59.04; H, 5.89; N, 6.07. Calc. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27).

Baker's yeast reduction of nitroketones 1a-g. General Procedure. In a typical experiment, 20 g of baker's yeast were slowly added to a solution of glucose (0.4 g) in water (75 ml) heated at 30-35°C, under mechanical stirring in aerobic condition, then the nitroketone (1 mmol) was added to the fermenting reaction mixture in 15 min. During the reaction, the volume of the mixture was mantained constant by further additions of water. The reaction was monitored by gas-chromatography, and stopped when no further GC conversion of the nitroketones to nitroalcohols was observed. For the aromatic nitroketones **1d-g** the bioreduction was slower and further amounts of fresh yeast (5g per mmol of substrate) and glucose (0.5g per mmol of substrate) were added every two days. Then Celite (2 g per mmol of substrate) and NaCl (to saturate the solution) were added, and the mixture was continously extracted with 150 ml of diethyl ether with a liquid-liquid extractor for 18 h. The organic phase was then dried over Na_2SO_4 and evaporated. The crude residues were purified by

flash column chromatography.

(*S*)-(+)-1-Nitro-4-octanol (2b). Bioreduction of **1b** (605 mg, 3.5 mmoles) was stopped after 2 d when GC conversion was 67%. Usual work-up and chromatography afforded **2b** (352 mg, 57%).

2b. Colourless oil. R_f (EtOAc/light petroleum, 1:2) 0.38; $[\alpha]_D^{20}$ + 2.0° (*c* 0.60, $CHCl_3$), 27% e.e. (Mosher ester); ^{1}H-NMR δ 0.89 (m, 3H), 1.17-1.65 (m, 8H), 2.00-2.30 (m, 2H), 3.62 (m, 1H), 4.42 (t, *J* 6.7 Hz, 2H); ^{13}C-NMR δ 13.9 (q), 22.6 (t), 23.8 (t), 26.6 (t), 33.4 (t), 37.2 (t), 71.0 (d), 75.6 (t); MS *m/z* (rel. intensity) 118 (33), 89 (32), 87 (45), 85 (23), 71 (94), 69 (100); IR (neat) 3621 (OH), 1549 (NO_2) cm^{-1}. (Anal. Found: C, 54.93; H, 9.94; N, 8.06. Calc for $C_8H_{17}NO_3$: C, 54.84; H, 9.79; N, 7.99). In a different experiment, the bioreduction of **1b** (560 mg, 3.24 mmoles) was stopped after 5 d when the conversion was 91%. In this case the ether extraction, carried out with a separatory funnel, was less efficient and **2b** was recovered in low yield (150 mg, 26%); $[\alpha]_D^{20}$ +1.3° (*c* 0.66, $CHCl_3$), e.e. 15%.

(1*S*,2*S*)- and (1*S*,2*R*)-2-(2-Nitroethyl)cyclohexanol (2c). Bioreduction of **1c** (700 mg, 4.1 mmoles) was stopped after 3d when the GC conversion was 52%. Usual workup and chromatography (EtOAc/ light petroleum, 1 : 2, R_f 0.44) afforded a 60/40 mixture of the two diastereoisomers (*1S,2S*)-**2c** (***cis*-2c**) and (*1S,2R*)-**2c** (***trans*-2c**) (322 mg, 45 %). Attempts to separate the mixture by chromatography and HPLC with different eluants failed.

***Cis*-2c** and ***trans*-2c**. Colourless oil; MS *m/z* (rel. intensity) 109 (8), 97 (14), 91 (6), 83 (16), 81 (37), 79 (39), 69 (21), 67 (37), 57 (50), 55 (100); IR (neat) 3438 (OH), 1550 (NO_2) cm^{-1}; ***cis*-2c** ^{1}H-NMR δ 0.90-2.00 (m, 10H), 2.13 (m,1H), 3.87 (br m, 1H), 4.45 (td, *J* 7.0, 3.2 Hz, 2H); ^{13}C-NMR δ 20.2 (t), 24.6 (t), 26.3 (t), 29.6 (t), 32.9 (t), 38.2 (d), 68.5 (d), 73.9 (t); ***trans*-2c** δ 0.90-2.00 (m,10H), 2.37 (m,1H), 3.22 (m, 1H), 4.52 (td, *J* 7.5, 1.4 Hz, 2H); ^{13}C-NMR δ 24.6 (t), 25.2 (t), 30.8 (t), 31.4 (t), 36.1 (t), 42.4 (d), 74.5 (t), 74.9 (d).

(*S*)-(-)-4-Nitro-1-phenyl-1-butanol (2d). Bioreduction of **1d** (700 mg, 3.6 mmoles) was stopped after 7d when the GC conversion was 89%. Usual work-up and chromatography afforded a yellow oil which was purified by Kugelröhr distillation (140-150 °C/0.3 mbar) obtaining pure **2d** (412 mg, 59%).

2d. Colourless oil. R_f (EtOAc/ light petroleum, 1:2), 0.34; $[\alpha]_D^{20}$ -40.7° (*c* 0.64, $CHCl_3$), e.e. 78% (Mosher ester); ^{1}H-NMR δ 1.75-1.90 (m, 2H), 2.00-2.20 (m, 2H), 4.40 (td, *J* 6.9, 2.3 Hz, 2H), 4.73 (dd, *J* 6.9, 5.5 Hz, 1H), 7.4-7.2 (m, 5H); ^{13}C-NMR δ 23.9 (t), 35.3 (t), 73.7 (d), 75.4 (t), 125.6 (d, 2C), 128.0 (d), 128.7 (d, 2C), 143.8 (s); MS *m/z* (rel. intensity) 177 (M^+ - H_2O, 0.6) 160 (3), 147 (10), 107 (100), 105 (39) 91 (14), 79 (87), 77 (72); IR (neat) 3686 (OH), 1550 (NO_2) cm^{-1}. (Anal. Found: C, 61.21; H,7.00; N, 6.61. Calc for $C_{10}H_{13}NO_3$: C, 61.53; H, 7.17; N, 6.71).

(*S*)-(-)-1-(2'-Methoxyphenyl)-4-nitro-1-butanol (2e). Bioreduction of **1e** (400 mg, 1.79 mmol) was stopped after 7 days (GC conversion of 64 %). Usual work-up and chromatography gave **2e** as yellow oil (252 mg, 63 %). Further purification can be achieved by Kugelröhr distillation (170-180 °C/0.3 mbar)..

2e. Colourless oil. R_f (EtOAc/ light petroleum, 1 : 2), 0.4; $[\alpha]_D^{20}$ -28.1° (*c* 0.62, $CHCl_3$), e.e. (Mosher ester) > 99%; ^{1}H-NMR δ 1.75-1.90 (m, 2H), 2.00-2.25 (m, 2H), 3.84 (s, 3H), 4.43 (td, *J* 7.0, 1.8 Hz, 2H), 4.91 (dd, *J* 7.4, 5.7 Hz, 1H), 6.87 (d, *J* 8.1 Hz, 1H), 6.96 (d, *J* 7.5 Hz, 1H), 7.20-7.35 (m, 2H). ^{13}C-NMR δ 24.0 (t), 33.4 (t), 55.2 (q), 69.6 (d), 75.5 (t), 110.5 (d), 120.8 (d), 126.5 (d), 128.6 (d), 128.9 (s), 156.2 (s); MS *m/z* (rel. intensity) 225 (M^+,7), 208 (3), 194 (8), 177 (35), 161 (20), 137 (100), 135 (95), 121 (70), 107 (98), 94 (45), 91 (50), 77 (90). IR ($CDCl_3$) 3692, 1550 cm^{-1} (Anal. Found: C, 58.26; H, 6.30;

N, 6.12. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22).

(*S*)-(-)-1-(3'-Methoxyphenyl)-4-nitro-1-butanol (2f). Bioreduction of **1f** (556 mg, 2.49 mmol) was stopped after 7 days (GC conversion of 67 %). Usual work-up and chromatography gave **2f** as yellow oil (174 mg, 31%). Further purification can be achieved by Kugelröhr distillation (200 °C/0.08 mbar).

2f. Colourless oil. R_f (EtOAc/ light petroleum ether, 1 : 2), 0.3; $[\alpha]_D^{25}$ -24.2° (*c* 0.31, $CHCl_3$), e.e. (Mosher ester) 76%; ^{1}H-NMR δ 1.65-2.20 (m, 5H), 3.79 (s, 3H), 4.39 (td, *J* 7.0, 2.2 Hz, 2H), 4.69 (t, *J* 6.4 Hz, 1H), 6.78-6.90 (m, 3H), 7.21-7.29 (m, 1H); ^{13}C-NMR δ 23.8 (t), 35.1 (t), 55.2 (q), 73.5 (d), 75.4 (t), 111.2 (d), 113.2 (d), 117.9 (d), 129.7 (d), 145.6 (s), 159.8 (s); MS *m/z* (rel. intensity) 225 (M^+, 12), 137 (84), 135 (39), 109 (99), 94 (30), 86 (64), 84 (100); IR 3605, 1551 (NO_2) cm^{-1} (Anal. Found: C, 59.01; H, 7.07; N, 5.88. Calc for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22).

(*S*)-(-)-1-(4'-Methoxyphenyl)-4-nitro-1-butanol (2g). Bioreduction of **1g** (500 mg, 2.24 mmol) was stopped after 7 days (GC conversion of 82 %). Usual work-up and chromatography gave **2g** as yellow oil (272 mg, 54%). Further purification can be achieved by Kugelröhr distillation (200-220 °C/0.17 mbar).

2g. Colourless oil. R_f (EtOAc/ light petroleum ether, 1 : 2), 0.28; $[\alpha]_D^{25}$ -32.0° (*c* 0.59, $CHCl_3$), e.e. (Mosher ester) 76%; ^{1}H-NMR δ 1.65-2.22 (m, 5H), 3.81 (s, 3H), 4.42 (td, *J* 7.0, 2.2 Hz, 2H), 4.69 (dd, *J* 7.3, 5.5 Hz, 1H), 6.90 (m, 2H), 7.26 (m, 2H); ^{13}C-NMR δ 24.0 (t), 35.2 (t), 55.3 (q), 73.3 (d), 75.4 (t), 114.0 (d, 2C), 126.9 (d, 2C), 135.9 (s), 159.2 (s); MS *m/z* (rel. intensity) 225 (M^+, 10), 137 (100), 135 (61), 109 (70), 94 (47); IR 3605, 1551 (NO_2) cm^{-1} (Anal. Found: C, 58.65; H, 6.88; N, 6.08. Calc for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22).

(*S*)-(-)-1-(Dimethyl-*t*-butylsilyloxy)-4-nitro-1-phenylbutane (5). To a stirred solution of imidazole (0.266 g, 3.91 mmol) in anhydrous CH_2Cl_2 (2.4 ml), a solution of TBDMSCl (0.294 g, 1.95 mmol) in anhydrous $CHCl_2$ (1 ml) was added, under N_2. The mixture was stirred 10' at r.t., then a solution of (-)-**2d** (0.262 g, 1.34 mmol, 78% e.e.) in anhydrous CH_2Cl_2 (1 ml) was added dropwise. After 24 h the reaction was diluted with CH_2Cl_2 (15 ml) and water (3.5 ml) and then washed with brine. The organic phase was dried over Na_2SO_4, evaporated *in vacuo*, and the residue chromatographed affording **5** (0.28g, 0.89 mmol, 67 %).

5. Colourless oil. R_f (EtOAc/light petroleum, 1:20), 0.46; $[\alpha]_D^{20}$ - 40.8 (*c* 1.05, MeOH); ^{1}H-NMR δ - 0.15 (s, 3 H), 0.03 (s, 3H), 0.89 (s, 9H), 1.77 (m, 2H), 2.04 (m, 2H), 4.36 (t, *J* 7 Hz, 2H), 4.73 (t, *J* 5.7 Hz, 1H), 7.29 (m, 5H); ^{13}C-NMR δ -5.1 (q), -4.7 (q), 18.1 (s), 23.4 (t), 25.8 (q), 36.9 (t), 73.9 (d), 75.6 (t), 125.6 (d), 127.2 (d), 128.2 (d), 144.3 (s); MS *m/z* (rel. intensity) 252 (M^+-*t*-Bu, 23), 221 (13), 210 (98), 179 (28) 131 (55), 104 (100), 91 (37), 75 (50), 73 (40); IR 1548 (NO_2) cm^{-1}; (Anal. Found: C, 61.78; H, 9.02; N, 4.38. Calc. for $C_{16}H_{27}NO_3Si$: C, 62.08; H, 8.80; N, 4.53).

(*S*)-(-)-Methyl 4-(dimethyl-*t*-butylsilyloxy)-4-phenylbutanoate (6). An aqueous solution of $KMnO_4$ (4.7 ml, 0.5 M, 2.35 mmol) was added to a stirred solution of **5** (181 mg, 0.586 mmol) in *t*-BuOH (3ml) and aqueous phosphate buffer (3.5 ml, pH 11, 0.5 M in KOH and 1.25 M in Na_2HPO_4), mantaining the temperature at 25 °C with an ice/water bath. After 1.75 h at r.t., the reaction mixture was treated with a saturated solution of Na_2SO_3 and then extracted with Et_2O to remove unreacted starting material **5** (31 mg recovered). The aqueous phase, acidified at pH 5 with 2N HCl, was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated affording crude 4-(dimethyl-*t*-butylsilyloxy)-4-phenylbutanoic acid (101 mg) which was esterified with diazomethane in Et_2O without further purification. 4-(Dimethyl-*t*-butylsilyloxy)-4-

phenylbutanoic acid: ^{1}H-NMR δ - 0.15 (s, 3 H), 0.03 (s, 3H), 0.88 (s, 9H), 2.01 (m, 2H), 2.38 (m, 2H), 4.76 (t, *J* 5.8 Hz, 1H), 7.29 (m, 5H) After evaporation of the solution, the residue was chromatographed affording **6** (65 mg, 0.211 mmol, 36%).

6. Colourless oil. R_f (EtOAc/pentane 1:15), 0.56; $[\alpha]_D^{20}$ - 44.7° (*c*, 0.694 $CHCl_3$); ^{1}H-NMR δ - 0.15 (s, 3 H), 0.02 (s, 3H), 0.89 (s, 9H), 1.97 (m, 2H), 2.35 (m, 2H), 3.64 (s, 3H), 4.74 (t, *J* 5.9 Hz, 1H), 7.29 (m, 5H); ^{13}C-NMR δ -5.1 (q), -4.7 (q), 18.2 (s), 25.8 (q), 29.8 (t), 35.5 (t), 73.6(d), 125.8 (d), 127.1 (d), 128.0 (d), 144.7 (s), 174.0 (s); MS *m/z* (rel. intensity) 308 (M^+, 0.1), 251 (M^+-*t*-Bu, 87), 219 (89), 117 (100), 91 (37), 75 (93); IR 1729 (C=O) cm^{-1}; (Anal. Found: C, 66.23; H, 9.29. Calc. for $C_{17}H_{28}O_3Si$: C, 66.17; H, 9.15).

A small amount of a side product (10 mg, R_f 0.17) obtained from cromatography was identified as methyl 4-oxo-4-phenylbutanoate: ^{1}H-NMR δ 2.76 (t, 6.6 Hz, 2H), 3.32 (t, 6.6 Hz, 2H), 3.7 (s, 3H), 7.45 (m, 3H), 7.96 (m, 2H); IR 1731 (C=O), 1686 (C=O) cm^{-1}; MS *m/z* (rel. intensity) 192 (M^+, 4), 161 (16) 105 (100), 77 (40).

(*S*)-(-)-5-Phenyl-4,5-dihydrofuran-2-(3H)-one (7). A solution of methyl ester **6** (27 mg, 0.087 mmoles) in 1 ml of $CHCl_3$ was treated at r.t. and under stirring with 3 drops of trifluoroacetic acid. After 7 days the solvent was evaporated under vacuum and the residue chromatographed to give pure 7 (14 mg, 99%).

7. Colourless oil. R_f (EtOAc/pentane 1:15), 0.17; $[\alpha]_D^{20}$ - 27.6° (*c* 0.680, $CHCl_3$); ^{1}H-NMR δ 2.15-2.35 (m, 2H), 2.65-2.85 (m, 2H), 5.52 (dd, *J* 7.8, 6.2 Hz, 1H), 7.4 (m, 5H); ^{13}C-NMR δ 28.9 (t), 30.9 (t), 81.2 (d), 125.4 (d), 128.4 (d), 128.9 (d), 143.5 (s), 171.5 (s); MS *m/z* (rel. intensity) 162 (M^+, 100), 117 (41), 107 (78), 105 (66), 91(19); IR 1772, 1171 cm^{-1} (Anal. Found: C, 73.79; H, 6.22. Calc for $C_{10}H_{10}O_2$: C, 74.10; H, 6.22).

(*S*)-(-)-4-Amino-1-phenyl-1-butanol (8). A solution of **2d** (626 mg, 3.21 mmoles) in MeOH (18 ml) was stirred for 18 h in presence of Raney Ni (1.4 g) under hydrogen atmosphere. The solution was then filtered on a Celite layer and evaporated under vacuum affording a yellow oil which solidified on standing. This solid was dissolved in 5% HCl (3 ml), the resulting solution extracted twice with diethyl ether (5 ml) and then NaOH(s) was added until pH 9 was reached. After saturation with NaCl(s) of the solution, this was extracted with diethyl ether (3 x 6 ml), and the organic layer dried overnight over sodium sulphate. Filtration and evaporation of the solvent afforded pure **8** (467 mg, 88%).

8. White solid, m.p. 92-93 °C. $[\alpha]_D^{20}$ - 43.5° (*c* 0.531, $CHCl_3$); ^{1}H-NMR δ 1.50-1.70 (m, 2H), 1.70-2.00 (m, 2H), 2.10-3.00 (m, 5H), 4.68 (dd, *J* 7.5, 3.9 Hz, 1H), 7.20-7.40 (m, 5H); ^{13}C-NMR δ 29.6 (t), 38.8 (t), 41.7 (t), 73.6 (d), 125.7 (d), 126.8 (d), 128.2 (d), 145.6 (s); MS *m/z* (rel. intensity) 165 (M^+, 12), 164 (19), 148 (41), 117 (82), 43 (100); IR 3692, 3609, 1601 cm^{-1} (Anal. Found: C, 72.33; H, 9.15; N, 8.35. Calc. for $C_{10}H_{15}NO$: C, 72.68; H, 9.15; N, 8.47).

(*R*)-(+)-2-Phenylpyrrolidine (11). A solution of trityl chloride (781 mg, 2.8 mmoles) in chloroform (3 ml) was added slowly to a stirred solution of **8** (467 mg, 2.8 mmoles) and NEt_3 (0.784 ml, 5.6 mmoles) in chloroform (4 ml) under nitrogen atmosphere with cooling at 0 °C. After 5 h the solution was left at r.t. overnight. The solution was washed with 10% citric acid (2 x 10 ml) and water, and then dried over sodium sulphate. After filtration and evaporation of the solvent **9** (1.109 g, 97 %) was obtained as dense brown oil.

9. ^{1}H-NMR δ 1.52 (m, 2H), 1.76 (m, 2H), 2.14 (t, *J* 6.4 Hz, 2H), 4.62 (t, *J* 6.2 Hz, 1H), 7.00-7.50

(m, 20H); MS *m/z* (rel. intensity) 330 (M^+-Ph), 243 (100), 165 (100).

This crude oil was then dissolved in anhydrous pyridine (4 ml) and treated at -10 °C with a solution of TsCl (1.56 g, 8.16 mmoles) in pyridine (2 ml), under stirring and nitrogen atmosphere. After 1 h the temperature was allowed to reach 0 °C and the solution stirred for 16 h at this temperature. The solvent was removed under vacuum, without heating, and the oily residue was partitioned between water (10 ml) and ethyl acetate (45 ml). The organic layer was washed several times with 10% citric acid and water, and dried overnight over sodium sulphate. Filtration and evaporation (without heating) of the solvent afforded **10** as a dense brown oil (1.385 g, 90%).

10. ^{1}H-NMR δ 1.30-2.20 (m, 4H), 3.07 (m, 1H), 3.44 (m, 1H), 4.42 (dd, *J* 8.1, 2.1 Hz, 1H), 7.00-7.55 (m, 20H); MS *m/z* (rel. intensity) 312 (M^+-Ph), 243 (100), 165 (65).

This crude oil was finally dissolved in a solution of chloroform (2.5 ml) and anhydrous MeOH (2.5 ml) and, with cooling at -5 °C, treated with trifluoroacetic acid (5 ml). After 2 h at -5 °C, the solution was stirred overnight at r.t. After evaporation of the solvent, the residue was partitioned between water (15 ml) and diethyl ether (20 ml). The organic layer was extracted twice with 5% HCl (10 ml) and all the aqueous layers were mixed. The resulting solution was treated with NaOH (s) until pH 9, saturated with NaCl(s) and extracted with ether (4 x 20 ml), drying overnight with sodium sulphate. After filtration the solvent was carefully distilled at 760 mmHg and the residue purified by bulb to bulb distillation (95 °C, 0.3 mbar) affording pure **11** (105 mg, 26%).

11. Colourless oil. $[\alpha]_D^{20}$ + 24.6° (*c*, 0.837, MeOH), 76% e.e.; ^{1}H-NMR δ 1.55-1.75 (m, 1H), 1.75- 2.00 (m, 3H), 2.05-2.25 (m, 1H), 2.90-3.06 (m, 1H), 3.10-3.25 (m, 1H), 4.10 (t, *J* 7.6 Hz, 1H), 7.13-7.40 (m, 5H); ^{13}C-NMR δ 25.5 (t), 37.0 (t), 46.9 (t), 62.6 (d), 126.5 (d), 127.5 (d), 128.3 (d), 143.8 (s); MS *m/z* (rel. intensity) 147 (M^+, 16), 146 (100), 131 (46), 91 (32), 72 (77); IR ($CDCl_3$) 3686, 2954, 1603 cm^{-1}.

(±)-*O*-Acetyl 1-nitro-4--octanol (12). Pyridine (2.84 ml) was slowly added to a solution of nitroalcohol (±)-**2b** (570 mg, 3.25 mmol) in Ac_2O (0.66 ml, 13 mmol), mantaining the temperature at 20 °C. After 24 h, usual work-up and chromatography afforded (±)-**12** (410 mg , 60%).

(±)-12. Oil, R_f (EtOAc/light petroleum ether, 1:2) 0.62; ^{1}H-NMR δ 0.86 (m, 3H), 1.14-1.65 (m, 8H), 1.67-2.07 (m 4H), 2.01 (s, 3H), 4.37 (t, 2H, *J* 7.5 Hz), 4.92 (m, 1H).

Enzymatic resolution of (±)-12. CCL (250 mg) was suspended into a phosphate buffer solution (15 ml, pH 8), and after 10', a solution of (±)-**12** (84 mg, 0.4 mmol) in isopropanol (1.5 ml) was added under vigorous stirring. After 48 h the reaction mixture was extracted with ether and dried overnight over Na_2SO_4. Chromatography (EtOAc/light petroleum, 1:2.5) afforded (*S*)-(+)-**2b** (30%), $[\alpha]_D^{20}$ +6.1° (*c* 0.49 $CHCl_3$), 60% e.e. (by ^{1}H-NMR of Mosher ester) and (*R*)-**12** (30%), 90% e.e. (by HRGC, chiral phase Megadex 1, MEGA capillary column, 25 m, 0.25 m, 0.25 mm i.d.).

(±)-*O*-Acetyl 1-phenyl-4-nitro-1-butanol (13). Pyridine (1.05 ml) was slowly added to a solution of nitroalcohol (±)-**2d** (137 mg, 0.70 mmol) in Ac_2O (0.245 ml, 2.8 mmol), mantaining the temperature at 20 °C. After 24 h, usual workup and chromatography afforded (±)-**13** (110 mg , 66%).

(±)-**13**. Oil, R_f (EtOAc/light petroleum ether, 1:2) 0.6; ^{1}H-NMR δ 1.80-2.15 (m, 2H), 2.07 (s, 3H), 4.36 (t, *J* 6.4 Hz, 2H), 5.76 (t, *J* 5.4 Hz,1H), 7.25-7.40 (m, 5 H).

Enzymatic resolution of (±)-13. CCL (250 mg) was suspended into a phosphate buffer solution (15 ml, pH 8), and after 10', a solution of (±)-**13** (95 mg, 0.4 mmol) in isopropanol (1.5 ml) was added under vigorous stirring. After 48 h the reaction mixture was extracted with ether and dried overnight over Na_2SO_4. Chromatography (EtOAc/light petroleum ether, 1:2) afforded (*R*)-(+)-**2d** (13%), $[\alpha]_D^{20}$ +11.7° (*c* 0.78, $CHCl_3$), 22% e.e. and (*S*)-**13** (21%), $[\alpha]_D^{20}$ -16.0° (*c* 0.569, $CHCl_3$), 20% e.e. (both e.e.'s calculated on the bases of the optical rotations. (S)-(-)-*O*-Acetyl 1-phenyl-4-nitro-1-butanol (**13**) (78% e.e.) has $[\alpha]_D^{20}$ -61.6° (*c* 1.19 in $CHCl_3$).

Acknowledgment

Authors thank Ministry of University and Scientific and Technological Research (M.U.R.S.T. 60% and 40%) and CNR for financial support. Technical support of Mrs. B. Innocenti (University of Firenze) is also acknowledged.

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(*Received in UK* 10 *December* 1993; *revised* 30 *November* 1994; *accepted* 2 *December* 1994)