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Reaction of *(1S,2S)*-2-Amino-1-phenyl-1,3-propanediol with Thioacids under the Mitsunobu Reaction Condition

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Abstract: The Mitsunibu thioesterification was applied to the title 2-amino-1,3-propanediol (**1**). The regio- and stereochemistry of the reaction was investigated in correlation with the nature of substituents attached to the nitrogen.

In the search for chiral nonracemic 1,3-dithiols, needed for the synthesis of optically active 1,3-dithianes, which we use as building blocks in enantioselective synthesis of isoquinoline alkaloids,[1] our attention was drawn to *(1S,2S)*-2-amino-1-phenyl-1,3-propanediol (**1**). This compound, an industrial waste material, has recently been studied in our laboratory.[2-4] The study included experiments undertaken to convert **1** into the corresponding dithiol.[4] Among others, we have considered the Mitsunobu reaction with the use of thioacids as a possibility of straightforward substitution of thiol for hydroxyl groups.

The importance of the Mitsunobu reaction in organic synthesis as a mild way of converting alcohols into a wide range of functionalities through the action of diethyl azodicarboxylate (DEAD), triphenylphosphine and an acid, is well established.[5,6] The ready and efficient inversion of configuration at the chiral center bearing the hydroxyl group is commonly used for stereoselective transformations of optically active alcohols, though racemization has occasionally been noticed in reactions in which an S_N1 process was strongly favored.[7,8]

In the case of aminoalcohols, however, the steric outcome of these reactions is more complicated because of intramolecular participation of the amine nitrogen and formation of intermediate heterocyclic systems,[6] which occasionally leads to rearrangement products as well. It has been demonstrated that the stereochemical result is strongly dependent on the nature of substituent/s attached to the nitrogen. Thus, reactions of N-*mono*- or N,N-*di*alkyl, or N-tosyl substituted 1,2-aminoalcohols proceed *via* intermediate aziridines or aziridinium ions, respectively, resulting in conformational retention at the stereogenic center, due to two succesive S_N2 processes.[6,9,10] A similar situation, with five-membered oxazolines as intermediates, has been postulated for N-acyl derivatives.[11] Indeed, suitably substituted 1,2-aminoalcohols have been succesfully converted into the corresponding aziridines[12-15] and/or oxazolines[16-18] under itramolecular Mitsunobu reaction conditions, e.g. run in absence of the acidic component. On the other hand, by applying the Mitsunobu procedure to N-alkoxycarbonyl (N-Cbz, N-Boc) protected aminoalcohols the participation of the neighbouring nitrogen could be suppressed[6,19] and the inversion of configuration could be achieved.[10,11]

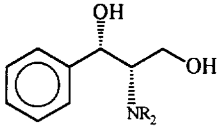
Recently, Kellogg *et al.*[10] have carried out studies on the Mitsunobu reaction applied to various N-substituted diastereomeric ephedrines and related 1,2-aminoalcohols, in the course of which the stereo- and regiochemistry of this reaction was investigated.

This publication prompted us to publish results of our own investigations of the sulfur modified Mitsunobu reaction applied to (*1S,2S*)-2-amino-1-phenyl-1,3-propanediol (**1**).

It should be mentioned that the aminodiol **1** has already been subjected to the Mitsunobu procedure, but in all cases studied the primary hydroxyl was protected either as a tosylate[10] or as silyl ether.[11,13]

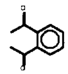
Although we realized that the presence of the second hydroxyl group in the molecule of **1** might cause additional complication during the Mitsunobu reaction, including the possibility of oxygen heterocycles formation[6,20] and acyl group migration, however, being aware of the dramatic influence of the pK_a of the acidic component on the efficiency of this reaction,[21,22] we hoped to be able to overcome this difficulty by using thioacids.

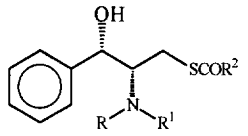
Our initial experiments started with unprotected aminodiol **1**. Subjecting it to the conditions of Mitsunobu esterification with thioacids ended with failure because of formation of unseparable mixtures of products. Far better results were obtained with N-phthaloyl derivative **2**. When **2** and thiolacetic acid were added to a preformed DEAD/PPh_3 complex in THF at 0°C and allowed to stir overnight at room temperature, *mono*thioacetate **3** was formed as the major product (46% yield, m.p. 106 - 108°C, $[\alpha]_D$ -75.0°), while the 1,3-*bis*thioester **4** (m.p.133 - 134°C, $[\alpha]_D$ -281.6°) was produced only in 26% yield. This finding was in accord with the general observation that in the case of primary/secondary diols the acylation of the primary hydroxyl group is predominant.[6,23] The yield of compound **4** could be increased to *ca* 41% by repeating the Mitsunobu procedure using *mono*thioester **3** as a substrate.



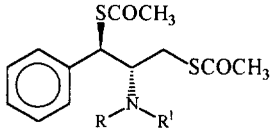
1. $R_2 = H_2$
2. R_2 = Phth

Bn : $CH_2C_6H_5$
Cbz : $COOCH_2C_6H_5$
Phth :





3. R + R^1 = Phth, $R^2 = CH_3$
13. R = R^1 = Bn, $R^2 = CH_3$
14. R = R^1 = Bn, $R^2 = C_6H_5$
15. R = H, R^1 = Cbz, $R^2 = CH_3$



4. R + R^1 = Phth
16. R = H, R^1 = Cbz

Compound **4** was identical with the product which we obtained from the reaction of *(1S,2S)*-2-phthalimido-1-phenyl-1,3-diiodide with potassium thioacetate in DMF, whose *1R,2S* stereochemistry was determined by X-ray crystallographic analysis[4] indicating inversion of configuration at the benzylic carbon atom. It turned out that the nitrogen protected with a phthaloyl group does not influence the steric course of nucleophilic substitution (S_N2) in aminoalcohols.

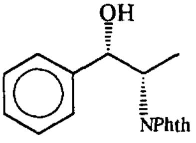
The structure of the *mono*thioacetate **3** was established on the spectroscopic and chemical grounds. In the ^1H NMR spectrum the chemical shift of the H-1 doublet (δ 5.26) was found in the same region as that of the unacylated starting diol **2** (δ 5.23). Of the two acetylthio groups protons evidenced in spectrum of **4** as two singlets at δ 2.27 and 2.38, only the more shielded ones (δ 2.25) were found in the spectrum of **3**.

Table 1. E.I. Mass Spectral Data Representing the Immonium Ions ($\rangle\overset{+}{N}=CH-CH_2X$).

Compound No.	R	R¹	X	m/z (%)
3	Phth		$SCOCH_3$	248 (20)
4	Phth		$SCOCH_3$	248 (100)
6	H	Bn	OH	150 (99.5)
7	Bn	Bn	OH	240 (100)
8	H	COOBn	OH	194 (100)
9	CH_3	Bn	OH	164 (57)
13	Bn	Bn	$SCOCH_3$	298 (100)
14	Bn	Bn	$SCOC_6H_5$	360 (62)
15	H	COOBn	$SCOCH_3$	252 (21)
16	H	COOBn	$SCOCH_3$	251 (60)
17	CH_3	Bn	$SCOC_6H_5$	284 (100)

The site of acylation could be conveniently established by mass spectral data analysis. Under electron impact, in the case of all aminodiols studied, the leading fragmentation pathway involved the C_1-C_2 bond cleavage, resulting in formation of immonium cations ($>\overset{+}{N}=CH-CH_2X$). These cations contained either the primary hydroxyl group (X=OH) or the introduced substituent (X=SCOR) and were easily identified in the spectra by very intense peaks (Table 1).

When compound **3** was stirred with Raney nickel in THF for 1 hour at room temperature, N-phthaloyl *nor*pseudoephedrine (**5**)[24] was isolated in quantitative yield.



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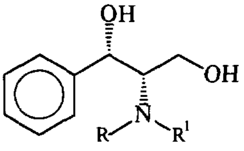
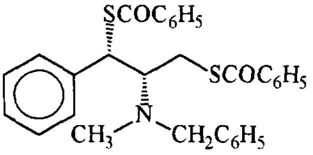


6. R = H, R¹ = Bn
7. R = R¹ = Bn
8. R = H, R¹ = Cbz
9. R = CH$_3$, R¹ = Bn



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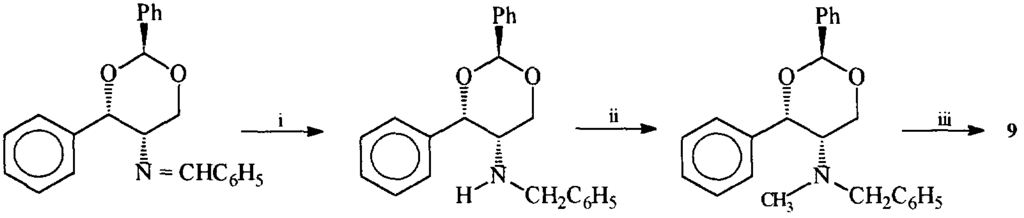
In another series of experiments we considered the choice of other nitrogen protecting groups such as alkyl and alkoxycarbonyl ones. Selective introduction of an alkyl group into this polifunctional system was not an easy task. Among various alkyl groups we were taking into consideration, the N-*mono*- and N,N-*di*benzyl ones could be introduced in a simple procedure and with satisfactory yield.

The *mono* N-benzyl derivative **6** was prepared analogously to the known procedure[25] by refluxing **1** with equimolar amount of benzaldehyde in methanol in the presence of anhydrous cupric sulfate followed by sodium borohydride reduction (76%, m.p. 71.5 - 72.5°C, $[\alpha]_D$ +79.9°).

Treatment of **1** with two molar equivalents of benzyl bromide in aqueous potassium carbonate at reflux for 3 hours[26] resulted in N,N-*di*benzyl derivative 7 (73%, m.p.102.5 - 104°C, $[\alpha]_D$ +92.3°). Attachment of both benzyl groups to the nitrogen could be deduced from the ^{1}H MNR spectrum, in which the four protons of the two methylene groups appeared as two doublets at δ 3.79 and δ 4.07 with a coupling constant J=13.1Hz. On acetylation with excess of acetic anhydride in pyridine, compound 7 incorporated two O-acetyl moieties which could be detected as two three-proton singlets at δ 1.98 and δ 2.16 in the ^{1}H NMR spectrum and as strong carbonyl absorptions at 1722 and 1735cm^{-1} in the IR spectrum.



10 **11** **12**

i : NaBH$_4$, MeOH ; ii : CH$_3$I/NaH, THF ; iii : 1%HCl

The synthesis of N-benzyl-N-methyl-aminodiol **9** needed a four-step reaction sequence. It started with the known[27] 1,3-dioxane **10**, obtained by dissolving hydrobromide of **1** in excess of benzaldehyde and treating the mixture with P_2O_5. Sodium borohydride reduction of **10** in methanol converted the Schiff base into N-benzyl derivative **11** (83%, m.p.65.5 - 67.5°C, $[\alpha]_D$+73.2°). The methylene protons of the N-benzyl group could be found as two doublets at δ 3.55 and δ 3.71 with a coupling constant J = 13.9Hz. Compound **11** under the action of NaH/CH$_3$I in THF was methylated to give N-benzyl-N-methyl-1,3-dioxane **12** (84%, m.p.74 - 75.5°C, $[\alpha]_D$ +89.2°), whose N-methyl group protons appeared as a three-proton singlet at δ 2.42. Acid-catalysed hydrolysis of the acetal function in **12** with 1% hydrochloric acid afforded the aminodiol **9** (98%, oil, $[\alpha]_D$ +86.1°). Under the action of Mitsunobu reagents with the use of both thiolacetic and thiobenzoic acids, the N-*mono*benzyl diol **6**, like the unsubstituted **1**, produced only unseparable mixture of products, while compound **7** was converted into monosubstitution products, thioacetate **13** (oil, $[\alpha]_D$ +71.4°) or thiobenzoate **14** (oil, $[\alpha]_D$ +107.0°), isolated in ca.64 and 50% yield, respectively. The doubly substituted products were formed in trace amounts, and were difficult to purify. Several attempts undertaken to substitute both hydroxyl functions by varying the reaction conditions (solvent, excess of the reagent, temperature, reaction time) failed. Exchange of the primary hydroxyl group could be confirmed by the mass spectra of both compounds, **13** and **14**, in which the presence of the corresponding immonium cations was evidenced by peaks at m/z 298 (100%) and m/z 360 (62%), respectively (Table 1).

The reaction with thiolacetic acid applied to Cbz-derivative **9**[25] produced the *mono*thioacetate **15** (45%, m.p. 95.5 - 97.5°C, $[\alpha]_D$ -20.4°) as the main product, and the *bis*thioacetate **16** (10%, m.p. 66 - 68°C, $[\alpha]_D$ -174.7°) as the minor one. The expected inversion of configuration at the benzylic C-1 stereogenic center in compound **16** followed from the value of the H-1/H-2 vicinal coupling constant, J=5.8Hz, which was characteristic of *erythro*-aminoalcohols. It has been well established that the benzylic proton in *erythro*-1,2-aminoalcohols assumes J values between 2 - 7Hz, while in the *threo*- diastereomers - between 7 - 9Hz.[10]

When compound **8** in THF was treated with PPh_3/DEAD in the presence of thiobenzoic acid, both hydroxyl groups were substituted affording the *bis*thiobenzoate **17** (42 - 62%, m.p. 102 - 103.5°C, $[\alpha]_D$ +115.6°) as the major product. This compound crystallized in pure form from crude products mixture when dissolved in methanol. Surprisingly, only traces of a *mono*substituted product could be isolated from the reaction mixture. The steric course of the latter experiment was expected to proceed with retention of configuration at the benzylic carbon. Indeed, this could be deduced from the value of the H-1/H-2 vicinal coupling constants of **17**, J = 7.97Hz, characteristic of *threo*-isomers.[10] The same was true for all *1S,2S* diastereomeric aminoalcohols described in this paper for which these values were 7.1 - 9.7Hz, with the exception of compound **3**, for which J = 6.64Hz.

The above presented results seem to confirm the postulated dependence of the steric course of the Mitsunobu reaction on the nature of nitrogen substitution when applied to aminoalcohols. In N-*mono*- or N,N-*di*alkyl substituted 2-amino-1,3-diols, like in 1,2-aminoalcohols, a retention of configuration should be expected, while in N-alkoxycarbonyl or phthaloyl derivatives this reaction involves inversion of configuration.

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Experimental Section:

General: Melting points: determined on a Koffler block. IR spectra: Perkin-Elmer 180 in KBr pellets. ^1H-NMR and ^{13}C-NMR: Varian Gemini 300, TMS as internal standard. Mass spectra, (EI): Jeol-D-100, 75 eV. Specific rotation: Perkin-Elmer Polarimeter 243B at 20°C. Merck Kieselgel 60 (70-230 mesh) was used for column chropatography and Merck DC-Alufolien Kieselgel 60 F_{254} for TLC. *(1S,2S)*-2-Amino-1-phenyl-1,3-propanediol was purchased from Fluka AG.

Preparation of N-protected aminodiols for the Mitsunobu thioesterification.

(1S,2S)-2-Benzylamino-1-phenyl-1,3-propanediol (**6**).

A mixture of compound **1** (1.67g, 10mmol) and benzaldehyde (1.06g, 10mmol) in methanol (10ml) and catalytic amount of anhydrous cupric sulfate was stirred at reflux for 3hrs. The catalyst was filtered off and sodium borohydride (0.6g, 15mmol) was added to the filtrate at 0°C. This mixture was stirred overnight at room temperature then water (10ml) was added and the solution concentrated at reduced pressure. The residue was acidified with 5% hydrochloric acid and extracted with ethyl ether. The acidic aqueous solution was rendered alkaline with 20% sodium hydroxide and extracted with ethyl ether. The combined organic extracts were dried (Na_2SO_4) and concentrated to give crystalline **6** (1.95g, 76%); m.p. 71.5 -72.5°C (ethyl ether/hexane), $[\alpha]_D$ +79.4° (c=1, acetone). IR (KBr) cm^{-1}: 3600 - 2200 (broad). ^1H NMR ($CDCl_3$) δ: 2.59 - 2.63 (s, broad,*exchanges with D_2O*, 2H, NH,OH), 2.79 (td, $J_{2,3'}$=3.6Hz, $J_{2,3}$=3.8Hz, $J_{2,1}$=7.1Hz, 1H, H-2), 3.36 (dd, $J_{3',2}$=3.6Hz, $J_{3',3}$=11.2Hz, 1H, H-3'), 3.65 (dd, $J_{3,2}$=3.9Hz, $J_{3,3'}$=11.2Hz, 1H, H-3), 3.66 and 3.79 (2d, J=13.2Hz,1H each, CH_2Ph), 4.64 (d, $J_{1,2}$=7.1Hz, 1H, H-1), 7.24 - 7.37 (m, 10H, Ar-H). EI MS m/z (%): 226 (4), 151 (26), 150 (99.5), 118 (3), 105 (4), 92 (17), 91 (100), 79 (6), 77 (17). Found: C 74.54; H 7.48; N 5.42. $C_{16}H_{19}NO_2$ (257.3) req.: C 74.68; H 7.44; N 5.44%.

(1S,2S)-2-Dibenzylamino-1-phenyl-1,3-propanediol (7).

A mixture of aminodiol **1** (1.67g, 10mmol), benzyl bromide (3.4g, 20mmol), potassium carbonate (5.5g, 40mmol) and water (8.5ml) was heated under reflux for 3h. After cooling the mixture was extracted with ethyl ether and the basic substances were taken into 1% hydrochloric acid. The aqueous acidic solution was rendered alkaline with 20% sodium hydroxide and reextracted with ethyl ether. The organic phase was dried (Na_2SO_4) and the solvent evaporated to give 3.22g of crude product, which was crystallized from ethyl ether/hexane to deposit pure **7** (2.54g, 73%); m.p. 102.5 - 104°C, $[\alpha]_D$ +92.3° (c=1, acetone). IR (KBr) cm^{-1}: 3600 - 2700 (broad). ^1H-NMR ($CDCl_3$) δ: 1.62 (s, *broad,* 1H, *exchanges with D_2O,*OH), 2.94 (ddd, $J_{2,1}$=9.7Hz, $J_{2,3}$=7.7Hz, $J_{2,3'}$=4.1Hz, 1H, H-2), 3.46 (dd, $J_{3',2}$=4.1Hz, $J_{3',3}$=11.4Hz, 1H, H-3'), 3.64 (dd, $J_{3,2}$=7.7Hz, $J_{3,3'}$=11.3Hz, 1H, H-3), 3.78 and 4.07 (2d, J=13.1Hz, 4H, NCH_2Ph), 4.18 (s, broad, 1H, *exchanges with D_2O,* OH), 4.59 (d, $J_{1,2}$=9.7Hz, 1H, H-1), 7.13 - 7.16 and 7.23 - 7.38 (2m, 15H, Ar-H). EI MS m/z (%): 241 (11), 240 (100), 180 (3), 91 (75), 89 (2), 79 (3), 77 (3). Found: C 79.56; H 7.21; N 4.02; $C_{23}H_{25}NO_2$ (347.4) req.: C 79.50; H 7.25; N 4.03%.

O,O-Diacetyl derivative of **7**; m.p. 106 - 108°C (ethyl ether/hexane), $[\alpha]_D$ +45.4° (c=1, acetone). IR (KBr) cm^{-1}: 1722 and 1735. ^1H-NMR ($CDCl_3$) δ: 1.98 and 2.16 (2s, 3H each, $COCH_3$), 3.39 (m, 1H, H-2), 3.72 and 3.94 (2d, J=13.7Hz, 4H, NCH_2Ph), 3.97 (dd, $J_{3',2}$=6.0Hz, $J_{3',3}$=11.0Hz, 1H, H-3'), 4.12 (dd, $J_{3,2}$=5.0Hz, $J_{3,3'}$=11.0Hz, 1H, H-3), 6.05 (d, $J_{1,2}$=8.5Hz, 1H, H-1), 7.18 - 7.31 (m, 15H, Ar-H). CI MS m/z (%): 283 (9), 282 (38), 92 (3), 91 (100), 77 (2). Found: C 75.08; H 6.71; N 3.19. $C_{27}H_{29}NO_4$ (431.5) req.: C 75.15; H 6.77; N 3.25%.

(1S,2S)-2-(N-benzyl-N-methylamino)-1-phenyl-1,3-propanediol (**9**).

a) *(2S,4S,5S)-5-Benzylamino-2,4-diphenyl-1,3-dioxane* (**11**).

Compound **10**[27] (7.2g, 22.7mmol) dissolved in methanol (150ml) was treated slowly with $NaBH_4$ (1.3g, 34.1mmol) at 0°C, then stirred at room temperature overnight. Water (10ml) was added and methanol removed under reduced pressure. The resulting slurry was extracted with ethyl ether until Dragendorff test was negative and the basic material was taken into 5% hydrochloric acid. The aqueous acidic solution was alkalized with 20% sodium hydroxide and extracted with ethyl ether. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure to give **11** (6.67g, 84%); m.p. 65 - 67.5°C (ethanol); $[\alpha]_D$ + 73.2° (c=1, acetone). IR (KBr) cm^{-1}: 3600 - 3300 (broad). ^1H-NMR ($CDCl_3$) δ: 1.93 (s, broad, *exchanges with D_2O*, 1H, NH), 2.74 (m, 1H, H-5), 3.55 and 3.71 (2d, J=13.9Hz, 2H, CH_2Ph), 4.10 (dd, $J_{6',5}$=1.7Hz, $J_{6',6}$=11.5Hz, 1H, H-6'), 4.23 (dd, $J_{6,5}$=1.6Hz, $J_{6,6'}$=11.5Hz, 1H, H-6), 5.13 (d, $J_{4,5}$=2.1Hz, 1H, H-4), 5.76 (s, 1H, H-2), 6.96 - 7.62 (m, 15H, Ar-H). EI MS m/z (%): 345 (M^+) (<1), 239 (8), 209 (8), 197 (30), 167 (10), 148 (12), 133 (100), 118 (38), 105 (50), 91 (97), 77 (55), 65 (38). Found: C 79.91; H 6.75; N 4.01; $C_{23}H_{23}NO_2$ (345.4) req.: C 79.97; H 6.71; N 4.06%.

b) *(2S,4S,5S)-5-(N-benzyl-N-methylamino)-2,4-diphenyl-1,3-dioxane* (**12**).

Compound **11** (3.93g, 11.3mmol) was dissolved in DMF (23 ml) and cooled to 0°C, then sodium hydride (0.54g, 22.6mmol) was added portionswise and the mixture was stirred at room temperature for 30 min before methyl iodide (0.8 ml) was added. The reaction mixture was left in the refrigerator for 3 days, then poured onto ice and allowed to reach room temperature. The solid was filtered off, dissolved in ethyl ether, washed with water, dried and concentrated to give compound **12** (3.95g, 96.4%); m.p. 74 - 75.5°C (ethanol),

$[\alpha]_D$ +89.2° (c=1.03, acetone). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (s, 3H, NCH_3), 8.26 (m, 1H, H-5), 3.52 and 4.05 (2d, J_{gem}=13.8Hz, 1H each, 2H, CH_2Ph), 4.20 (dd, $J_{6',5}$=3.1Hz, $J_{6',6}$=12.5Hz, 1H, H-6'), 4.76 (d, broad, $J_{6,6'}$=12.5Hz, 1H, H-6), 5.27 (d, $J_{4,5}$=3.7Hz, 1H, H-4), 5.79 (s, 1H, H-2), 6.79 - 7.59 (m, 15H, Ar-H). EI MS m/z (%): 395 (M^+) (1), 253 (1), 197 (7), 162 (7), 147 (100), 146 (70), 132 (15), 105 (10), 91 (57), 77 (8). Found: C 80.05; H 7.04; N 3.92; $C_{24}H_{25}NO_2$ (359.4) req.: C 80.19; H 7.01; N 3.90%.

c) *(1S,2S)-2-(N-benzyl-N-methylamino)-2-phenyl-1,3-propanediol* (**9**).

Compound **12** (3.1g, 8.6mmol) in 1% hydrochloric acid (18ml) was heated at reflux under argon for 2hrs. After cooling, benzaldehyde was removed by extraction with ethyl ether and the remainding aqueous solution was rendered alkaline with 20% sodium hydroxide and extracted with ethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated to give compound **8** (2.3g, 99%), oil, $[\alpha]_D$ +86.1° (c=1, acetone). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (s, 3H, NCH_3), 2.90 (dddd, $J_{2,1}$=9.8Hz, $J_{2,3}$=8.2Hz, $J_{2,3'}$=4.1Hz, 1H, H-2), 3.39 (dd, $J_{3',2}$=4.1Hz, $J_{3',3}$=11.5Hz, 1H, H-3'), 3.59 (dd, $J_{3,2}$=8.2Hz, $J_{3,3'}$=11.5Hz, 1H, H-3), 3.93 (ABq, J=13.0Hz, 2H, CH_2Ph), 4.49 (d, $J_{1,2}$=9.8Hz, 1H, H-1), 7.25 - 7.36 (m, 10H, Ar-H). EI MS m/z (%): 271 (M^+) (1), 165 (7), 164 (57), 92 (8), 91 (100), 77 (5). Found: C 74.32; H 7.82; N 4.73. $C_{17}H_{21}NO_2$ (271.3) · 1/4 H_2O req.: C 74.00; H 7.86; N 5.08.

General procedure for Mitsunobu reaction:

A complex of triphenylphosphine (2.2mmol) and diethyl azodicarboxylate (2.2mmol) in THF (5ml) was formed at 0°C under argon atmosphere for 30 min. Aminodiol (1mmol) in THF (4 - 5ml) was added dropwise followed by the thioacid (2.2mmol). The mixture was stirred at 0°C for 1hr, then at room temperature overnight. THF was removed under reduced pressure and the residue dissolved in benzene (ca 5ml) and chilled. The precipitate was filtered off, solvent evaporated from the filtrate and the crude reaction mixture was dissolved in ethyl ether (ca 10ml) and left at room temperature overnight. The side-products were removed again by filtration and the filtrate concentrated to an yellow oil, which was chromatographied on silicagel (1:10) with hexane - ethyl acetate (gradient 98:2 to 80:20).

(1S,2S)-1-Phenyl-2-phthalimido-3-mercapto-1-propanol 3-acetate (**3**).

Was obtained from N-phthaloyl derivative **2**^{2} (4mmol) and thiolacetic acid in THF. Yield: 46%; m.p. 106 - 108°C (ethanol), $[\alpha]_D$ -75.0°(c=1, acetone), IR (KBr) cm^{-1}: 3520, 1770, 1710, 1678. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (s, 3H, $COCH_3$), 3.31 (dd, $J_{3',2}$=4.5Hz, $J_{3',3}$=14.2Hz,1H, H-3'), 3.53 (dd, $J_{3,2}$=10.6Hz, $J_{3,3'}$=14.2Hz, 1H, H-3), 3.82 (d, $J_{OH,1}$=8Hz, 1H, *exchanges with* D_2O, OH), 4.78 (ddd, $J_{2,1}$=6.3Hz, $J_{2,3}$=10.8Hz, $J_{2,3'}$=4.2Hz, 1H, H-2), 5.26 (t, broad, $J_{1,2}$=ca7Hz, $J_{1,OH}$=ca 7Hz, *after exchange with* D_2O d, $J_{1,2}$=6.6Hz, 1H, H-1) 7.22 - 7.40 and 7.67 - 7.80 (2m, 9H, Ar-H). EI MS m/z (%): 356 $(M+1)^+$ (<1), 280 (15), 249 (27), 248 (20), 206 (30), 188 (10), 175 (15), 174 (100), 173 (36), 147 (6), 130 (10), 107 (19), 91 (4), 79 (10), 77 (13). Found: C 64.17; H 4.73; N 3.92. $C_{19}H_{17}NO_4S$ (355.4) req.: C 64.21; H 4.82; N 3.94.

(1R,2S)-1-Phenyl-2-phthalimido-1,3-propaneditihiol diacetate (**4**).

Yield: 26%; m.p. 133 - 134°C (ethanol); $[\alpha]_D$-281.6° (c=1, acetone).This compound was identical with a derivative prepared from *(1S,2S)*-1-Phenyl-2-phthalimido-1,3-diiodide and potassium thioacetate in DMF^4.

(1S,2S)-2-Dibenzylamino-1-phenyl-3-mercapto-1-propanol 3-acetate (**13**).

Yield: 69%; colorless oil, $[\alpha]_D$ +71.4° (c=1, acetone). IR (KBr) cm^{-1}: 3420, 1685. ^{1}H NMR ($CDCl_3$) δ : 2.22 (3, 3H, $COCH_3$), 2.76 (dd, $J_{3',2}$=6.1Hz, $J_{3',3}$=13.9Hz, 1H, H-3'), 2.92 (td, $J_{2,1}$=9.3Hz, $J_{2,3}$=5.9Hz, $J_{2,3'}$=6.1Hz, 1H, H-2), 3.31 (dd, $J_{3,2}$=5.9Hz, $J_{3,3'}$=13.9Hz, 1H, H-3), 3.65 and 4.00 (2d, J=13.0Hz, 2H each, N-CH_2Ph), 4.46 (d, $J_{1,2}$=9.3Hz, 1H, H-1), 4.57 (s, broad, 1H, *exchanges with* D_2O,, OH), 7.08 - 7.11 and 7.24 - 7.38 (2m, 15H, Ar-H). EI MS m/z (%): 316 (2), 299 (18), 298 (100), 256 (7), 181 (3), 149 (2), 132 (2), 117

(3), 107 (2), 106 (3), 105 (6), 91 (25), 89 (3), 77 (14). Found: C 73.26; H 6.59; N 3.39. $C_{25}H_{27}NO_2S$ (405.5) · $1/4H_2O$) req.: C 73.22; H 6.76; N 3.42%.

(1S,2S)-2-Dibenzylamino-1-phenyl-3-mercapto-1-propanol 3-benzoate (**14**).

Yield: 48%; colorless oil; $[\alpha]_D$+107.1° (c=0.7 acetone). IR (KBr) cm^{-1}: 3410, 1660. ^{1}H-NMR ($CDCl_3$) δ: 2.96 (dd, $J_{3',2}$=5.9Hz, $J_{3',3}$=13.7Hz, 1H, H-3'), 3.09 (td, $J_{2,1}$=9.1Hz, $J_{2,3'}$=2.9Hz, $J_{2,3}$=5.9Hz, 1H, H-2), 3.50 (dd, $J_{3,2}$=5.9Hz, $J_{3,3'}$=13.7Hz, 1H, H-3), 3.74 and 4.05 (2d, J=13.0Hz, 2H each, CH_2Ph), 4.53 (d, $J_{1,2}$=9.1Hz, 1H, H-1), 4.61 (s, broad, 1H, *exchanges with D_2O*, OH), 7.12 - 7. 86 (m, 20H, Ar-H). EI MS m/z (%): 362 (3), 361 (16), 360 (62), 149 (5), 132 (4), 119 (2), 115 (2), 107 (5), 106 (14), 105 (100), 104 (2), 97 (3), 95 (3), 92 (5), 91 (62), 86 (2), 84 (2), 81 (2), 79 (9), 78 (8), 77 (15). Found: C 75.81; H 6.30; N 2.83. $C_{30}H_{29}NO_2S$ (467.6) · $1/2H_2O$ req.: C 75.59; H 6.34; N 2.93%.

(1S,2S)-2-Benzyloxycarbonylamino-1-phenyl-3-mercapto-1-propanol 3-acetate (**15**).

Yield: 44%; m.p. 95.5 - 97.5°C (ethyl ether/hexane); $[\alpha]_D$ -20.4° (c=1.05 acetone). IR (KBr) cm^{-1}: 3340 (broad), 1695 (broad). ^{1}H NMR ($CDCl_3$) δ: 2.37 (s, 3H, $COCH_3$), 2.99 (dd, $J_{3',2}$=6.7Hz, $J_{3',3}$=14.2Hz, 1H, H-3'), 3.26 (dd, $J_{3,2}$=7.9Hz, $J_{3,3'}$=14.2Hz, 1H, H-3), 3.41 (d, $J_{NH,2}$=4.1Hz, 1H, *exchanges with D_2O*, NH), 3.92 (m, 1H, H-2), 4.81 (s, broad, 1H, OH), 4.99 (ABq, J=12.4Hz, 2H, CH_2Ph), 5.29 (d, $J_{1,2}$=8.8Hz, 1H, H-1), 7.22 - 7.33 (m, 10H, Ar-H). EI MS m/z (%): 284 (20), 253 (5), 252 (21), 226 (4), 210 (7), 209 (4), 208 (26), 179 (8), 178 (75), 166 (26), 118 (9), 117 (9), 108 (17), 107 (42), 105 (14), 92 (30), 91 (100), 89 (6), 79 (65), 77 (60). Found: C 63.43; H 5.88; N 3.88. $C_{19}H_{21}NO_4S$ (359.4) req.: C 63.49; H 5.89; N 3,90%.

(1R,2S)-2-Benzyloxycarbonylamino-1-phenyl-1,3-propanedithiol diacetate (**16**).

Yield: 10%; m.p. 66 - 68°C (ethanol); $[\alpha]_D$ -175.5° (c=1, acetone); IR (KBr) cm^{-1}: 3310, 1715, 1695. ^{1}H-NMR ($CDCl_3$), δ: 2.26 (2s, 3H each, $COCH_3$), 2.96 (dd, $J_{3',2}$=9.6Hz, $J_{3',3}$=14.0Hz, 1H, H-3'), 3.07 (dd, $J_{3,2}$=4.3Hz, $J_{3,3'}$=14.0Hz, 1H, H-3), 4.30 (dddddd,$J_{2,1}$=5.4Hz, $J_{2,NH}$=9.7Hz, $J_{2,3}$=4.4Hz, $J_{2,3'}$=9.7Hz, 1H, H-2), 4.83 (d, $J_{NH,2}$=10.0Hz, 1H, NH), 4.88 (d, $J_{1,2}$=5.8Hz, 1H, H-1), 5.06 (ABq, J=12.4Hz, 2H, CH_2Ph), 7.26 7.37 (m, 10H, Ar-H). EI MS m/z (%): 252 (60), 208 (18), 123 (11), 91 (100). Found: C 60.35; H 5.42; N 3.28; $C_{21}H_{23}NO_4S_2$ (417.5) req.: C 60.41; H 5.55; N 3.35%.

(1S,2S)-2-N-methyl-N-benzylamino-1-phenyl-1,3-propanedithiol dibenzoate (**17**).

Yield: 42 - 62%. m.p. 102 - 103.5°C (ethanol), $[\alpha]_D$+115.6° (c=1, acetone). IR (KBr) cm^{-1}: 1660, 1645; ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H, N-CH_3), 3.07 (dd, $J_{3',2}$=5.5Hz, $J_{3',3}$=13.7Hz, 1H, H-3'), 3.30 (dd, $J_{3,2}$=9.2Hz, $J_{3,3'}$=13.7Hz, 1H, H-3), 3.54 (m, 1H, H-2), 3.93 (ABq, J=13.7Hz, 2H, CH_2Ph), 6.26 (d, $J_{1,2}$=8.0Hz, 1H, H-1), 7.16 - 7.62 (m, 16H, Ar-H), 7.93 and 8.13 (2d, J=7.2Hz, 2H each, Ar-H). EI MS m/z (%): 359 (3), 284 (100), 223 (2), 178 (2), 146 (5), 132 (2), 121 (2), 106 (7), 105 (97), 91 (75), 77 (29). Found: C 72.59; H 5.78; N 2.70. $C_{31}H_{29}NO_2S_2$ (511.7) req.: C 72.76; H 5.71; N 2.74%.

(1S,2S)-N-Phthaloylnorpseudoephedrine (**5**).

Compound **3** (0.16g, 0.45mmol) in THF (10ml) and Raney nickel catalyst (50% slurry in water, pH >9; ca.1.5g) were stirred at room temperature for 1h. The catalyst was filtered off, washed with $CHCl_3$ and the combined filtrates were concentrated under reduced pressure to give crystalline **5** (0.11g, 87%). m.p. 160 - 161.5°C (methanol), (lit.:[24] m.p. 156 - 158), $[\alpha]_D$+51.6° (c=1, acetone), (lit.:[24] $[\alpha]_D$ +50.0°), identical by TLC and spectral data with an authentic sample.[24]

References

1. Representative examples: Rozwadowska, M.D.; Matecka, D. *Tetrahedron* **1988**, *44*, 1221.; Rozwadowska, M.D.; Matecka, D.; Brózda, D. *Liebigs Ann. Chem.* **1991**, 73.
2. Rozwadowska, M.D. *Tetrahedron: Asymmetry* **1993**, *4*, 1619; **1994**, *5*, 1327.

3. Rozwadowska, M.D. *Pol. J. Chem.* **1994**, *68*, 2271.
4. Fiedorow, P.; Ratajczak-Sitarz, M.; Rozwadowska, M.D.; Rozwadowski, Z. *in press.*
5. Mitsunobu, O. *Synthesis* **1981**, 1.
6. Hughes, D.L. *Organic Reactions* **1992**, *42*, 335; *Org. Prep. Proceed. Int.* **1996**, *28*, 127.
7. Warmerdam, E.G.; Brussee, J.; Krause, C.G.; van der Gen, A. *Tetrahedron* **1993**, *49*, 1063.
8. Brown, R.F.C.; Jackson, W.R.; McCarthy, T.D. *Tetrahedron Lett.* **1993**, *34*, 1195; *Tetrahedron* **1994**, *50*, 5469.
9. Freedman, J.; Vaal, M.; Huber, E.W. *J. Org. Chem.* **1991**, *56*, 670.
10. Poelert, M.A.; Hulshof, L.A.; Kellogg, R.M. *Rec. Trav. Chim. Pay-Bas* **1994**, *113*, 355.
11. a) Lipshutz, B.H.; Miller, T.A. *Tetrahedron Lett.* **1990**, *31*, 5253; b) Lipshutz, B.H.; Huff, B.E.; McCarthy,K.E.; Miller, T.A.; Mukarram, S.M.J.; Siahaan, T.J.; Vaccaro, W.D.; Webb, H.; Falick, A.M. *J. Am. Chem. Soc.* **1990**, *112*, 7032.
12. Pfister, J.R. *Synthesis* **1984**, 969.
13. Fujii, N.; Nakai, K.; Habashita, H.; Hotta, Y.; Tamamura, H.; Otaka, A.; Ibuka, T. *Chem. Pharm. Bull.* **1994**, *42*, 2241.
14. Chrney, R.J.; Wang, Li *J. Org. Chem.* **1996**, *61*, 2544.
15. Solomon, M.E.; Lynch, C.L.; Rich, D.H. *Synthetic Commun.* **1996**, *26*, 2723.
16. Roush, D.M.; Patel, M.M. *Synthetic Commun.* **1985**, *15*, 675.
17. Galeotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807.
18. Wipf, P.; Miller; C.P. *Tetrahedron Lett.* **1992**, *42*, 6267.
19. Castejon, P.; Pasto, M.; Moyano, A.; Pericas, M.A.; Riera, A. *Tetrahedron Lett.* **1995**, *36*, 3019.
20. Carlockm, J.T.; Mack, M.P. *Tetrahedron Lett.* **1978**, 5153.
21. Martin, S.F.; Dodge, J.A. *Tetrahedron Lett.* **1991**, *32*, 3017.
22. Dodge, J.A.; Trujillo, J.I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.
23. Mitsunobu, O.; Kimura, J.; Inzumi, K.; Yanagida, N. *Bull. Chem. Soc. Jap.* **1976**, *49*, 510.
24. Boerner, A.; Krause, H. *Tetrahedron Lett.* **1989**, *30*, 929; *Journal f. prakt. Chemie* **1990**, *332*, 307.
25. Brunner, H.; Altman, S. *Chem. Ber.* **1994**, *127*, 2285.
26. Dix, D.; Imming, P. *Arch. Pharm. (Weinheim)* **1995**, *328*, 510.
27. Wienges, K.; Klotz, K.-P.; Droste, H. *Chem. Ber.* **1980**, *113*, 710.

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