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A One-Pot Reduction-Transimination-Reduction Synthesis of N-substituted ß-Ethanolamines from Cyanohydrins.

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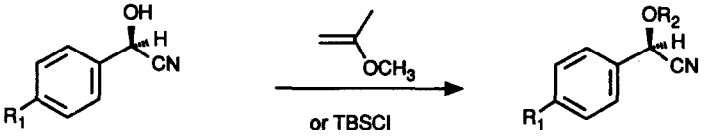
Abstract: An efficient (74% - 97% yield) three-step one-pot synthesis of (*R*)-Halostachine and analogues from O-protected optically active cyanohydrins is described. The reaction sequence involves a DIBAL reduction of the nitrile to an imine, transimination to a secondary imine and sodium borohydride reduction to the corresponding N-substituted ß-ethanolamine. Both O-protected as well as unprotected reaction products can be obtained.

In a previous communication[1] we reported on the synthesis of optically active *erythro* N-substituted ß-ethanolamines from cyanohydrins by a three-step sequence. The transformation involved conversion of the nitrile to a primary imine by reaction with a Grignard reagent, transimination with a primary amine to form a secondary imine, and sodium borohydride reduction. *Erythro* N-substituted ß-alkyl-ß-ethanolamines possessing two chiral centres were thus obtained in good yield. This procedure does not allow the synthesis of N-substituted ß-unsubstituted-ß-ethanolamines with only one chiral centre, such as Isoproterenol[2], Normacromerine[3], Phenylephrine[4] and (*R*)-Halostachine[5] (**5a**). This shortcoming could be overcome by extending the principle of transimination to primary imines obtained by reduction of cyanohydrins with di*iso*-butylaluminium hydride (DIBAL).



1 **2**

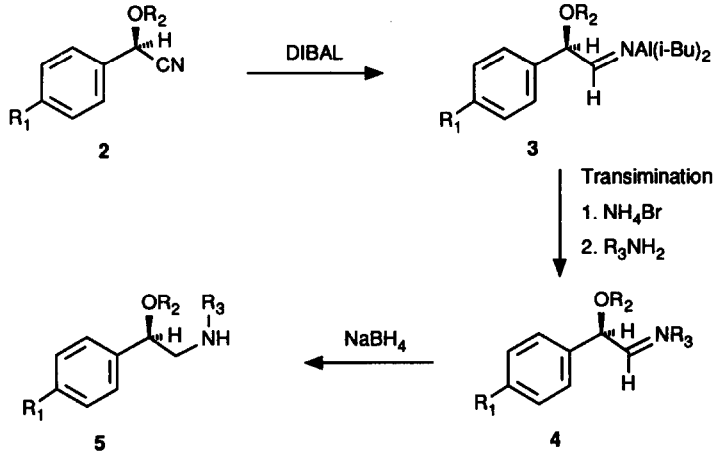
1	R_1	2	R_1	R_2	yield
a	H	**a**	H	MIP	99%
b	OCH_3	**b**	H	TBS	99%
		c	OCH_3	MIP	99%
		d	OCH_3	TBS	98%

MIP: 2-methoxy-*iso*-propyl TBS: *tert*-butyldimethylsilyl

Scheme 1. Preparation of O-protected cyanohydrins.

The two types of O-protected cyanohydrins (**2**) used as starting materials were prepared by conversion of (*R*)-cyanohydrins[6,7] (**1**) with 2-methoxypropene to the 2-methoxy-*iso*-propyl (MIP) ethers or by silylation[6] with *tert*-butyldimethylsilyl (TBS) chloride (Scheme 1.).

The cyano group of the O-protected cyanohydrin (**2**) was reduced by DIBAL at low temperature[8] (-70°C). When reduction was complete (GC), ammonium bromide in dry methanol was added to destroy excess DIBAL and to convert the imine-aluminium complex (**3**) into the free N-H imine[9]. Introduction of the N-alkyl group was then achieved by applying the recently described[1] transimination reaction, that is; conversion of the primary imine into the more stable secondary imine (**4**) by addition of excess amine. Overnight sodium borohydride reduction afforded O-protected N-substituted ß-ethanolamines in good overall yield. The O-MIP group was completely removed[10] during acidic work-up to the N-substituted ß-ethanolamines (**5**) (Scheme 2.). In this manner (*R*)-Halostachine (**5a**), naturally occurring in *Halostachis caspica* was prepared in good yield (79%) and with high enantiomeric purity (**5a**.HCl: $[\alpha]_D^{20}$ -53°; lit.[5] $[\alpha]_D^{20}$ -52.46°). Analogues (**5b-h**) were prepared in similar yields. In the case of the silylated products, the enantiomeric excess could be directly determined by HPLC analysis and was found to be over 99% in all cases ((*S*)-enantiomer not present above detection limit).



5	R_1	R_2	R_3	yield*	5	R_1	R_2	R_3	yield*
a	H	H	CH_3	79%	**e**	OCH_3	H	CH_3	90%
b	H	TBS	CH_3	97%	**f**	OCH_3	TBS	CH_3	94%
c	H	H	$CH(CH_3)_2$	74%	**g**	OCH_3	H	$CH(CH_3)_2$	78%
d	H	TBS	$CH(CH_3)_2$	96%	**h**	OCH_3	TBS	$CH(CH_3)_2$	80%

* Isolated yields.

Scheme 2. One-pot reduction-transimination-reduction synthesis of N-substituted ß-ethanolamines.

In conclusion, the one-pot reduction-transimination-reduction of cyanohydrins is a valuable addition to the earlier reported Grignard addition-transimination-reduction sequence and opens a new route to N-substituted ß-ethanolamines without a ß-alkyl substituent in good chemical and optical yields.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Jeol FX-200. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane (TMS). The optical purity was determined by optical rotations measurements using a Propol Automatic polarimeter or by HPLC analysis using a CHIRALCEL OD column (Eluent: **2a, 2b, 5d** and **5f**: hexane : *iso*-propanol = 99.75 : 0.25. **2c, 2d, 5b** and **5f**: hexane : *iso*-propanol = 99.0 : 1.0). Melting points were uncorrected.

(*R*)-(+)-[(2-Methoxy-*iso*-propyl)oxy]benzeneacetonitrile (2a).
9.0 g (68 mmol) of (*R*)-(+)-α-hydroxybenzeneacetonitrile (**1a**) was dissolved in 2-methoxypropene (25 mL). A catalytic amount (13 mg) of $POCl_3$ was added and the solution was stirred for 45 minutes at room temperature. Triethylamine (29 mg) was then added, the mixture was taken up in ether (100 mL) and successively washed with water (25 mL) and a saturated $NaHCO_3$ solution (25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*.
Yield: 13.75 g (99%) of **2a** (clear oil).
^{1}H NMR: 1.40 and 1.58 (s, 6H, $C(CH_3)_2$); 3.22 (s, 3H, OCH_3); 5.47 (s, 1H, CH(CN)); 7.43 (m, 5H, arom.).
^{13}C NMR: 24.0 and 24.6 ($C(CH_3)_2$); 49.5 (OCH_3); 61.1 (CH(CN)); 102.5 ($C(CH_3)_2$); 119.0 (CN); 126.7, 128.7 and 129.0 (C arom.); 134.8 (C_1 arom.).
$[\alpha]_D^{20}$ +47° (c = 1 $CHCl_3$); e.e. > 99% (HPLC).

(*R*)-(+)-[(2-Methoxy-*iso*-propyl)oxy]-4-methoxybenzeneacetonitrile (2c).
Prepared in the same manner as described for **2a**, using (*R*)-(+)-α-hydroxy-4-methoxybenzeneacetonitrile **1b** as the cyanohydrin.
Yield: 99% of **2c** (white crystals). mp 40-42°C.
^{1}H NMR: 1.38 and 1.56 (s, 6H, $C(CH_3)_2$); 3.21 (s, 3H, OCH_3); 3.82 (s, 3H, 4-OCH_3); 5.41 (s, 1H, CH(CN)); 6.92 (d, 2H, J = 8.7 Hz, arom.); 7.40 (d, 2H, J = 8.7 Hz, arom.).
^{13}C NMR: 23.9 and 24.4 ($C(CH_3)_2$); 49.2 (OCH_3); 54.7 (4-OCH_3); 60.5 (CH(CN)); 102.2 ($C(CH_3)_2$); 113.9 (C_3 and C_5 arom.); 119.1 (CN); 126.9 (C_1 arom.); 128.1 (C_2 + C_6 arom.); 158.7 (C_4 arom.).
$[\alpha]_D^{20}$ +41° (c = 1 $CHCl_3$); e.e. > 99% (HPLC).

(*R*)-(-)-α-[(Methylamino)methyl]benzenemethanol, (*R*)-Halostachine (5a).
To a cooled solution (-70°C) of 1.02 g (5 mmol) of **2a** (e.e. > 99% (HPLC)) in 40 mL of dry ether was added 12.5 mL of a 1 M DIBAL solution in hexanes (12.5 mmol). After stirring at -70°C for 3 hours 1.25 g NH_4Br (12.5 mmol) in 20 mL of dry methanol was added. The cooling bath was removed and 3 mL of an 8.03 M CH_3NH_2 solution (24 mmol) in ethanol was added. Stirring was continued for 45 minutes (-70°C → room temperature). The mixture was cooled in an ice bath and 0.37 g of $NaBH_4$ (10 mmol) was added in three portions. The reaction mixture was stirred overnight at room temperature. Ether (25 mL) and a 1 N HCl solution (70 mL) were added and separated after extraction. The water layer (pH ≈ 3) was made alkaline with a 5 N NaOH solution until a clear solution appeared and extracted with ether (4x 50 mL). These four combined ether layers were dried (K_2CO_3) and concentrated to leave a clear oil, which crystallized upon standing.
Yield: 0.59 g (79%) of **5a** (white solid).
^{1}H NMR: 2.2 (broad, 2H, OH and NH); 2.46 (s, 3H, NCH_3); 2.74 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{AX} = 8.7 Hz); 2.81 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{BX} = 4.6 Hz); 4.74 (dd, 1H, CH(OH), J = 4.6

and 8.7 Hz); 7.32 (m, 5H, arom.).
^{13}C NMR: 35.6 (NCH_3); 59.0 (CH_2); 71.4 (CH(OH)); 125.6, 127.1 and 128.1 (C arom.); 143.2 (C_1 arom.).
5a was converted into the HCl salt and crystallized from *iso*-propanol for optical rotation and melting point measurements. $[\alpha]_D^{20}$ -53° (c = 1 H_2O), lit.[5]: $[\alpha]_D^{20}$ -52.46°. mp 110-111°C, lit.[5]: mp 113-114°C.

(*R*)-(-)-α-[(Methylamino)methyl]-α-[(*tert*-butyldimethylsilyl)oxy]benzenemethane (5b).
Prepared in the same manner as **5a**, using **2b** (e.e. > 99% (HPLC)) as the cyanohydrin and methylamine in the transimination reaction. After the $NaBH_4$ reduction the reaction mixture was poored into water (100 mL) and extracted with ether (3x 50 mL). The combined ether layers were washed with water (50 mL), dried (K_2CO_3) and concentrated *in vacuo*.
Yield: 97% of **5b** (clear oil).
^{1}H NMR: -0.15 and 0.04 (s, 6H, $Si(CH_3)_2$); 0.89 (s, 9H, $C(CH_3)_3$)); 1.8 (broad, 1H, NH); 2.44 (s, 3H, NCH_3); 2.63 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{AX} = 8.2 Hz); 2.79 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{BX} = 4.1 Hz); 4.81 (dd, 1H, CH(OTBS), J = 4.1 and 8.2 Hz); 7.31 (m, 5H, arom.).
^{13}C NMR: -5.0 and -4.5 ($Si(CH_3)_2$); 18.1 ($C(CH_3)_3$); 25.8 ($C(CH_3)_3$); 36.1 (NCH_3); 60.1 (CH_2); 74.0 (CH(OTBS)); 126.0, 127.3 and 128.1 (C arom.); 143.4 (C_1 arom.).
$[\alpha]_D^{20}$ -68° (c = 1 $CHCl_3$); e.e. > 99% (HPLC).

(*R*)-(-)-α-[[(1-Methylethyl)amino]methyl]benzenemethanol (5c).
Prepared in the same manner as **5a**, using **2a** (e.e. > 99% (HPLC)) as the cyanohydrin and *iso*-propylamine in the transimination reaction.
Yield: 74% of **5c** (white solid).
^{1}H NMR: 1.08 (d, 6H, $CH(CH_3)_2$, J = 6.2 Hz); 1.9 (broad, 2H, OH + NH); 2.64 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{AX} = 8.7 Hz); 2.83 (sept., 1H, $CH(CH_3)_2$, J = 6.2 Hz); 2.93 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{BX} = 3.6 Hz); 4.66 (dd, 1H, CH(OH), J = 3.6 and 8.7 Hz); 7.32 (m, 5H, arom.).
^{13}C NMR: 23.0 ($CH(CH_3)_2$); 48.6 ($CH(CH_3)_2$); 54.8 (CH_2); 71.9 (CH(OH)); 125.7, 127.3 and 128.2 (C arom.); 142.4 (C_1 arom.).
5c was converted into the HCl salt and crystallized from *iso*-propanol for optical rotation and melting point measurements. $[\alpha]_D^{20}$ -48° (c = 1 H_2O). mp 154-155 °C.
$C_{11}H_{18}NOCl$: Calc. C 61.25% H 8.41% N 6.49%; Found C 61.09% H 8.51% N 6.26%.

(*R*)-(-)-α-[[(1-Methylethyl)amino]methyl]-α-[(*tert*-butyldimethylsilyl)oxy]benzenemethane (5d).
Prepared in the same manner as **5b**, using **2b** (e.e > 99% (HPLC)) as the cyanohydrin and *iso*-propylamine in the transimination reaction.
Yield: 96% of **5d** (slightly yellow oil).
^{1}H NMR: -0.16 and 0.05 (s, 6H, $Si(CH_3)_2$); 0.90 (s, 9H, $C(CH_3)_3$)); 1.02 and 1.06 (d, 6H, $CH(CH_3)_2$, J = 6.2 Hz); 2.3 (broad, 1H, NH); 2.72 (d, 2H, CH_2, J = 6.2 Hz); 2.81 (sept., 1H, $CH(CH_3)_2$, J = 6.2 Hz); 4.78 (t, 1H, CH(OTBS), J = 6.2 Hz); 7.31 (m, 5H, arom.).
^{13}C NMR: -5.5 and -5.0 ($Si(CH_3)_2$); 17.6 ($C(CH_3)_3$); 22.2 and 22.5 ($CH(CH_3)_2$); 25.3 ($C(CH_3)_3$); 47.7 ($CH(CH_3)_2$); 56.0 (CH_2); 74.0 (CH(OTBS)); 125.5, 126.9 and 127.5 (C arom.); 143.0 (C_1 arom.).
$[\alpha]_D^{20}$ -63° (c = 1 $CHCl_3$); e.e. > 99% (HPLC).
5d was converted into the HCl salt and crystallized from *iso*-propanol for an analytical sample.
$C_{17}H_{32}NOSiCl$: Calc. C 61.88% H 9.77% N 4.24%; Found C 61.72% H 9.06% N 4.04%. mp 167°C.

(*R*)-(-)-α-[(Methylamino)methyl]-4-methoxybenzenemethanol (5e).
Prepared in the same manner as **5a**, using **2c** (e.e. > 99% (HPLC)) as the cyanohydrin and methylamine in the transimination reaction.
Yield: 90% of **5e** (slightly yellow solid).
^{1}H NMR: 2.2 (broad, 2H, OH + NH); 2.47 (s, 3H, NCH_3); 2.70 (dd, ABX, 1H, CH_2, J_{AB} = 12.3 Hz J_{AX} = 8.2 Hz); 2.80 (dd, ABX, 1H, CH_2, J_{AB} = 12.3 Hz J_{BX} = 4.1 Hz); 3.81 (s, 3H, OCH_3); 4.69 (dd, 1H, CH(OH), J = 4.1 and 8.2 Hz); 6.88 (d, 2H, arom., J = 8.7 Hz); 7.29 (d, 2H, arom., J = 8.7 Hz).
^{13}C NMR: 35.8 (NCH_3); 55.1 (OCH_3); 59.2 (CH_2); 71.1 (CH(OH)); 113.6 (C_3 and C_5 arom.); 126.9 (C_2 and C_6 arom.); 135.3 (C_1 arom.); 158.8 (C_4 arom.).
5e was converted into the HCl salt and crystallized from *iso*-propanol for optical rotation and melting point measurements. $[\alpha]_D^{20}$ -46° (c = 1 H_2O). mp 141-143°C.
$C_{10}H_{16}NO_2Cl$: Calc. C 55.17% H 7.41% N 6.43%; Found C 54.86% H 7.42% N 6.38%.

(*R*)-(-)-α-[(Methylamino)methyl]-α-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzenemethane (5f).
Prepared in the same manner as **5b**, using **2d** (e.e. > 99% (HPLC)) as the cyanohydrin and methylamine in the transimination reaction.
Yield: 94% of **5f** (slightly yellow oil).
^{1}H NMR: -0.15 and 0.03 (s, 6H, $Si(CH_3)_2$); 0.88 (s, 9H, $C(CH_3)_3$)); 1.9 (broad, 1H, NH); 2.44 (s, 3H, NCH_3); 2.59 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{AX} = 8.2 Hz); 2.74 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{BX} = 4.6 Hz); 3.80 (s, 3H, OCH_3); 4.76 (dd, 1H, CH(OTBS), J = 4.6 and 8.2Hz); 6.85 (d, 2H, arom., J = 8.7 Hz); 7.23 (d, 2H, arom., J = 8.7 Hz).
^{13}C NMR: -5.1 and -4.7 ($Si(CH_3)_2$); 17.9 ($C(CH_3)_3$); 25.6 ($C(CH_3)_3$); 35.9 (NCH_3); 54.9 (OCH_3); 60.6 (CH_2); 73.5 (CH(OTBS)); 113.3 (C_3 and C_5 arom.); 127.0 (C_2 and C_6 arom.); 135.4 (C_1 arom.); 158.6 (C_4 arom.).
$[\alpha]_D^{20}$ -67° (c = 1 $CHCl_3$); e.e. > 99% (HPLC).

(*R*)-(-)-α-[[(1-Methylethyl)amino]methyl]-4-methoxybenzenemethanol (5g).
Prepared in the same manner as **5a**, using **2c** (e.e. > 99% (HPLC)) as the cyanohydrin and *iso*-propylamine in the transimination reaction.
Yield: 78% of **5g** (slightly yellow solid).
^{1}H NMR: 1.07 (d, 6H, 2x CH_3, J = 6.2 Hz); 2.0 (broad, 2H, OH + NH); 2.64 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{AX} = 9.2 Hz); 2.83 (sept., 1H, $CH(CH_3)_2$, J = 6.2 Hz); 2.90 (dd, ABX, 1H, CH_2, J_{AB} = 11.8 Hz J_{BX} = 3.6 Hz); 3.81 (s, 3H, OCH_3); 4.61 (dd, 1H, CH(OH), J = 3.6 and 9.2 Hz); 6.88 (d, 2H, arom., J = 8.7 Hz); 7.34 (d, 2H, arom., J = 8.7 Hz).
^{13}C NMR: 22.7 and 22.9 ($CH(CH_3)_2$); 48.6 ($CH(CH_3)_2$); 54.8 (CH_2); 55.1 (OCH_3); 71.5 (CH(OH)); 113.6 (C_3 and C_5 arom.); 126.9 (C_2 and C_6 arom.); 135.3 (C_1 arom.); 158.8 (C_4 arom.).
5g was converted into the HCl salt and crystallized from *iso*-propanol for optical rotation and melting point measurements. $[\alpha]_D^{20}$ -63° (c = 1 H_2O). mp: 157-159°C.

(*R*)-(-)-α-[[(Methylethyl)amino]methyl]-α-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzenemethane (5h)
Prepared in the same manner as **5b**, using **2d** (e.e. > 99% (HPLC)) as the cyanohydrin and *iso*-propylamine in the transimination reaction.
Yield: 80% of **5h** (slightly yellow oil).
^{1}H NMR: -0.17 and 0.04 (s, 6H, $Si(CH_3)_2$); 0.88 (s, 9H, $C(CH_3)_3$)); 1.02 and 1.06 (d, 3H, $CH(CH_3)_2$, J = 6.2 Hz); 2.2 (broad, 1H, NH); 2.71 (d, 2H, CH_2, J = 6.3 Hz); 2.81 (sept., 1H, $CH(CH_3)_2$, J = 6.2

Hz); 3.80 (s, 3H, OCH_3); 4.75 (t, 1H, CH(OTBS), J = 6.3 Hz); 6.85 (d, 2H, arom., J = 8.2 Hz); 7.23 (d, 2H, arom., J = 8.2 Hz).
^{13}C NMR: -5.0 and -4.5 ($Si(CH_3)_2$); 17.9 ($C(CH_3)_3$); 22.6 and 22.9 ($CH(CH_3)_2$); 25.7 ($C(CH_3)_3$); 48.2 ($CH(CH_3)_2$); 55.0 (OCH_3); 56.5 (CH_2); 73.9 (CH(OTBS)); 113.4 (C_3 and C_5 arom.); 127.1 (C_2 and C_6 arom.); 135.6 (C_1 arom.); 158.7 (C_4 arom.).
$[\alpha]_D^{20}$ -62° (c = 1 $CHCl_3$); e.e. > 99% (HPLC).

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8. DIBAL reductions at higher temperatures resulted in formation of dimers. This was probably caused by overreduction of imine **3** to the corresponding amine and subsequent transimination.
9. The choice of ammonium bromide instead of more frequently applied ammonium chloride as proton donor was on account of its better solubility in methanol. This resulted in a homogeneous reaction mixture during transimination.
10. When neutral or basic work-up is carried out, the O-MIP product is obtained.