

Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1667-1674, 1995 Copyright © 1995 Elsevier Science Ltd Printed in Great Britain. All rights reserved 0957-4166/95 \$9.50+0.00

0957-4166(95)00211-1

# **Nucleophilic Ring Opening of Cyclic Sulphamidites**

Hanna S.H. Gautun and Per H.J. Carlsen

Organic Chemistry Laboratories, University of Trondheim-NTH,N-7034 Trondheim, Norway

Abstract: The cyclic sulphamidites (2S,4S)- and (2R,4S)-3-benzyl-4-benzyloxymethyl-2-oxo-1,2,3-oxathiazolidine 1 were prepared from S-glycidol in 60-66 % overall yield. Nucleophilic ring opening of 1 by cyanide, azide and benzyloxy anions have been studied with respect to regio and stereospecificity. A mild procedure for benzylation of alcohols was introduced.

As part of an ongoing project dealing with 2-amino-1,3-propandiol derivatives we have been studying the development of methods for transforming the amino alcohol moiety into other desirable, chiral compounds, e.g. vicinal diamino alcohols and unnatural  $\alpha$ - and  $\beta$ -amino acids. The most widely used precursors for such compounds are the naturally occuring  $\alpha$ -amino acids.<sup>1</sup> Unfortunately, these starting materials only offer specific substitution patterns in their carbon backbone. Utilizing the easily accessible epoxy alcohols as chiral sources for the 2-amino-1,3-propandiol moiety opens up new routes towards the desired substitution patterns as outlined in Scheme 1.



#### Scheme 1

However, the similar reactivity of the three functional groups make selective protection, and in some cases activation necessary in order to preform the desired transformations. This selectivity problem may be overcome by application of the corresponding oxazolidinones,<sup>2</sup> oxazolines,<sup>3</sup> or by enzymatic methods.<sup>4</sup>

In recent years cyclic sulphamidates have proven to be useful intermediates for transforming amino alcohols to other compounds.<sup>5,6</sup> Usually these sulphamidates are prepared by treatment of the respective amino alcohols with thionyl chloride and subsequent oxidation with ruthenium tetroxide. Unfortunately, such an oxidation is not always feasible due to the presence of other oxidizable groups in the substrate. In some cases this problem may be overcome by direct treatment of the amino alcohol with sulphuryl chloride.<sup>6,7</sup> This method, however, often leads to complex product mixtures. Another problem that may be encountered is that the resulting sulphamidate is too reactive to be isolated.<sup>8</sup> These considerations, together with the benefit of reducing the number of reactions would encourage the use of the more stable sulphamidites. Although there are several reports on regioselective ring opening of cyclic sulphites by soft nucleophiles<sup>9,10</sup> there are, to our knowledge, no reports of selective, nucleophilic ring opening of cyclic sulphamidites. Thus, we decided to investigate the potential of this type of reaction. In order to reduce any substituent effects we chose the rather simple serinol based sulphamidite 1 as a model compound.

Our initial studies were preformed on racemic material. Here the cyclic sulphamidites 1 were prepared from glycidol in an overall yield of 47 % (Scheme 2) as a mixture of two diastereoisomers, 1a and 1b. The ratio varied between 1:2 and 1:1 (GC analysis), depending on the work-up conditions. Since the diastereoisomers 1a and 1b were inseparable by flash chromatography, their relative configurations remained unknown. The crude product mixtures were used directly in the subsequent ring opening reactions.



*i*) BnNCO, Na<sub>2</sub>CO<sub>3</sub>, tol., 111 °C, 76 %; *ii*) NaH, THF, 2 °C - r.t., 86 %; *iii*) BnBr, NaH, DMF, r.t. 73 %; *iv*) NaOH, H<sub>2</sub>O, EtOH, reflux, 87 %; *v*) SOCl<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 91-99 %.

## Scheme 2

The cyclic sulphamidite functionality has two centers capable of reacting with nucleophiles, the activated  $C_5$  position and the sulphur position, as shown in Scheme 3. Our initial aim was to study the regioselectivity of the reaction.



The reactions were allowed to run until the starting material was completely consumed (GC and TLC analysis of the reaction mixture), and then worked up under acidic conditions (0.1 M HCl). This caused the intermediate sulphinate ester / sulphinamide to hydrolyze to the respective products, **5** and **6**. The content of **5** reflected the degree of attack at the sulphur position. As can be seen from Table 1, the relatively soft cyanide and azide anions attacked regioselectively at the  $C_5$  position of the sulphamidite ring, affording high yields of the products **6a** and **6b**. The benzyloxy anion, on the other hand, gave a mixture of products indicating a degree of attack

## Cyclic sulphamidites

at the sulphur atom of 68 %. Earlier observations on nucleophilic ring openings of cyclic sulphites<sup>9</sup> have demonstrated an increased reactivity towards the harder sulphur atom site, relative to the softer  $C_5$  site, for harder, less polarizable nucleophiles. This correlates well with the results in Table 1.

	Reaction Conditions	<b>5</b> : 6ª	Isolate Yield (%)
a	NaCN, DMF, 120 °C, 10 h.	0:100	80
b	NaN <sub>3</sub> , DMF, 120 °C, 6 h.	0:100	90
с	BnOH, NaH, DMF, 120 °C, 8 h.	68 : 32	24 <sup>b</sup>

Table 1. Nucleophilic Ring Opening of Cyclic Sulphamidites 1

a) GC analysis before and after work-up gave the same product ratios. b) Yield of 5 + 6c.

Our next aim was to examine the robustness of this procedure towards racemization. Optically active 1 was prepared from S(-)-glycidol (80 % e.e.) using the same strategy as for the synthesis of the racemic material. However, a few modifications of the applied procedures were necessary in order to maintain the optical activity (Scheme 4).



*i*) Method A: Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 18 h., 78 %; Method B: K<sub>2</sub>CO<sub>3</sub>, DMF, 70 °C, 86 %; *ii*) Et<sub>3</sub>N, BnBr, DMF, 120 °C, 93 %; *iii*) NaOH, H<sub>2</sub>O, EtOH, reflux, 87 %; *iv*) SOCl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 95 %.

## Scheme 4

Thus, cyclization of the benzyl glycidyl carbamate 2 by NaH in THF lead to total loss of the optical activity, probably due to internal transacylation,<sup>11</sup> involving an internal attack of the alcholate anion on the carbonyl function in the ring. Two alternative methods were applied for the preparation of the oxazolidinone *S*-3. Refluxing of *S*-glycidol and benzyl isocyanate in the presence of triethylamine (1.8 eq) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 M) according to a method described by Katsumura *et al*<sup>12</sup> gave 78 % of *S*-3 exhibiting  $[\alpha]_D$  -27.68 (c = 1.20, CHCl<sub>3</sub>). On the other hand, warming of glycidol and benzyl isocyanate in the presence of 2 mole % of K<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> in DMF at 70 °C also afforded 3 in good yield (80 - 86 %),  $[\alpha]_D$  -27.49 (c = 1.0, CHCl<sub>3</sub>). We were

not able to determine the e.e. of **3**. However, comparison with the optical data reported by Katsumura<sup>12</sup> indicated that little or no racemization had occurred. The observed racemization of **3** in the presence of NaH prompted us to seek a milder method for preparing the benzyl ether *S*-**4**, avoiding strong bases. Application of Widmers method<sup>13</sup> for benzylation of base labile hydroxyl groups using benzyl trichloro-acetamidate furnished 65 % of **4**. The yields obtained by this method suffered from difficulties in separating the product and the benzylating agent. Therefore, a new, mild modification of the benzylating reaction was developed using benzyl bromide and triethylamine in DMF at 120 °C. This afforded the desired, optically active compound, *S*-**4**, in 93 % yield. Alkaline hydrolysis of the oxazolidinone to the amino alcohol *R***-5** (83 % yield) followed by treatment with thionyl chloride gave two diastereoisomeric sulphamidites **1** in an overall yield of 60-66 %.

Next (+)-1 was treated with NaCN according to the standard procedure (DMF, 110 °C). Unfortunately, the isolated product proved to be optically inactive **6a**. Derivatisation with *R* and *S*- $\alpha$ -methoxyphenyl acetic chloride and subsequent GC analysis confirmed the presence of a racemate. Ring opening of 1 with LiCN (DMF, 110 °C) gave the same result. Other, less alkaline conditions offering nucleophilic addition of NC described in the literature; TMS-CN in DMF, TMS-CN + YbCl<sub>3</sub> x 6 H<sub>2</sub>O cat. in DMF,<sup>14</sup> and LiCN in THF<sup>15</sup> promoted little or no reaction at all. The mechanism for the formation of racemic **6a** is uncertain, but may be rationalised by assuming the involvement of the relatively acidic protons  $\alpha$  to the electron withdrawing nitrile group. A tentative mechanism involving a [1,3] shift is outlined in Scheme 5.



## Scheme 5

Ring opening of 1 with NaN<sub>3</sub>, on the other hand, afforded optically active **6b** (90 % yield),  $[\alpha]_D +7.2$  (c = 1.18, CHCl<sub>3</sub>). All attempts to determine the e.e. of **6b** failed. However, reduction of **6b** to the diamine 7 followed by derivatization with Mosher's chloride indicated 80±2 % e.e. (GLC analysis). This value when corrected for the enantiomeric purity of the starting material (S-glycidol, e.e. 80 %), indicated that essentially no racemization had taken place during the synthesis of 7 from 1. These results were also confirmed by <sup>1</sup>H NMR in the presence of Eu(tfc)<sub>3</sub>.

In conclusion, optically active sulphamidites 1 have been prepared from glycidol (80 % e.e.) in an overall yield of 60-66 %. 1 was ring opened regioselectively at the C-5 position by NC<sup>-</sup> and N<sub>3</sub><sup>-</sup>. Ring opening with NaCN or LiCN in DMF caused complete racemization of the product, while ring opening with NaN<sub>3</sub> furnished **6b** (80±2 % e.e.), indicating little or no racemization.

### Experimental

All reactions were carried out under a nitrogen atmosphere, using commercial chemicals of p.a. quality without further purification unless otherwise stated. All solvents were dried prior to use as described elsewhere<sup>16</sup>. Melting points were determined on a Buchi apparatus and are uncorrected. Flash chromatography was carried out using Merck's Kieselgel 60 (230 - 400 mesh). GLC analysis was performed on a Perkin Elmer Auto System gas chromatograph equipped with a Chrompack CP sil 5CB capillary column (25 m). Optical rotations were measured with a Perkin Elmer 241 Polarimeter. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) were obtained with a JEOL JNM-EX 400 FT NMR SYSTEM spectrometer. All NMR spectra refer to deuterochloroform solutions with tetramethylsilane (TMS) as reference. IR spectra were recorded with a Nicolet 20SXC FT-IR spectrometer. Mass spectra were registered by an AEI MS 902 mass spectrometer. The elemental analysis were performed by Analytische Laboratorien<sup>17</sup>.

**Benzyl glycidyl carbamate** (2) A mixture of glycidol (1.25 g, 16.9 mmole) and sodium carbonate (0.20 g, 1.9 mmole) in toluene (20 ml) was added a solution of benzyl isocyanate (2.25 g, 16.9 mmole) in toluene (20 ml). The mixture was refluxed for 2 h., cooled and filtered. Evaporation of the solvent from the filtrate afforded 3.04 g of a light yellow oil. Purification by flash chromatography (acetone : n-hexane = 20 : 80) afforded 2.66 g (76 % yield) of **2** as a colorless oil. <sup>1</sup>H NMR:  $\delta$  2.65 (dd, J = 2.9 Hz, J = 2.5 Hz, 1H), 2.84 (br. t, J = 4.4 Hz, 1H), 3.20-3.24 (m, 1H), 3.92 (dd, J = 6.4 Hz, J = 12.2 Hz, 1H), 4.38 (d, J = 5.9, 2H), 4.47 (dd, J = 2.9 Hz, J = 12.2 Hz, 1H), 5.12 (br. s, 1H), 7.28-7.36 (m, 5H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  44.5, 45.1, 49.7, 65.5, 127.5, 128.6, 138.2, 156.0 p.p.m.; IR (neat) 3337 (br. m), 3063 (w), 3031 (w), 2930 (w), 1708 (s), 1532 (m), 1455 (m), 1434 (w), 1247 (m), 1143 (m), 1129 (m), 1080 (w), 1042 (w), 1003 (w) cm<sup>-1</sup>; MS (170 °C, 50 eV) *m/z* (% rel. int.) 207 (*M*<sup>+</sup>, 7), 151 (10), 150 (99), 133 (32), 132 (16), 107 (17), 106 (54), 105 (16), 104 (20), 92 (7), 91 (100), 89 (5), 79 (26), 78 (15), 77 (23), 65 (13), 63 (5), 57 (9), 56 (18), 55 (10); HRMS: Observed *M*<sup>+</sup> 207.0897. Calc. C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub> 207.0895

(2R)-Benzyl glycidyl carbamate (R-2) was prepared from freshly distilled S-(-)-glycidol according to the above mentioned procedure in 73 % yield. mp. 31.5 - 32.5 °C;  $[\alpha]_D$  -22.2 (c = 1.02, CHCl<sub>3</sub>).

**Racemic 3-benzyl-4-hydroxymethyl-2-oxazolidinone (3)** A suspension of NaH (0.51 g, 21,3 mmole) in THF (40 ml) was cooled on an ice-water bath to 2 °C and a solution of 2 (4.30 g, 20.8 mmole) in THF (80 ml) added dropwise over a period of 30 min. The temperature was maintained below 5 °C for 2 h. and then allowed to rise to 20 °C. The pH of the mixture was adjusted to 5 by addition of aq. HCl (9 M), and the solvent evaporated under reduced pressure. The residue was treated with water (60 ml) and extracted with  $CH_2Cl_2$  (3 x 75 ml). Washing of the combined organic phases with brine (1 x 60 ml), drying (MgSO<sub>4</sub>) and evaporation of the solvent afforded 4.40 g of a light yellow oily product. Flash chromatography (acetone : n-hexane = 40 : 60) gave 3.69 g (86 % yield) of pure 3 as a white, crystalline material. mp. 68.5 - 69.5 °C; <sup>1</sup>H NMR:  $\delta$  2.90 (br s, 1H), 3.53 (br d, 1H), 3.68-3.76 (m, 2H), 4.26-4.33 (m, 2H), 4.26 (d, *J* = 15.1 Hz, 1H), 4.71 (d, *J* = 15.1 Hz, 1H), 7.28-7.37 (m, 5H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  46.3, 55.9, 60.4, 64.6, 128.1, 129.0, 136.1, 159.2 p.p.m.; IR (neat) 3422 (m), 2963 (m), 2945 (m), 2928 (m), 1722 (s), 1488 (m), 1474 (s), 1447 (s), 1356 (m), 1333 (m), 1252 (s), 1210 (m), 1196 (m), 1173 (m), 1091 (s), 1031 (s), 968 (m), 769 (m), 752 (m), 700 (s), 623(m), 604 (m), 588 (m), 572 (m), 536 (m) cm<sup>-1</sup>; MS (170 °C, 50 eV) *m/z* (% rel.int.) 208 (*M*+1, 2), 207 (*M*<sup>+</sup>, 14), 176 (30), 91 (100); HRMS: Observed *M*<sup>+</sup> 207.0898. Calc.  $C_{11}H_{13}NO_3$  207.0895

(4S)-3-benzyl-4-hydroxymethyl-2-oxazolidinone (S-3) Method A: (According to Katsumura et  $al^{12}$ ) A solution of freshly distilled S-(-)-glycidol (2.00 g, 27.0 mmole), benzyl isocyanate (3.59 g, 27.0 mmole) and triethylamine (4.91 g, 4.9 mmole) in CH<sub>2</sub>Cl<sub>2</sub> (17.9 ml) was refluxed for 18 h. The reaction was cooled to room temperature, more CH<sub>2</sub>Cl<sub>2</sub> (150 ml) and 0.1 M HCl (75 ml) was added, followed by dropwise addition 2 M

HCl until the pH was approximately 4. The phases were separated and the organic phase washed with water (2 x 50 ml) and brine (1 x 50 ml). Drying (MgSO<sub>4</sub>) and evaporation of the solvent gave 4.76 g of a yellow, semicrystalline product. Flash chromatography (acetone : n-hexane = 40 : 60) afforded 4.36 g (78 % yield) of *S*-3 as a white, crystalline material, exhibiting the same spectroscopic properties as the racemic product. mp. 71-73 °C,  $[\alpha]_D$  -27.68 (c = 1.20, CHCl<sub>3</sub>)[lit.<sup>12</sup> *R*-3; 84 %, 74-75 °C,  $[\alpha]_D$  +29.8 (c = 1.03, CHCl<sub>3</sub>)]. *Method B*: A solution of freshly distilled *S*-(-)-glycidol (0.15 g, 2.0 mmole), benzyl isocyanate (0.27 g, 2.0 mmole) and K<sub>2</sub>CO<sub>3</sub> (0.0035 g, 0.03 mmole) in DMF (10 ml) was stirred at 70 °C for 3 h. The reaction was cooled to room temperature and the solvent evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), washed with water (1 x 5 ml) and brine (1 x 5 ml), and dried (MgSO<sub>4</sub>). Evaporation of the solvent and flash chromatography afforded 0.36 g (86 % yield) of *S*-3 as a white, crystalline product, with spectroscopic properties in accordance to the racemic product. mp. 71.5-73.0 °C,  $[\alpha]_D$  -27.49 (c = 1.02, CHCl<sub>3</sub>).

(4*S*)-3-Benzyl-4-benzyloxymethyl-2-oxazolidinone (*S*-4) A mixture of *S*-3 (1.37 g, 6.62 mmole), triethylamine (1.21 g, 11.98 mmole) and benzyl bromide (5.45 g, 31.87 mmole) in DMF (13 ml) was heated at 120 °C for 13 h. The reaction was then cooled to room temperature, diluted with ether (100 ml), and washed with water (3 x 15 ml) and brine (1 x 15 ml). Drying (MgSO<sub>4</sub>) and evaporation of the solvent in vacuo gave 4.19 g of a brown liquid product. Flash chromatography (acetone : n-hexane = 25 : 75) afforded 1.83 g (93 % yield) of pure *S*-4 as a light yellow oil.  $[\alpha]_D$  +6.68 (c = 1.19, CHCl<sub>3</sub>); <sup>1</sup>H NMR:  $\delta$  3.45 (d, *J* = 4.9 Hz, 2H), 3.77 (m, 1H), 4.12 (dd, *J* = 5.9 Hz, *J* = 8.3 Hz, 1H), 4.15 (d, *J* = 15.1 Hz, 1H), 4.29 (dd with the appearance of a tripl., *J* = 8.8 Hz, 1H), 4.44, 4.46 (AB system *J* = 12.0 Hz, 2H), 4.74 (d, *J* = 15.1 Hz, 1 H), 7.23 -7.39 (m, 10H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  46.6, 54.1, 64.9, 69.1, 73.4, 127.8, 127.9, 128.1, 128.2, 128.6, 128.7, 136.1, 137.3, 158.5 p.p.m.; IR (neat) 3063 (w), 3030 (w), 2915 (m), 2864 (m), 1750 (s), 1497 (m), 1477 (m), 1454 (m), 1439 (m), 1421 (m), 1361 (m), 1252 (m), 1203 (m), 1183 (m), 1097 (m), 1067 (m), 1046 (m), 762 (m), 738 (m), 700 (m) cm<sup>-1</sup>; MS (170 °C, 50 eV) *m/z* (% rel. int.) 298 (M+1, 3), 297 (M<sup>+</sup>, 15), 206 (29), 176 (51), 92 (19), 91 (100), 65 (13); HRMS: Observed *M*<sup>+</sup> 297.1366. Calc. C<sub>18</sub>H<sub>19</sub>NO<sub>3</sub> 297.1365

(2*R*)-2-Benzylamino-3-benzyloxy-propan-1-ol (*R*-5) To a solution of *S*-4 (5.47 g, 18.4 mmoles) in 96 % ethanol (140 ml) was added aq. sodium hydroxide (2 M, 95 ml) and the mixture refluxed for 7 h. The mixture was then cooled and the ethanol evaporated in vacuo. The resulting aqeous emultion was then extracted continously with ethyl acetate. Drying of the organic phase (MgSO<sub>4</sub>) and evaporation of the solvent afforded 5.04 g of a white oil. Flash chromatography (ethyl acetate : 25 % aq. NH<sub>4</sub>OH = 95 : 5) gave 4.33 g (87 % yield) of a colorless oil (>99 % pure on GC) which crystallized upon storage at - 20 °C. mp 35 - 36 °C;  $[\alpha]_D$  +13.3 (c = 1.01, CHCl<sub>3</sub>); <sup>1</sup>H NMR:  $\delta$  2.97 (m, 1H), 3.52 (dd, *J* = 4.9 Hz, *J* = 11.2 Hz, 2H), 3.57 (m, 2H), 3.69 (dd, *J* = 4.4 Hz, *J* = 11.2 Hz, 1H), 3.85 (s, 2H), 4.48, 4.52 (AB system, *J* = 12.2 Hz, 2H), 7.24 - 7.38 (m, 10H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  51.0, 57.8, 61.2, 70.1, 73.4, 127.4, 127.7, 127.8, 128.4, 128.5, 128.6, 137.9, 139.0 p.p.m.; IR (neat) 3331 (br, m), 3087 (m), 3029 (m), 2922 (m), 2854 (m), 1604 (m), 1496 (m), 1453 (m), 1412 (w), 1365 (w), 1092 (s), 1053 (m), 1028 (m), 736 (w), 698 (m) cm<sup>-1</sup>; MS (170 °C, 50 eV) *m/z* (% rel. int.) 271 (*M*<sup>+</sup>, 0.8), 240 (8), 150 (23), 108 (6), 107 (6), 106 (17), 104 (8), 92 (16), 91 (100), 77 (10), 65 (8), 58 (7), 56 (7); HRMS: Observed: *M*<sup>+</sup> 271.1569. Calc. for C<sub>17</sub>H<sub>21</sub>NO<sub>2</sub> : *M* 271.1572

(2S,4S)- and (2R,4S)-3-Benzyl-4-benzyloxymethyl-2-oxo-1,2,3-oxathiazolidine (1) A solution of thionyl chloride (0.44 g, 3.7 mmole) in  $CH_2Cl_2$  (35 ml) was cooled to -78 °C and a solution of **R-5** (0.55 g, 2.0 mmole) and triethylamine (0.76 g, 7.5 mmole) in  $CH_2Cl_2$  (20 ml) added via syringe, over a period of 20 min. The reaction was stirred at - 78 °C for 3 h. The solvent was then evaporated and the residue washed with dry ether (4 x 40 ml). Evaporation of the solvent yielded 0.61 g (95 % yield) of a dark brown oil (diastereomeric ratio 65 : 35, inseparable by flash chromatography). <sup>1</sup>H NMR: (1a)  $\delta$  3.31 (part of an ABX pattern, coupling

in dd, J = 6.8 Hz, J = 9.3 Hz, 1H), 3.38 (part of an ABX pattern coupeling in dd, J = 4.9 Hz, J = 9.3 Hz, 1H), 3.77 (m, 1H), 4.20, 4.28 (AB pattern, J = 14.2 Hz, 2H), 4.39 (dd, J = 4.4 Hz, J = 8.8 Hz, 1H), 4.43 (s, 2H), 4.87 (dd, J = 7.3 Hz, 8.8 Hz, 1H), 7.21 - 7.39 (m, 10H) p.p.m.; (1b)  $\delta$  3.59 - 3.70 (m, 3H), 4.31 (d, J = 3.4Hz, 2H), 4.46 (d, J = 2.0 Hz, 2H), 4.55 (dd, J = 6.4 Hz, J = 8.8 Hz, 1H), 4.73 (dd, J = 5.9 Hz, J = 8.8 Hz, 1H), 7.21 - 7.39 (m, 10H) p.p.m.; <sup>13</sup>C NMR: (1a)  $\delta$  49.4, 58.7, 70.0, 72.8, 73.5, 127.7, 127.9, 128.0, 128.5, 128.6, 129.0, 136.5, 137.5 p.p.m.; (1b)  $\delta$  49.9, 60.4, 71.1, 73.6, 74.7, 127.7, 127.9, 128.1, 128.4, 128.8, 136.2, 137.6 p.p.m.; IR (neat) 3063 (w), 3031 (w), 2959 (m), 2925 (m), 2902 (m), 2861 (m), 1725 (w), 1040 (w), 1603 (w), 1496 (m), 1454 (m), 1365 (m), 1276 (w), 1207 (w), 1156 (s), 1118 (s), 1102 (s), 1076 (m), 1027 (m), 955 (m), 736 (s), 698 (s) cm<sup>-1</sup>; MS (200 °C, 70 eV) *m/z* (% rel.int.) 317 (*M*<sup>+</sup>, 0.4), 196 (18), 92 (8), 91 (100); HRMS: Observed: *M*<sup>+</sup> 317.1092. Calc. for C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>S : *M* 317.1086.

General procedure for nucleophilic ring opening of 1: A solution of 1 (0.20 g, 0.6 mmole) in DMF (7 - 14 ml) was added to the nucleophile (1.3 - 2.7 eq.) and stirred at 110 °C until all sulphamidite was consumed. The reaction was then cooled to room temperature and diluted with ether (50 ml) and extracted thrice with aq. HCl (0.1 M). Aq. NaOH (2 M) was added to the combined aq. phases until a of pH 9 - 10 was obtained, and then it was extracted with ether (5 x 50 ml). Washing of the combined organic phases with brine (1 x 50 ml), drying (MgSO<sub>4</sub>) and evaporation of the solvent afforded a crude oily product.

**3-Benzylamino-4-benzyloxy-butyronitrile (6a)** Treatment of 1 (0.46 g, 1.5 mmole) with sodium cyanide (0.26 g, 4.0 mmole) according to the general procedure gave 0.54 g of a crude product, which was purified by flash chromatography (acetone : n-hexane = 20 : 80) to yield 0.33 g (80 % yield) of a light yellow oily product,  $[\alpha]_D$  0 (c = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  1.79 (br. s, 1H), 2.54 (d, *J* = 5.9 Hz, 2H), 3.09 (m, 1H), 3.54 (d, *J* = 5.4 Hz, 2H), 3.78, 3.83 (AB pattern, *J* = 13.2 Hz, 2H), 4.48 - 4.54 (m, 2H), 7.29 - 7.51 (m, 10H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  20.7, 51.1, 53.4, 70.4, 73.4, 118.0, 127.2, 127.7, 127.9, 128.0, 128.5, 137.6, 139.6 p.p.m.; IR (neat) 3329 (w), 3029 (w), 2922 (s), 2854 (s), 2247 (w), 1603 (w), 1495 (m), 1453 (s), 1418 (w), 1364 (m), 1258 (w), 1206 (m), 1101 (s), 1028 (m), 736 (s), 698 (s) cm<sup>-1</sup>; MS (180 °C, 50 eV) *m/z* (% rel.int.) 280 (*M*<sup>+</sup>, 0.3), 159 (31), 107 (11), 106 (9), 92 (9), 91 (100), 65 (6). *Elem. Anal.* found % (cald. for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O) C, 76.98 (77.11); H, 7.20 (7.19); N, 9.95 (9.99).

(2S) 2-Benzylamino-3-benzyloxy-propyl-1-azid (6b) A solution of 1 (0.31 g, 1.0 mmole) in DMF (13 ml) was treated with sodium azide (0.36 g, 5.5 mmole) according to the general procedure. This gave 0.32 g of an orange oil, which was purified by flash chromatography (diethyl ether : n-hexane = 35 : 65) furnishing 0.26 g (90 % yield) of a light yellow, oily product.  $[\alpha]_D +7.2$  (c = 1.18, CHCl<sub>3</sub>); <sup>1</sup>H NMR:  $\delta$  1.71 (br. s, 1 H), 2.96 (pentet, J = 5.4 Hz, 1H), 3.37 and 3.43 (part of ABX pattern, J = 5.4 Hz, J = 12.2 Hz, 2H), 3.49 and 3.52 (part of ABX pattern, J = 5.4 Hz, J = 9.8 Hz, 2H), 3.80, 3.83 (AB pattern, J = 13.2 Hz, 2H), 4.49, 4.52 (AB pattern, J = 11.7 Hz, 2H), 7.22 - 7.41 (m, 10 H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  51.5, 52.2, 56.6, 69.8, 76.7, 127.1, 127.7, 127.8, 128.1, 128.5, 138.0, 140.1 p.p.m.; IR (neat) 3334 (w), 2900 (w), 2858 (w), 2099 (s), 1453 (m), 1273 (m), 1099 (m), 1028 (m), 735 (m), 697 (m) cm<sup>-1</sup>; MS (180 °C, 50 eV) *m/z* (% rel.int.) 241 (3), 240 (11), 175 (15), 133 (9), 107 (9), 92 (8), 91 (100), 79 (16), 77 (6), 65 (14); *Elem. Anal.* found % (calcd. for C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O) C, 69.11 (68.90); H, 6.91 (6.80); N, 18.87 (18.90).

**2-Benzylamino-1,3-dibenzyloxypropane** (6c) A suspension of NaH (0.02 g, 0.8 mmole) in DMF (2 ml) was stirred on an ice-water bath for 20 min. To this mixture was added a solution of **1** (0.20 g, 0.6 mmole) in DMF (5 ml). The reaction was warmed to 110 °C and treated according to the general procedure for ring opening of **1**, giving 0.06 g of a brown oily product containing 68 % **5** and 32 % **6c**. The presence of **6c** was confirmed by co-injection (GLC) with an authentic sample prepared by benzylation of **5**, and by spectroscopy after flash chromatography (ethyl acetate : n-hexane = 30 : 70). <sup>1</sup>H NMR:  $\delta$  1.92 (br. s, 1H), 3.06 (m, 1H), 3.52 (dd, J

= 5.7 Hz, J = 9.3 Hz, 2H), 3.56 (dd, J = 4.9 Hz, J = 9.3 Hz, 2H), 3.82 (s, 2H), 4.48 (s, 4H), 7.20-7.34 (m, 15 H); <sup>13</sup>C NMR:  $\delta$  52.7, 56.6, 70.4, 73.2, 126.8, 127.5, 127.6, 128.1, 128.3, 138.3, 140.6; IR (neat) 3326 (w), 3062 (w), 3028 (m), 2899 (m), 2858 (m), 1495 (m), 1453 (s), 1364 (m), 1099 (s), 1028 (m); MS (170 °C, 50 eV) m/z (% rel. int.) 241 (4), 240 (22), 107 (6), 92 (5), 91 (100), 77 (6), 65 (10); *Elem. Anal.* found % (calcd. for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>) C, 79.80 (79.75); H, 7.53 (7.53); N, 3.89 (3.87).

(2*S*)-*N*-2-benzyl-3-benzyloxy-propane-1,2-diamine (7) A solution of **6b** (0.07 g, 0.24 mmole) and triphenylphosphine (0.07 g, 0.27 mmole) in THF (4 ml) containing water (0.02 ml) was stirred at room temperature for 14 h. and then concentrated in vacuo. Flash chromatography (methanol : ethyl acetate : NH<sub>4</sub>OH = 20 : 80 : 1) of the residue afforded 0.04 g (62 % yield) of **7** as a colorless oil.  $[\alpha]_D$  +16.7 (c = 0.69, CHCl<sub>3</sub>); <sup>1</sup>H NMR:  $\delta$  1.87 (br.s, 3 H), 2.71 (dd, *J* = 5.9 Hz, *J* = 12.2 Hz, 1H), 2.79 (m, 1H), 2.85 (dd, *J* = 4.9 Hz, *J* = 12.2 Hz, 1H), 3.49 (dd, *J* = 5.4 Hz, *J* = 9.8 Hz, 1H), 3.54 (dd, *J* = 4.9 Hz, *J* = 9.8 Hz, 1H) 3.77, 3.82 (AB system, *J* = 13.2 Hz, 2H), 4.50 (s, 2H), 7.21 - 7.36 (m, 10H) p.p.m.; <sup>13</sup>C NMR:  $\delta$  42.9, 51.4, 58.5, 70.8, 73.3, 126.9, 127.7, 128.1, 128.4, 138.3, 140.7 p.p.m.; IR (neat) 3364 (m), 3309 (m), 3086 (m), 3061 (m), 3028 (m), 2899 (m), 2860 (s), 1603 (m), 1496 (m), 1453 (s), 1363 (m), 1099 (s), 1028 (m), 737 (s), 698 (s) cm<sup>-1</sup>; MS (170 °C, 50 eV) *m/z* (% rel.int.) 240 (16), 189 (7), 92 (10), 91 (100), 82 (30).

Acknowledgement: The authors wish to thank Borregaard Fine Chemicals and The Norwegian Research Council for financial support.

#### References

- 1. Coppola, G.M.; Schuster, H.F." Asymmetric Synthesis" John Wiley & Sons, New York, 1987.
- 2. See for example: a) Katsumura, S.; Yamamoto, N.; Morita, M.; Han, Q. Tetrahedron Asym. 1994, 5, 161-164; b) Sibi, M.P.; Renhowe, P.A. Tetrahedron Lett. 1990, 31, 7407-7410.
- See for example: (a) Gant, T.G.; Meyers, A.I. *Tetrahedron* 1994, 50, 2297-2360. (b) Atami, A.; El Hallaoui, A.; El Hajji, S. Synt. Commun. 1991, 21, 2383-2390.
- 4. Liu, K.K.-C.; Nozaki, K.; Wong, C.-H. Biocatalysis 1990, 3, 169-177.
- Baldwin, J.E.; Spivey, A.C.; Schofield, C.J. Tetrahedron Asymmetry 1990, 1, 881-884; White, G.J.; Garst, M.E. J. Org. Chem. 1991, 56, 3177-3178.
- 6. Alker, D.; Doyle, K.J.; Harwood, L.M.; McGregor, A. Tetrahedron Asymmetry 1990, 1, 877-880.
- Rosenberg, S.H.; Dellaria, J.F.; Kempf, D.J.; Hutchins, C.W.; Woods, K.W.; Maki, R.G.; de Lara, E.; Spina, K.P.; Stein, H.H.; Cohen, J.; Baker, W.R.; Plattner, J.J.; Kleinert, H.D.; Perun, T.J. J. Med. Chem. 1990, 33, 1582-1590.
- 8. Kuyl-Yeheskiely, E.; Lodder, M.; van der Marel, G.A.; Boom, J.H. Tetrahedron Lett. 1992, 33, 3031-3016.
- 9. Carlsen, P.H.J.; Aase, K. Acta Chem. Scand. 1993, 47, 617-619; Nymann, K.; Svendsen, J.S.; ibid 1994, 48, 183-186.
- Kim, B.M.; Sharpless, B.K. Tetrahedron Lett. 1990, 31, 4317-4320; Gao, Y.; Zepp, C.M. Tetrahedron Lett. 1991, 32, 3155-3158; Lohray, B.B.; Ahuja, J.R. J. Chem. Soc. Chem. Commun. 1991, 95-97; Guiller, A.; Gagnieu, C.H.; Pacheco, H. Tetrahdron Lett. 1985, 6343-6344. El Meslouti, A.; Beaupere, D.; Demailly, G.; Uzan, R. Tetrahedron Lett. 1994, 35, 3913-3916. Carlsen, P.H.J.; Aase, K. Acta Chem. Scand. 1993, 47, 737-738.
- 11. (a) Roush, W.R.; Brown, R.J.; DiMare, M. J. Org. Chem. 1983, 48, 5083-5093. (b) Roush, W.R.; Adam, M.A. ibid 1985, 50, 3752-3757.
- 12. Katsumura, S.; Kondo, A.; Han, Q. Chem. Lett. 1991, 7, 1245-1248.
- 13. Widmer, U. Syn. Commun. 1987, 568-570.
- 14. Matsubara, S.; Onishi, H.; Utimoto, K. Tetrahedron Lett. 1990, 31, 6209-6212.
- 15. Ciaccio, J.A.; Stanescu, C.; Bontemps, J. Tetrahedron Lett. 1992, 33, 1431-1434.
- 16. Perrin, D.D.; Armarago, W.L.F. Purification of Laboratory Chemicals 3rd ed.; Pergamon Press: Oxford, 1988.
- 17. Analytische Laboratorien, Fritz-Pregl-Strasse 24, D-51647 Gummersbach, Germany.

(Received in UK 4 May 1995; accepted 6 June 1995)