ENANTIOMERICALLY PURE ß-AMINO SULFIDES AND ß-AMINO THIOLS FROM EPHEDRINE

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Abstract-Ephedrine and pseudoephedrine are converted by means of a Mitsunobu reaction to respectively *trans*- and *cis*-aziridines, which can be ring-opened at the benzylic center with inversion of configuration by thiols and thiol acids. The *trans*-aziridine from ephedrine reacts also with H_2S in acetone under which conditions the amino thiol is trapped as the thiazolane. The same aziridine also undergoes cycloaddition with CS_2.

Demand continues for a multitude of new chiral nonracemic compounds prepared, if at all possible, by means of relatively low cost approaches. Catalytic asymmetric synthesis[1] is particularly attractive as a route to such compounds. To meet this challenge many new enantiomerically pure catalysts have been developed in recent years.[2]

The ß-amino alcohols play a central role in this development; these now find use also as ligand precursors for catalytically active transition metals.[3] Both synthetically prepared amino alcohols as well as amino alcohols from the chiral pool (*e.g.* cinchona or ephedra alkaloids) have been broadly used themselves, either as chiral catalysts or as chiral ligands for transition metal catalysis.[4]

In view of this interest in amino alcohols it is surprising indeed that little research has been done using ß-amino *thiols* or *sulfides*. The lack of simple synthetic routes to suitable derivatives is undoubtedly a major barrier. We now report a general and straightforward synthetic route to thiol analogs of the ephedra alkaloids using readily available (1*R*,2*S*)-ephedrine (1) and (1*S*,2*S*)-

pseudoephedrine (**2**) as starting materials. Heterocyclic chemistry revolving about aziridines is a key component of the strategy. Virtually any strategy that starts from **1** and **2** involves activation of the hydroxyl group. Such activation of **1** and **2** is bound to be followed by internal attack by the nitrogen giving rise to

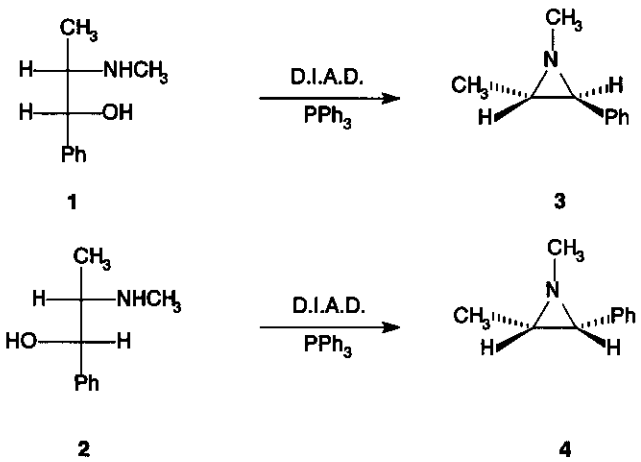


Figure 1

aziridines (**3**/**4**) with inversion of configuration at the benzylic center. Subsequent opening of these aziridines at the benzylic position with inversion of configuration would yield the desired products with overall retention of configuration. Optimalization of both aziridine formation and the subsequent ring opening is a prerequisite to application, however.

Several routes to **3** and **4** from the ß-amino alcohols (**1**/**2**) have been described, examples being the Wenker synthesis involving treatment of the ß-amino alcohols with H_2SO_4 followed by base[5] or with triphenylphosphine dihalogenides.[6] The best approach, however, is application of the Mitsunobu reaction as described by Pfister[7] a few years ago. This reaction, carried out under mild conditions, gives access to both optically pure (and polymerization sensitive) *trans*-**3** from ephedrine (**1**) and *cis*-**4** from pseudoephedrine (**2**) in high yield (Figure 1).

Acid catalysis aids in opening these aziridine bases with nucleophiles. When **3** in CH_2Cl_2 was treated with thiolacetic acid at room temperature an exothermic reaction took place that cleanly gave a single product in high purity (Figure 2).

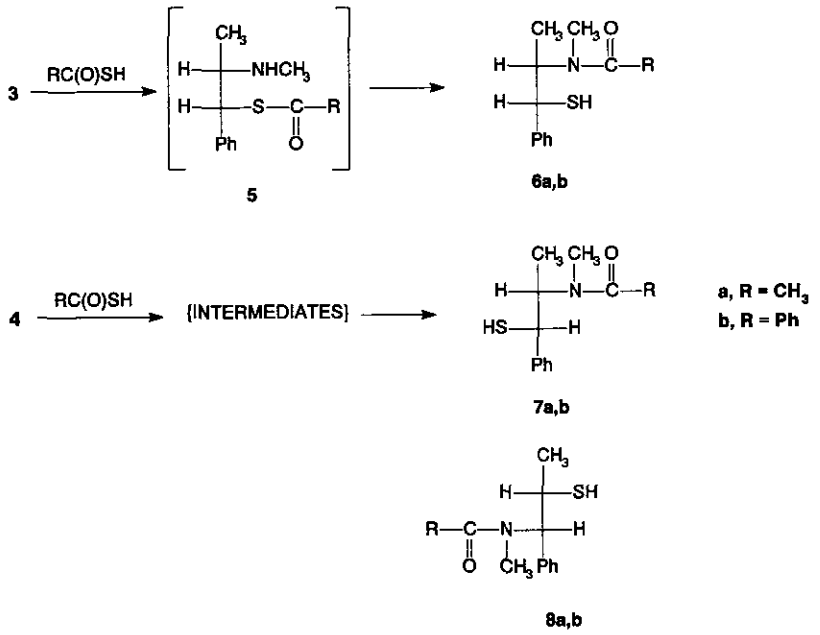
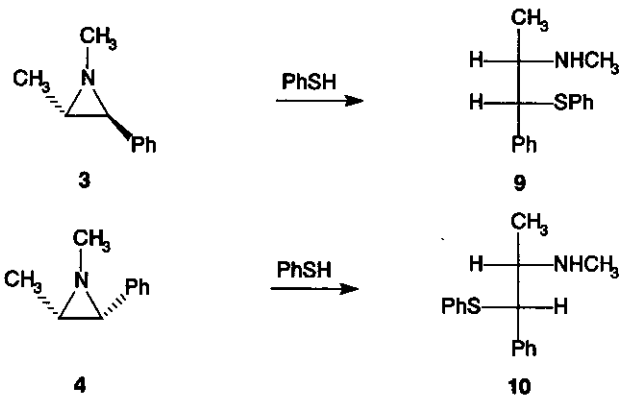


Figure 2

From the ^{1}H-nmr spectrum it could be concluded that the reaction had taken place selectively at the benzylic position but that not the thiolacetate (**5a**) was present but rather amide (**6a**). Probably **5a** is an intermediate but it immediately rearranges intramolecularly to produce the amide, analogously to esters of ephedrine.[8] Amide (**6a**) exhibits hindered rotation around the amide bond as observed from the ^{1}H-nmr spectrum in which nearly all signals are doubled. These doubled signals collapse to one when the temperature is increased to 130 °C in DMSO-d_6. Structural and stereochemical assignment follows in all cases readily from the nmr spectra. The ephedrine series has J_{vic} values of 2-7 Hz for the carbon backbone, whereas the pseudo series has J_{vic} = 7-10 Hz. The

coupling observed between -SH and the benzylic H establishes that ring opening has occurred at the benzylic position.

When *cis*-aziridine (**4**) was treated under the same conditions with thiolacetic acid the ß-thiol acetamide (**7a**) was formed with overall retention of configuration. However, about 10% of the nucleophilic attack took place at the nonbenzylic position to yield regioisomer (**8a**). The main product (**7a**) could be isolated in a pure form by column chromatography. Reaction of **3/4** with thiol-benzoic acid instead of thiolacetic acid proceeded in an analogous fashion to yield **6b**, **7b** and **8b**.



3 **9** **4** **10**

Figure 3

On reaction with thiophenol *trans*-aziridine (**3**) was opened cleanly to afford **9** (Figure 3). *cis*-Aziridine (**4**) was far less reactive and complete conversion to afford **10** took about 4 days whereas the *trans*-aziridine was completely converted by stirring overnight. Ring opening of **4** proceeded nevertheless completely regioselectively to afford **10** in 73% yield. The assignments of regiochemistry to **9** and **10** are based on the analogies in ^{1}H-nmr spectra to **6** and **7**, and is expected because of the strong preference for benzylic ring opening under neutral conditions.

An appealing target compound is thiolephedrine (**11**) itself. Thiolephedrine and

related compounds have only been reported in the literature summarily. Syntheses proceed *via* Bunte salts, although only in low to moderate yields.[9] Low yields characterize also the synthesis of pseudothiolephedrine under rigorous conditions employing hydrogen sulfide in liquid hydrogen fluoride.[10]

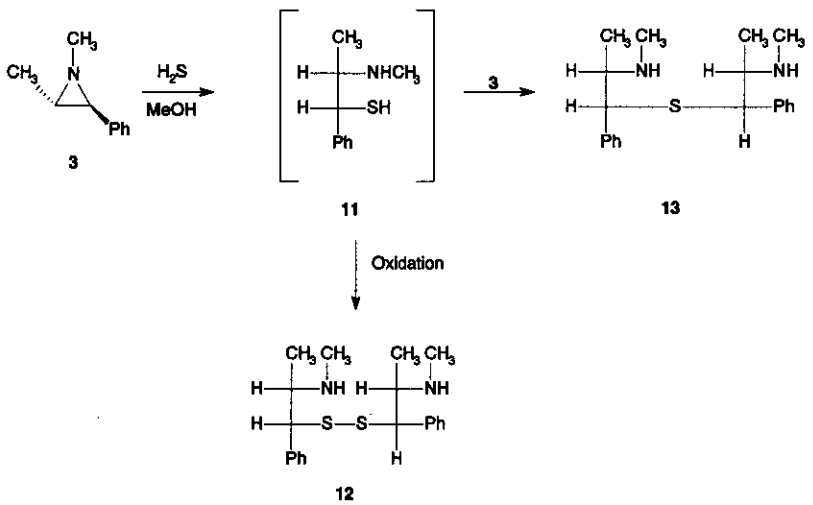
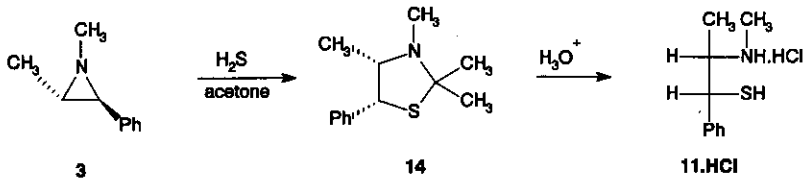


Figure 4

A very straightforward route would be the direct ring opening of *trans*-aziridine (**3**) by bubbling H_2S through a solution of the aziridine in methanol (Figure 4). Selective ring opening at the benzylic carbon atom by attack of H_2S to afford **11** does take place, but complications are known to take place because of subsequent reactions.[11] The initially formed ß-aminothiol (**11**) can react with the aziridine leading to the formation of sulfide (**13**), or give rise to the formation of disulfide (**12**) owing to oxidation of the free thiol by oxygen in the air. No attempts were made to separate the disulfide from the sulfide. The ratios of these products differed strongly depending upon the reaction conditions. Formation of the sulfide could be minimized by slow addition of a solution of the aziridine to a saturated solution of H_2S in methanol. Although in some experiments disulfide (**12**) was cleanly obtained it was hard to reproduce



3 14 11.HCl

Figure 5

these experimental results. In most cases a mixture of sulfide, disulfide and polymeric material was obtained.

We therefore looked for an alternative route to thiolephedrine, *e.g.* by conducting the ring opening of **3** in acetone (Figure 5). In the event in a very clean reaction H_2S opens the aziridine and intermediate (**11**) is trapped in the form of its acetonide (**14**). This heterocyclic compound can be hydrolyzed by co-distillation of acetone together with water under acidic conditions. Removal of the acetone that is liberated during the hydrolysis is necessary to shift the equilibrium to the side of the products. Thiolephedrine (**11**) is isolated in the form of the HCl salt after distilling off the water. When this compound was made HCl free with dilute base the corresponding disulfide (**12**) is obtained instead of the free thiolephedrine (**11**), because of oxidation by air. The less reactive *cis*-aziridine (**4**) failed to react with H_2S under these conditions.

Another option to synthesize protected ß-aminothiols is the reaction between an aziridine and carbon disulfide[12] leading to the corresponding thiazolidinethione (**15**) (Figure 6). Pseudoephedrine derived *cis*-aziridine (**4**) was again unreactive in this reaction, but the *trans*-aziridine (**3**) gave stereoselectively the expected cycloaddition product (**15**). The aziridine used should be pure, otherwise polymerization takes place. The resulting thiazolidinethione (**15**) is resistant to acid hydrolysis but could be reduced with $LiAlH_4$ to *N*-methylthiolephedrine (**16**). This conversion establishes also the stereochemistry of **15**, which is formed with inversion of configuration at the benzylic position of **3**. This appears to be the best route to the sulfur analog of *N*-methylephedrine. Again oxygen should be carefully excluded because the product is easily air oxidized to disulfide (**17**).

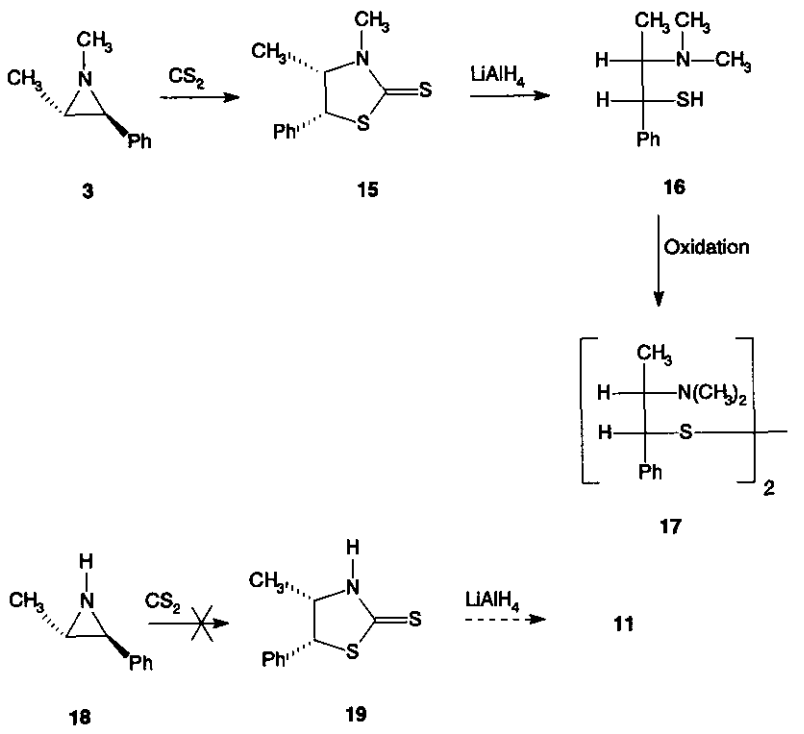


Figure 6

To obtain thiolephedrine itself by ring opening with CS_2 use would have to be made of the norephedrine based aziridine (Figure 6). This aziridine (**18**) could also be synthesized by Mitsunobu reaction on one of the ephedra alkaloids. The reaction time necessary to convert norephedrine into the three membered ring was, however, extremely long (3 days) when compared to the synthesis of **3** and **4**. It is reported that no product is formed by Mitsunobu reaction on a comparable primary ß-aminoalcohol, but most likely, this should be attributed to the "short" reaction time (6h) employed by the authors.[7]

Unfortunately attempts to allow CS_2 to react with (2*S*,3*S*)-1*H*-2-methyl-3-phenyl aziridine (**18**) only led to the formation of polymeric material, instead of the desired thiazolidine (**19**).

At the moment we are broadening the scope of this synthetic strategy for the preparation of chiral non-racemic ß-amino sulfides and we are testing these compounds as chiral ligands in asymmetric C-C bond formation reactions. Furthermore we are intrigued by the observed difference in reactivity between the *cis*- and *trans*-aziridine and are trying to gain further insight into the possible reasons for this behavior with the aid of molecular mechanics and *ab initio* calculations. Several of the thiols described here have proven to be excellent activators for the addition of diethylzinc to benzaldehyde; extremely good enantiomeric excesses have been obtained.[13]

EXPERIMENTAL SECTION

General remarks

^{1}H Nmr spectra were recorded on a JEOL JNM-PMX 60 si NMR spectrometer (at 60 MHz), on a Varian Gemini-200 (at 200 MHz) or on a Varian VXR-300 spectrometer (at 300 MHz). ^{13}C-Nmr spectra were recorded on a Varian Gemini-200 (at 50.32 MHz) or on a Varian VXR-300 spectrometer (at 75.48 MHz). All reagents and solvents were purified and dried when necessary, following standard procedures. Commercially available **1** and **2** were obtained from Aldrich Chemical Company, Inc. Diisopropyl azodicarboxylate was purchased from Janssen Chimica.

trans-(2S,3S)-1,2-Dimethyl-3-phenylaziridine (3)

This compound was prepared from (1*R*,2*S*) ephedrine (**1**) by a literature procedure.[7] *trans*-Aziridine (**3**) was isolated (81% yield) as a clear oil after bulb-to-bulb distillation (bath temperature; 75 °C, 1.0 mm Hg); $[\alpha]_D^{20}$ = +83.2 ° (c 1.18, CH_2Cl_2); {lit.,[7] $[\alpha]_D^{25}$ = +51.8 ° (no concentration or solvent reported)}; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.33 (d, J = 5.3 Hz, 3H), 2.0-2.1 (m, 2H), 2.52 (s, 3H), 7.2-7.3 (s, 5H); ^{13}C nmr ($CDCl_3$): δ 10.42 (q), 37.92 (q), 42.19 (d), 49.17 (d), 125.43 (d), 126.23 (d), 127.81 (d), 129.81 (d), 140.33 (s); HRms calcd m/z 147.104; found 147.105.

cis-(2S,3R)-1,2-Dimethyl-3-phenylaziridine (4)

This compound was prepared from (1*S*,2*S*)-pseudoephedrine in the same way as **3**. Starting from **2** the product was obtained (85% yield) as a clear oil after bulb-to-bulb distillation (50 °C, 0.9 mm Hg); $[\alpha]_D^{20}$ = +131.0 ° (c 0.80, EtOH); ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.90 (d, J = 5.7 Hz, 3H), 1.66 (m, 1H), 2.42 (d, J = 7.2 Hz), 2.48 (s, 3H), 7.26 (s, 5H); ^{13}C nmr ($CDCl_3$): δ 12.54 (q), 42.82 (q), 47.40 (d), 47.49 (d), 126.20 (d), 126.33 (d), 127.58 (d), 127.73 (d), 137.37 (s); HRms calcd m/z 147.104; found 147.105.

(1R,2S)-1-Phenyl-2-(N-methyl-N-acetamido)propanethiol (6a)

trans-Aziridine (**3**) (0.70 g, 4.76 mmol) was dissolved in 20 ml of dichloromethane and cooled to 0 °C. Thiolacetic acid (0.38 g, 5.00 mmol) was added and the reaction mixture was stirred under nitrogen. After 2 h more dichloromethane was added and the organic layer was washed with saturated $NaHCO_3$ solution (2 x 35 ml). After drying ($MgSO_4$) and evaporation of the solvent the crude product was subjected to column chromatography (silica gel, ether), **6a** was obtained (860 mg, 81% yield) as a viscous oil; $[\alpha]_D^{20}$ = -91.0 ° (c 2.1, CH_2Cl_2); ^{1}H nmr ($CDCl_3$, 200 MHz): δ 1.38 and 1.47 (d, J = 6.7 Hz and J = 6.4 Hz, 3H), 1.75 and 1.84 (s, 3H), 1.88 and 1.97 (d, J = 6.9 Hz and J = 5.2 Hz, SH), 2.61 and 2.67 (s, 3H), 4.03 (m, 1H), 4.14 and 5.03 (m, 1H), 7.2-7.3 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 15.77 (q), 22.01 (q), 47.70 (q), 54.71 (d), 59,94 (d), 126.90 (d), 127.45 (d), 127.98 (d), 128.46 (d), 128.78 (d), 142.26 (s), (C=O, not observed); according to GC this material had a purity of over 98%.

(1R,2S)-1-Phenyl-2-(N-methyl-N-benzamido)propanethiol (6b)

This compound was prepared in the same way as **6a**. Starting from **3**, **6a** was obtained in pure form after column chromatography (silica gel, ether) yielding **6b** (88% yield) as a white solid, mp 89.8-90.3 °C. No trace of the other regioisomer was detected either by ^{1}H nmr or by tlc analysis. $[\alpha]_D^{20}$ = -64.9 ° (c 1.74, CH_2Cl_2); ^{1}H nmr ($CDCl_3$, 200 MHz): δ 1.49 (d, J = 6.8 Hz, 3H), 1.92 (d, J

= 6.8 Hz, SH), 1.47 and 2.78 (s, 3H), 4.01 (m, 1H), 4.18 and 5.10 (m, 1H), 6.63 (d, J = 6.4 Hz, 1H) 6.8-7.4 (m, 9H); ^{13}C nmr ($CDCl_3$): 15.73 (q), 32.25 (q), 47.45 (d), 55.12 (d), 126.20 (d), 126.80 (d), 127.04 (d), 127.06 (d) 127.13 (d), 127.51 (d), 128.17 (d), 129, 13 (d), 136.68 (s), 142.38 (s), (C=O not observed). No exact mass could be determined, due to ß-elimination of hydrogen sulfide. This was confirmed by the m/z 251 (285-34) peak in the mass spectrum. The purity of this material was over 99% according to GC.

(1S,2S)-1-Phenyl-2-(N-methyl-N-acetamido)propanethiol (7a)

This compound was synthesized in the same way as **6a**. Starting from *cis*-aziridine (**4**) (0.75 g), **7a** was obtained (0.80 g, 70% yield) as a white solid, after chromatography (silica gel, ethyl acetate/hexane 1:2); mp 108-110 °C (decomp.) (lit.,[9a] 112-113 °C); ^{1}H nmr ($CDCl_3$, 200 MHz): δ 0.85 and 0.91 (d, J = 6.8 Hz and J = 6.4 Hz, 3H), 1.83 and 1.86 (d, J = 5.6 Hz and J = 1.6 Hz, SH), 2.07 and 2.23 (s, 3H), 2.77 and 2.83 (s, 3H), 3.91 and 4.97 (br s, 1H), 4.06 (m, 1H), 7.2-7.3 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 15.70 (q), 16.68 (q), 22.40 (q), 47.54 (d), 48.27 (d), 59.67 (d), 127.52 (d), 127.60 (d), 128.00 (d), 128.69 (d), 128.71 (d), 128.98 (d), 129.00 (d), 140.65 (s), 142.12 (s).

The other regioisomer (**8a**) was obtained (12%) as a white almost pure semisolid. ^{1}H Nmr ($CDCl_3$, 200 MHz): δ 1.25 and 1.32 (d, J = 6.6 Hz and J = 6.6 Hz, 3H), 1.62 and 1.74 (d, J = 7.7 Hz and J = 4.1 Hz, SH), 2.09 and 2.40 (s, 3H), 2.74 and 2.79 (s, 3H), 3.61 and 3.82 (m, 1H), 4.62 and 5.66 (d, J = 10.8 Hz and J = 11.1 Hz, 1H), 7.2-7.4 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 21.67 (q), 22.30 (q), 23.71 (q), 35.07 (q), 35.67 (q), 62.73 (d), 69.12 (d), 127.66 (d), 128.34 (d), 128.65 (d), 128.93 (d), 136.70 (s), 137.69 (s); (C=O, not observed).

(1S,2S)-1-Phenyl-2-(N-methyl-N-benzamido)propanethiol (7b)

This compound was synthesized in the same way as compound **7a**. From the *cis*-aziridine (**4**) (0.70 g), the main product was obtained (1.09 g, 82% yield) as a white solid, after purification by column chromatography (silica gel, hexane/ethyl

acetate 2:1), mp 95.7-96.2 °C; $[\alpha]_D^{20}$ = +154.8 ° (c 1.50, CH_2Cl_2); ir: (nujol) 2348 (SH), 1620 (C=O); ^1H nmr ($CDCl_3$, 200 MHz): δ 0.99 and 1.08 (d, J = 6.0 Hz and J = 6.8 Hz, 3H), 1.92 and 2.06 (d, J = 4.1 and J = 5.7 Hz, SH), 2.90 and 3.07 (s, 3H), 4.16 (m, 1H), 4.1 and 5.1 (br s, 1H), 7.0-7.6 (m, 10H); ^{13}C nmr ($CDCl_3$): δ 15.58 (q), 15.68 (q), 16.76 (q), 16.84 (q), 26.45 (q), 47.69 (d), 48.55 (d), 59.95 (d), 126.97 (d), 127.35 (d), 127.67 (d), 127.90 (d), 128.43 (d), 128.55 (d), 128.93 (d), 129.34 (d), 129.48 (d), 141.06 (s), 142.33 (s), 172.12 (s); Anal. Calcd for $C_{16}H_{19}NOS$: C, 71,54; H, 6.71. Found: C, 71.01; H, 6.61. The other regioisomer was obtained in about 10% yield although not completely pure as was clear from the ^1H nmr spectrum.

(1R,2S)-1-Phenyl-1-phenylthio-2-(N-methylamino)propane (9)

To a solution of the *trans*-aziridine (**3**) (0.50 g, 3.4 mmol) in 5 ml methanol was added at room temperature a slight excess of thiophenol (0.41 g, 3.7 mmol). The solution was allowed to stand overnight in a stoppered bottle. The solvent and the excess thiophenol were removed under reduced pressure. The product was further purified by eluting over a short pad of alumina with ether. A slightly yellow oil (0.69 g, 87% yield) was obtained; $[\alpha]_D^{20}$ = -219.1 ° (c 1.99, CH_2Cl_2); ^1H nmr ($CDCl_3$, 200 MHz): δ 1.16 (d, J = 6.5 Hz), 1.54 (br s, 1H), 2.40 (s, 3H), 2.99 (m, 1H), 4.33 (d, J = 5.8 Hz, 1H), 7.1-7.4 (m, 10H); ^{13}C nmr ($CDCl_3$): δ 16.99 (q), 33.78 (q), 59.21 (d), 126.47 (d), 127.02 (d), 128.23 (d), 128.51 (d), 131.13 (d), 135.27 (s), 139.97 (s); Anal. Calcd for $C_{16}H_{19}NS$: C, 74.66; H, 7.44. Found: C, 73.95; H, 7.33. Better analysis results could not be obtained for this compound.

(1S,2S)-1-Phenyl-1-phenylthio-2-(N-methylamino)propane (10)

This compound was synthesized and purified in the same way as **5** (*vide supra*). The product was obtained (73% yield) as a colorless oil; $[\alpha]_D^{20}$ = +253.1° (c 1.60, CH_2Cl_2); ^1H nmr ($CDCl_3$, 200 MHz): δ 1.00 (d, J = 6.4 Hz, 3H), 1.8 (br s, 1H), 2.49 (s, 3H), 2.95-3.08 (m, 1H), 4.17 (d, J = 7.9 Hz, 1H), 7.0-7.3 (m, 10H);

^{13}C nmr ($CDCl_3$): δ 17.51 (q), 33.80 (q), 58.69 (d), 59.92 (d), 126.91 (d), 127.13 (d), 128.21 (d), 128.27 (d) 128.56 (d) 128.68 (d), 131.95 (d), 134.93 (s), 140.24 (s); Anal. Calcd for $C_{16}H_{19}NS$: C, 74.66; H, 7.44. Found: C, 73.64; H, 7.30. Better analysis results could not be obtained for this compound.

(4S,5R)-3-(N-Methyl)-4-methyl-5-phenyl-2,2-dimethyl-1,3-thiazolane (14)

trans-Aziridine (**3**) (0.59 g, 4.01 mmol) was dissolved in 5 ml dry acetone and H_2S was gently bubbled through for 15 min. The saturated solution was left standing overnight in a stoppered bottle. After evaporation of the solvent the remaining oil was subjected to column chromatography (silica gel, diethyl ether:hexane 1:15) to yield **14** as a white solid (0.76 g, 86% yield); $[\alpha]_D^{20}$ = +143.8 ° (c 0.91, CH_2Cl_2); mp 70-72 °C; ir: 1029 (C=S); ^1H nmr ($CDCl_3$, 200 MHz): δ 0.81 (d, J = 6.4 Hz, 3H), 1.46 (s, 3H), 1.73 (s, 3H), 2.25 (s, 3H) 3.36 (m, 1H), 4.27 (d, J = 6.0 Hz, 1H), 7.2-7.5 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 17.26 (q), 24.02 (q), 29.64 (q), 32.24 (q), 53.25 (d), 63.69 (d), 126.78 (d), 127.64 (d), 129.57 (d), 142.26 (d). Anal. Calcd for $C_{13}H_{19}NS$: C, 70.54; H, 8.65; N, 6.27; S, 14.46. Found: C, 70.08; H, 8.66; N, 6.27; S, 14.46. HRms calcd m/z 221.124; found: 221.124.

(1R,2S)-1-Phenyl-2-(N-methylamino)propanethiol (11)

Hydrolysis of **14** (0.60 g, 2.71 mmol) was performed by dissolving this compound in a large volume of 2N HCl (200 ml) and distilling off most of the water and the liberated acetone. The reaction can be monitored by measuring the temperature of the distillate. When the temperature reaches 100 °C the reaction is completed. Distilling off all the water gives quantitatively thiolephedrine (**11**) in the form of its HCl salt. Recrystallization from EtOH (96%) gave analytically pure material (0.33 g, 71%), **11**.HCl. mp 198.5-201.2 °C (dec.); ^1H nmr (D_2O, 200 MHz): δ 1.37 (d, J = 6.6 Hz, 3H), 2.74 (s, 3H), 3.73 (m, 1H), 4.46 (d, J = 6.5 Hz, 1H), 7.45 (m, 5H); ^{13}C nmr (D_2O): δ 28.24 (q), 46.93 (q), 61.54 (d), 76.86 (d), 144.25 (d), 145.05 (d), 145.69 (d), 154.63 (s); Anal. Calcd for $C_{10}H_{16}ClNS$: C, 55.16; H, 7.41; N, 6.43; S, 14.72. Found: C, 55.16; H, 7.41; N,

6.68; S, 14.39.

When **11**.HCl was made acid free by washing with dilute base (2N NaOH) the corresponding disulfide (**12**) was obtained after extraction with dichloromethane and removal of the solvent. For purification purposes this was isolated in the form of its bis HCl salt, **12**.2HCl was recrystallized from EtOH (96%); mp 236.3-237.1 °C (decomp.); ^{1}H nmr (D_2O, 200 MHz): δ 1.41 (d, J = 6.4 Hz, 6H), 2.63 (s, 6H), 3.66 (d, J = 8.1 Hz, 2H), 3.78 (m, 2H), 7.3 (m, 4H), 7.5 (m, 6H); ^{13}C nmr (D_2O): δ 29.92 (q), 46.67 (q), 73.52 (d), 73.62 (d), 145.31 (d), 145.97 (d), 151.34 (s); Elemental analysis indicated the presence of one molecule of crystal water. Anal. Calcd for $C_{20}H_{30}N_2Cl_2S_2.H_2O$: C, 53.20; H, 7.14; N, 6.20; S, 14.20. Found: C, 53.15; H, 7.12; N, 6.35; S, 13.87.

(4S,5R)-cis-3-Methylamino-4-methyl-5-phenylthiazolidine-2-thione (15)

To a solution of **3** (0.20 g, 1.36 mmol) in 5 ml carbon tetrachloride was added at room temperature an excess of carbon disulfide (3 ml). The solution was gently refluxed for 12 h. Evaporation of the solvent and the excess carbon disulfide yielded **15** quantitatively as a yellow oil, which crystallized on standing. The solid material was recrystallized from diethyl ether/hexane 1:2 yielding (246 mg, 81%) white needles; mp 68.0-68.1 °C; $[\alpha]_D^{20}$ = -153.0 ° (c 0.52, EtOH); {lit.,[9a]: 65-66 °C; $[\alpha]_D^{25}$ = -155 ° (c 1, EtOH)}

Bis-((1R,2S)-2-dimethylamino-1-phenyl-1-propyl) Disulfide (17)

15 (0.50 g, 2.24 mmol) was reduced with $LiAlH_4$ (0.30 g, 7.91 mmol) according to a literature procedure.[9a] Instead of ether 50 ml dry THF was used. Glauber salt ($Na_2SO_4.10H_2O$) was used for the work-up of this reaction. After quick filtration over Celite the solvent was removed in vacuo. Despite the precautions 5-10% of the disulfide was formed as indicated by the 60 Mhz nmr spectrum. All of the crude material was dissolved in 20 ml ethanol and a stream of air was bubbled through this solution for 1 h. After evaporation of the solvent the disulfde (**17**) was isolated (0.24 g, 54% yield) as a white solid; no trace of the free thiol was found; mp 196.4-197.4 °C (decomp.); {lit.,[9a] mp 196-197 °C}. ^{1}H

nmr ($CDCl_3$, 200 MHz): δ 0.70 (d, J = 6.5 Hz, 6H), 2.14 (s, 12H), 3.02 (m, 2H), 3.58 (d, J = 10.1 Hz, 2H), 7.1-7.4 (m, 10H);^{13}C nmr ($CDCl_3$): δ 9.12 (q), 40.11 (q), 59.07 (d), 63.35 (d), 127.09 (d), 128.17 (d), 129.47 (d), 140.36 (s). HRms m/z calcd 388.201; found: 388.201.

(2S,3S)-1H-2-Methyl-3-phenylaziridine (18)

This compound was synthesized in analogously with compound (**3**). The only difference was found in the reaction time; whereas **3** was formed in a couple of hours the conversion of **18** required three days. Starting from (1*R*,2*S*)-norephedrine (6.56 g) the product was isolated (4,79 g, 83% yield) after bulb-to-bulb distillation (100 °C, 0.6 mm Hg) as a clear oil; ^{1}H nmr ($CDCl_3$, 200 MHz): δ 1.26 (br s, 1H), 1.26 (d, J = 5.5 Hz, 3H), 2.12 (br s, 1H), 2.65 (d, J = 2.7 Hz, 1H), 7.1-7.4 (m, 5H); ^{13}C nmr ($CDCl_3$): δ 19.58 (q), 37.06 (d), 40.44 (d), 125.51 (d), 126.93 (d), 128.43 (d), 140.40 (s). HRms m/z calcd 133.089; found: 133.089.

ACKNOWLEDGEMENT

DSM Research (Andeno) is thanked for financial support of M.A.P., R.P.H. is supported by the Dutch National Research Organization (N.W.O.) administered by the Office for Chemical Research (S.O.N.)

REFERENCES

1. See for example: *Chem. Rev.*, **1992**, *92*, No. 5, which is devoted to enantioselective synthesis.
2. For a review: K. Soai and S. Niwa, *Chem. Rev.*, **1992**, *92*, 833.
3. J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice Hall, Englewood Cliffs, N. J. 1971.
4. a. M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **1986**, *108*, 6071.
   b. A. A. Smaardijk and H. Wynberg, *J. Org. Chem.*, **1987**, *52*, 135.

c. B. T. Cho and Y. S. Chen, *Tetrahedron: Asymmetry*, **1992**, *3*, 1539.

5. S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, **1966**, 5113.

6. a. I. Okada, K. Ichimura, and R. Sudo, *Bull. Chem. Soc. Jpn.*, **1970**, *43*, 1185.

b. R. Appel and R. Kleinstück, *Chem. Ber.*, **1974**, *107*, 5.

7. J. R. Pfister, *Synthesis*, **1984**, 969.

8. L. H. Welsh, *J. Am. Chem. Soc.*, **1947**, *69*, 128; L. H. Welsh, *J. Am. Chem. Soc.*, **1949**, *71*, 3500.

9. a. K. V. Bhat and W.C. McCarthy, *J. Pharm. Sci.*, **1965**, *54*, 225 (*Chem. Abstr.*, **1965**, *63*, 1821h).

b. K. V. Bhat and W.C. McCarthy, *J. Pharm. Sci.*, **1965**, *54*, 488 (*Chem. Abstr.*, **1965**, *63*, 1823d).

c. H. Nishimura and H. Takamatsu, *Yakugaku Zasshi*, **1964**, *84*, 797 (*Chem. Abstr.*, **1965**, *62*, 1587e).

10. J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, **1976**, *41*, 3107.

11. D. Rosenthal, G. Brandrup, K. H. Davis, Jr., and M. E. Wall, *J. Org. Chem.*, **1965**, *30*, 3689.

12. T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **1971**, *36*, 1068.

13. R. P. Hof, M. A. Poelert, N. C. M. W. Peper, and R. M. Kellogg, to be submitted.

Received, 14th June, 1993