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SYNTHESIS OF OPTICALLY ACTIVE ETHANOLAMINES.

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Abstract: (1*R*,2*S*)-2-amino-1-arylethanols of high optical purity have been obtained from optically active *tert*-butyldimethylsilyl protected cyanohydrins by a Grignard reaction, directly followed by reduction of the intermediate imine Chiral induction gave a large preponderance of the erythro isomers

Optically active β-ethanolamines form an important class of compounds because of their usefulness as chiral auxiliaries, chiral building blocks, and as biologically active compounds The ethanolamines have been obtained in optically active form in several different ways, e g , by resolution[1,2], by asymmetric hydrogenation[3,4], and from chiral starting materials[5,6]

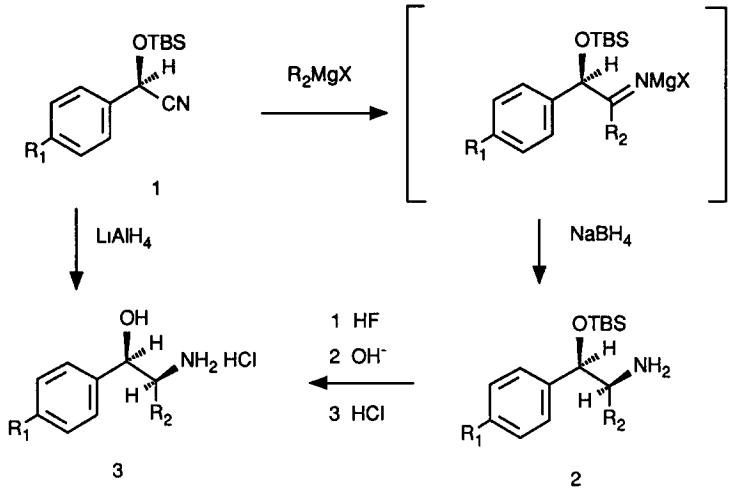
Synthesis of *erythro* and *threo* ethanolamines in racemic form by the addition of a Grignard reagent to trimethylsilylated cyanohydrins followed by hydrogenation of the intermediate imine has been reported[7] In this study, *erythro-threo* mixtures with ratios of 1 1/1 up to 24/1 were obtained depending upon the reaction conditions used Ratios were determined by NMR spectroscopy Due to the acid-lability of the trimethylsilyl group (TMS) the products were isolated in the desilylated form

We now report the synthesis of optically active (O-silylated) ethanolamines starting from *tert*-butyldimethylsilyl cyanohydrins (**1a,1e**) of high optical purity[8,9] using the procedure described by Krepski *et al*[7] with some modification

Use of the *tert*-butyldimethylsilyl group (TBS) has several advantages compared to the TMS group First, no loss of the silyl group occurs during work-up, second, the sodium borohydride reduction at room temperature gives a higher percentage (80-98%) of the *erythro* isomer, and third, the TBS-protected ethanolamine HCl salts can easily be recrystallized and separated from the *threo* forms to afford optically active *erythro* compounds in good yields The relative stereochemistry at carbon atoms 1 and 2 can be conveniently determined by measuring the coupling constant of the vicinal protons[7]

Remarkable is the low solubility of the O-TBS ethanolamine HCl salts in water If etheral solutions of these compounds were washed with 0 1 N HCl, only a trace of the HCl salt could be detected in the aqueous layer

The optical purity of the reaction products could most conveniently be determined after removal of the protecting group Deprotection of the silylated ethanolamine with *tetra*-n-butylammonium fluoride (TBAF) proceeded only sluggishly and was accompanied by extensive racemization and formation of byproducts Aqueous hydrogen fluoride in acetonitrile did not produce these undesired effects and afforded nearly pure ethanolamines, which were converted to their HCl salts In this way norephedrine HCl (**3b**), for example, was obtained in good yield and was found to be identical to an authentic sample All ethanolamines (**3**) as free base, showed high e e 's (93-99%) by ^{1}H NMR analysis in the presence of a chiral shift reagent



3	R_1	R_2	3	R_1	R_2
a	H	H	e	OCH_3	H
b	H	CH_3	f	OCH_3	CH_3
c	H	C_2H_5	g	OCH_3	C_2H_5
d	H	C_6H_5	h	OCH_3	C_6H_5

The compounds **3a** and **3e** (R_2 = H) were obtained by $LiAlH_4$ reduction of the protected cyanohydrins To our surprise, the compounds were deprotected during the reduction To the best of our knowledge, cleavage of a TBS-ether under these conditions has not been reported before TBS-ethers are known to be stable towards a variety of reducing agents, such as diisopropylaluminium hydride or diisobutylaluminium hydride[10] Recently, the first example of reductive cleavage of TBS-ethers, using sodium hydride in aprotic polar solvents, was reported[11] It appears that hydrides can effect, in certain cases, a reaction that was hitherto thought to be limited to the fluoride ion The presence of a second polar group at close range may well turn out to be a necessary condition for this reaction to occur

In order to establish if this reductive cleavage was restricted to cyanohydrins, we performed the $LiAlH_4$ reaction (1 h reflux) on TBS-norephedrine (**2b**) Again this led to complete removal of the protecting group, and norephedrine was obtained in good yield

Experimental.

^1H NMR and ^{13}C NMR spectra were recorded on a JEOL FX-200 The optical purity of the ethanolamines (10 mg of **3**, free base) was determined with the aid of 50 mg of (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TAE) in 0 5 mL $CDCl_3$ on a Bruker AM-400 instrument Probe temperature 23°C A racemic mixture showed under these circumstances separation of the enantiomers The limit of detection of the other enantiomer was 1% Optical rotations were measured using a Perkin Elmer 141 polarimeter IR-spectra (KBr) were recorded on a PYE UNICAM SP3 200 instrument Mass spectra (chemical ionization) were recorded on a KRATOS CONCEPT 1S mass spectrometer A mixture of 10% ammonia and 90% methane was used as reagent gas
(*R*)-(+)-α-[(*tert*-butyldimethylsilyl)oxy]-benzeneacetonitrile (**1a**) (e e >98%) and (*R*)-(+)-α-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzeneacetonitrile (**1e**) (e e >99%) were synthesized by the method described before[8,9]

Silylated ethanolamines.

General procedure
A solution of the Grignard reagent (24 mmol) was prepared in 90 mL of ether in an inert atmosphere The silyl-protected cyanohydrin (16 mmol) dissolved in 50 mL of anhydrous ether was added dropwise The mixture was stirred and refluxed for 4h, cooled to room temperature and 100 mL of anhydrous methanol was added slowly Solid $NaBH_4$ (33 mmol) was added in two portions (The methanol was added first to destroy the excess of Grignard reagent and better results were obtained) After stirring overnight at room temperature, 100 mL of water was added and the mixture was extracted with ether (3 x 100 mL) The combined organic layers were washed twice with brine, dried on $MgSO_4$, and evaporated This crude silylated ethanolamine (yield 90 - 100%) was dissolved in absolute ethanol and neutralized with a 0 48 N ethanolic HCl solution (4 mL 12 N HCl mixed with 96 mL abs ethanol) The ethanol was evaporated and the residue was recrystallized from a solvent as specified for each individual compound

Deprotection.

General procedure
To 11 5 mmol silylated ethanolamine dissolved in 15 mL of acetonitrile was added 2 9 mL of 40% HF in water and stirred for 17 h at 50°C Water (200 mL) was added and the pH was raised to 12 with 1N NaOH The mixture was extracted with CH_2Cl_2 (4 x 50 mL) The combined organic layers were washed with brine (2 x 10 mL), dried on Na_2CO_3, filtered and evaporated The residue was neutralized with 0 48N ethanolic HCl The ethanol was evaporated and the residue was recrystallized as specified for the individual compounds

(1*R*,2*S*)-(-)-2-Amino-1-phenyl-1-[(*tert*-butyldimethylsilyl)oxy]-propane, HCl salt (**2b**)
Recrystallized from abs ethanol Yield 61% (>99% erythro)
$[\alpha]^{20}_D$ -44 1°, (*c* 1, $CHCl_3$) mp 203-205°C (dec)
^1H NMR ($CDCl_3$) δ 8 33 (br, 3H, NH_3), 7 34 (m, 5H, arom), 5 04 (d, 1H, J = 3 9 Hz, C_6H_5CH), 3 41 (m, 1H CHN), 1 29 (d, 3H, J = 6 7 Hz, CH_3), 0 94 (s, 9H, *tert*-bu), 0 21 (s, 3H, CH_3Si), -0 20 (s, 3H, CH_3Si)

(1*R*,2*S*)-(-)-2-Amino-1-phenyl-1-propanol, HCl salt (**3b**)
Recrystallized from ethylacetate Yield 73%
$[\alpha]^{20}_D$ -33 6° (*c* 1, H_2O) mp 168-169°C E e >99%
Lit[1] $[\alpha]^{20}_D$ -33 27° (*c* 3 3, H_2O) mp 171-172°C
^1H NMR (1 6 N DCl/D_2O) δ 7 45 (m, 5H, arom), 5 01 (d, 1H, J = 4 4 Hz), C_6H_5CH), 3 72 (m, 1H, CHN), 1 20 (d, 3H, J = 6 7 Hz, CH_3) An authentic sample gave the same NMR spectrum

^{13}C NMR (D_2O) 138 93 (C-1), 129 44 (C-3,5), 129 21 (C-4), 126 93 (C-2,6), 73 53 (C-OH), 52 76 (C-N), 13 11 (CH_3)
IR 3380, 3000, 1600, 1480, 1396, 1040, 746, 701 cm^{-1}
$C_9H_{14}NOCl$ Calc C 57 60 H 7 52 N 7 46 Found C 57 64 H 7 41 N 7 38

(1*R*,2*S*)-(-)-2-Amino-1-phenyl-1-[(*tert*-butyldimethylsilyl)oxy]-butane, HCl salt (**2c**)
Recrystallized from abs ethanol Yield 70% (>98% erythro)
$[\alpha]^{20}_D$ -37 9°, (*c* 1, $CHCl_3$) mp 79-82°C
^{1}H NMR ($CDCl_3$) δ 8 26 (br, 3H, NH_3), 7 37 (m, 5H, arom), 5 10 (d, 1H, J = 3 9 Hz, C_6H_5CH), 3 26 (m, 1H, CHN), 1 73 (m, 2H, CH_2), 1 07 (t, 3H, J = 7 5 Hz, CH_3), 0 93 (s, 9H, *tert*-bu), 0 19 (s, 3H, CH_3Si), -0 20 (s, 3H, CH_3Si)

(1*R*,2*S*)-(-)-2-Amino-1-phenyl-1-butanol, HCl salt (**3c**)
Recrystallized from abs ethanol/ethylacetate Yield 83%
$[\alpha]^{20}_D$ -33 1° (*c* 1, H_2O) mp 137-139°C E e 93%
^{1}H NMR (1 6 N DCl/D_2O) δ 7 45 (m, 5H, arom), 5 06 (d, 1H, J = 4 6 Hz), C_6H_5CH), 3 55 (m, 1H, CHN), 1 60 (m, 2H, CH_2), 0 98 (t, 3H, J = 7 5 Hz, CH_3)
^{13}C NMR (D_2O) 138 53 (C-1), 129 44 (C-3,5), 129 30 (C-4), 127 08 (C-2,6), 72 71 (C-OH), 58 49 (C-N), 21 43 (CH_2CH_3), 9 75 (CH_3)
IR 3350, 3050, 1610, 1488, 1400, 1036, 701 cm^{-1}
$C_{10}H_{16}NOCl$ Calc C 59 55 H 8 00 N 6 94 Found C 59 53 H 7 90 N 6 64

(1*R*,2*S*)-(-)-2-Amino-1,2-diphenyl-1-[(*tert*-butyldimethylsilyl)oxy-ethane, HCl salt (**2d**)
The crude product was stirred in P E 60-80 and the crystals were filtered Yield 83% (>95% erythro)
$[\alpha]^{20}_D$ -71 8° (*c* 1, $CHCl_3$) mp 213-214°C
^{1}H NMR ($CDCl_3$) δ 8 76 (br, 3H, NH_3), 7 22 (m, 5H, arom), 7 08 (m, 5H, arom), 5 21 (d, 1H, J = 4 6 Hz, C_6H_5CH), 4 18 (m, 1H, CHN), 0 78 (s, 9H, *tert*-bu), -0 02 (s, 3H, CH_3Si), -0 36 (s, 3H, CH_3Si)

(1*R*,2*S*)-(-)-2-Amino-1,2-diphenyl-1-ethanol, HCl salt (**3d**)
Recrystallized from abs ethanol/ethylacetate Yield 92%
$[\alpha]^{20}_D$ -69 1° (*c* 1, H_2O) mp 199-201°C (dec) E e >99%
Lit [12] $[\alpha]^{20}_D$ -69 3° (*c* 1, H_2O) mp 213-214°C Lit [13] (1S,2R) $[\alpha]_D$ +66 8° (*c* 0 5, $CHCl_3$), mp 208-209°C Lit[14] (1S,2R) $[\alpha]_D$ +69 6° (*c* 0 65, H_2O) mp 210-212°C
^{1}H NMR (1 6 N DCl/D_2O) δ 7 35 (m, 10H, arom), 5 29 (d, 1H, J = 6 2 Hz), C_6H_5CH), 4 69 (d, 1H, J = 6 2 Hz, CHN)
^{13}C NMR (D_2O) 138 82 (C-1), 133 39 (C-1'), 129 91, 129 41, 128 57 and 127 25 (arom), 74 23 (C-OH), 60 42 (C-N) MS 44(60), 106(100), 124(10), 214(20) $[M+H]^+$
IR 3400, 3000, 1602, 1495, 1400, 1051, 700 cm^{-1}

(1*R*,2*S*)-(-)-2-Amino-1-(4-methoxyphenyl)-1-[(*tert*-butyldimethylsilyl)oxy]-propane, HCl salt (**2f**)
The crude product was stirred in P E 60-80 and the crystals were filtered Yield 71% (>99% erythro)
$[\alpha]^{20}_D$ -42 3° (*c* 1, $CHCl_3$) mp 209-212°C (dec)
^{1}H NMR ($CDCl_3$) δ 8 27 (br, 3H, NH_3), 7 28 (d, 2H, J = 8 7 Hz, arom), 6 86 (d, 2H, J = 8 7 Hz, arom), 4 99 (d, 1H, J = 3 6 Hz, C_6H_5CH), 3 79 (s, 3H, CH_3O), 3 39 (m, 1H, CHN), 1 27 (d, 3H, J = 6 4 Hz, CH_3), 0 94 (s, 9H, *tert*-bu), 0 20 (s, 3H, CH_3Si), -0 20 (s, 3H, CH_3Si)

(1*R*,2*S*)-(-)-2-Amino-1-(4-methoxyphenyl)-1-propanol, HCl salt (**3f**)
The crude product was suspended in ether and the crystals were filtered Yield 94%
$[\alpha]^{20}_D$ -31 6° (*c* 1, H_2O) mp 209-211°C E e 96%
^{1}H NMR (1 6 N DCl/D_2O) δ 7 39 (d, 2H, J = 8 7 Hz, arom), 7 06 (d, 2H, J = 8 7 Hz, arom), 5 00 (d, 1H, J = 4 6 Hz), C_6H_5CH), 3 85 (s, 3H, CH_3O), 3 72 (m, 1H, CHN), 1 20 (d, 3H, J = 6 7 Hz, CH_3)
^{13}C NMR (D_2O) 159 52 (C-4) 131 46 (C-1), 128 42 (C-2,6), 114 87 (C-3,5), 73 26 (C-OH), 56 04 (OCH_3), 52 79 (C-N), 13 26 (CH_3)
IR 3320, 3000, 1610, 1501, 1399, 1255, 1171, 1046, 800 cm^{-1}
$C_{10}H_{16}NO_2Cl$ Calc C 55 17 H 7 41 N 6 40 Found C 55 11 H 7 47 N 6 31

(1*R*,2*S*)-(-)-2-Amino-1-(4-methoxyphenyl)-1-[(*tert*-butyldimethylsilyl)oxy]-butane, HCl salt (**2g**)
Recrystallized from acetonitrile Yield 61% (>98% erythro)
$[\alpha]^{20}_D$ -47 7° (*c* 1, $CHCl_3$) mp 96-99°C (dec)
^{1}H NMR ($CDCl_3$) δ 8 23 (br, 3H, NH_3), 7 31 (d, 2H, J = 8 5 Hz, arom), 6 86 (d, 2H, J = 8 5 Hz, arom), 5 02 (d, 1H, J = 3 9 Hz, C_6H_5CH), 3 79 (s, 3H, CH_3O), 3 21 (m, 1H, CHN), 1 76 (m, 2H CH_2), 1 07 (t, 3H, J = 7 3 Hz, CH_3), 0 91 (s, 9H, *tert*-bu), 0 16 (s, 3H, CH_3Si), -0 20 (s, 3H, CH_3Si)

(1*R*,2*S*)-(-)-2-Amino-1-(4-methoxyphenyl)-1-butanol, HCl salt (**3g**)
The crude product was suspended in ether and the crystals were filtered Yield 95%
$[\alpha]^{20}_D$ -31 0° (*c* 1, H_2O) mp 189-192°C E e 95%
^{1}H NMR (1 6 N DCl/D_2O) δ 7 39 (d, 2H, J = 8 6 Hz, arom), 7 06 (d, 2H, J = 8 6 Hz, arom), 5 00 (d, 1H, J = 4 6 Hz), C_6H_5CH), 3 85 (s, 3H, CH_3O), 3 50 (m, 1H, CHN), 1 60 (m, 2H, CH_2), 0 99 (t, 3H, J = 7 5 Hz, CH_3)
^{13}C NMR (D_2O) 159 49 (C-4) 131 14 (C-1), 128 48 (C-2,6), 114 87 (C-3,5), 72 30 (C-OH), 58 58 (C-N), 56 04 (OCH_3) 21 43 (CH_2CH_3), 9 87 (CH_3)
IR 3300, 3000, 1610, 1502, 1400, 1250, 1170, 1040, 830 cm^{-1}
$C_{11}H_{18}NO_2Cl$ Calc C 57 02 H 7 83 N 6 04 Found C 56 77 H 7 83 N 5 90

(1*R*,2*S*)-(-)-2-Amino-1-(4-methoxyphenyl)-1-[(*tert*-butyldimethylsilyl)oxy]-2-phenylethane, HCl salt (**2h**)
The crude product was suspended in P E 60-80 at 60°C, after cooling the crystals were collected Yield 78% (>90% erythro)
$[\alpha]^{20}_D$ -73 8° (*c* 1, $CHCl_3$) mp 156-158°C
^{1}H NMR ($CDCl_3$) δ 8 70 (br, 3H, NH_3), 7 22 (m, 5H, arom), 6 96 (d, 2H, J = 8 5 Hz, arom), 6 65 (d, 2H, J = 8 5 Hz, arom), 5 17 (d, 1H, J = 4 6 Hz, C_6H_5CH), 4 16 (m, 1H, CHN), 3 73 (s, 3H, CH_3O), 0 77 (s, 9H, *tert*-bu), -0 03 (s, 3H, CH_3Si), -0 36 (s, 3H, CH_3Si)

(1*R*,2*S*)-(-)-2-Amino-1-(4-methoxyphenyl)-2-phenyl-1-ethanol, HCl salt (**3h**)
Recrystallized from abs ethanol/ethylacetate Yield 87%
$[\alpha]^{20}_D$ -56 9° (*c* 1, H_2O) mp 194-196°C E e >99%
^{1}H NMR (1 6 N DCl/D_2O) δ 7 38 (m, 5H, arom), 7 24 (d, 2H, J = 8 7 Hz, arom), 6 97 (d, 2H, J = 8 7 Hz, arom), 5 24 (d, 1H, J = 6 7 Hz), C_6H_5CH), 4 65 (d, 1H, J = 6 7 Hz, CHN) 3 83 (s, 3H, CH_3O)
^{13}C NMR (D_2O) 159 67 (C-4), 133 44 (C-1'), 131 34 (C-1), 129 91, 129 41, 128 74 and 128 60 (arom), 114 76 (C-3,5), 73 82 (C-OH), 60 47 (C-N), 55 95 (OCH_3)
IR 3400, 3000, 1610, 1500, 1397, 1253, 1178, 1060, 1040, 820, 700 cm^{-1}
MS 44(25), 77(10), 106(100), 137(60), 244(20) $[M+H]^+$

Reduction and deprotection.

(*R*)-(-)-2-Amino-1-phenyl-1-ethanol (**3a**)
Prepared from (*R*)-(+)-α-[(*tert*-butyldimethylsilyl)oxy]-benzeneacetonitrile (**1a**) To a solution of 0 7 g (18 4 mmol) $LiAlH_4$ in 15 mL of dry THF was slowly added a solution of **1a** (3 g, 12 1 mmol) in 5 mL of THF After 1 h reflux the mixture was cooled to room temperature and 0 7 mL H_2O in 5 mL of THF, 0 7 mL of 15% NaOH and 2 1 mL of H_2O was added respectivily The precipitate was filtered and washed with THF The filtrate was dried on Na_2SO_4, filtered, and evaporated The residue was recrystallized from P E 40-60 Yield 1 1 g (67%) of **3a** (free amine)
$[\alpha]^{20}_D$ -42 2° (*c* 1, EtOH) mp 54-58°C E e 95% [Lit [15] (*S*), $[\alpha]^{23}_D$ +44 8° (*c* 2, EtOH) mp 61-63°C]
^{1}H NMR (1 6 N DCl/D_2O) δ 7 47 (m, 5H, arom), 5 05 (m, 1H, C_6H_5CH), 3 32 (m, 2H, CH_2)
^{13}C NMR (D_2O) HCl salt 140 01 (C-1), 129 59 (C-3,5), 129 33 (C-4), 126 58 (C-2,6), 70 17 (C-OH), 45,87 (CH_2)
IR 3360, 3000, 1590, 1540, 1400, 1050, 760, 701 cm^{-1}
$C_8H_{12}NOCl$ Calc C 55 34 H 6 97 N 8 07 Found C 55 16 H 6 99 N 8 00

(*R*)-(-)-2-Amino-1-(4-methoxyphenyl)-1-ethanol (**3e**)
Prepared as described for **3a** using (*R*)-(+)-α-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzeneacetonitrile (**1e**) The residue was recrystallized from CH_2Cl_2/P E 40-60

Yield 68% of **3e** (free amine) $[\alpha]^{20}_{D}$ -38 6° (*c* 1, abs EtOH) mp 102-103°C E e 96%
^{1}H NMR (1 6 N DCl/D_2O) δ 7 38 (d, 2H, J = 9 Hz, arom), 7 03 (d, 2H, J = 9 Hz, arom), 4 88 (m, 1H, $C_6H_5\underline{CH}$), 3 81 (s, 3H, CH_3O), 3 15 (m, 2H, CH_2)
^{13}C NMR (D_2O) HCl salt 159 58 (C-4), 132 66 (C-1), 128 10 (C-2,6), 114 96 (C-3,5), 69 82 (C-OH), 56 01 (OCH_3), 45 79 (CH_2)
IR 3390, 3000, 1608, 1492, 1398, 1248, 1051, 810, 700 cm^{-1}
$C_9H_{14}NO_2Cl$ Calc C 53 08 H 6 93 N 6 88 Found C 52 50 H 6 89 N 6 61

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