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Attempted Enantioselective Synthesis of Terbutaline. Unexpected Partial Racemization During Lithium Aluminium Hydride Reduction of a Secondary Amide

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Abstract

Syntheses leading to compounds related to the bronchodilator (−)-terbutaline via optically active cyanohydrins suffered unexpected partial racemization during lithium aluminium hydride reduction of key amide intermediates.

Introduction

We have been using the dipeptide-catalysed enantioselective addition of hydrogen cyanide to aryl aldehydes as a key step in the preparation of enantiomerically enriched pharmaceuticals.[1–4] We recently described the enantioselective synthesis of compounds related to the bronchodilators (−)-salbutamol (6; Ar = 4-hydroxy-3-(hydroxymethyl)phenyl) and (−)-terbutaline (6; Ar = 3,5-dihydroxyphenyl).[1] The reaction sequence involved the use of expensive t-butyldimethylsilyl protecting groups and a diisobutylaluminium hydride reduction of a protected cyanohydrin. In this paper we describe attempts to convert the key enantiomerically enriched cyanohydrins into β-hydroxy amines by an alternative route based on a previously published Japanese patent.[5]

Results and Discussion

Reactions Involving 3-Phenoxybenzaldehyde Cyanohydrin (2a)

The sequence shown in Scheme 1 can be applied to the synthesis of (−)-terbutaline (6; Ar = 3,5-dihydroxyphenyl) and (−)-salbutamol (6; Ar = 4-hydroxy-3-(hydroxymethyl)phenyl). The sequence was first evaluated with 3-phenoxybenzaldehyde (1a) as its cyanohydrin (2a) was available in reasonable

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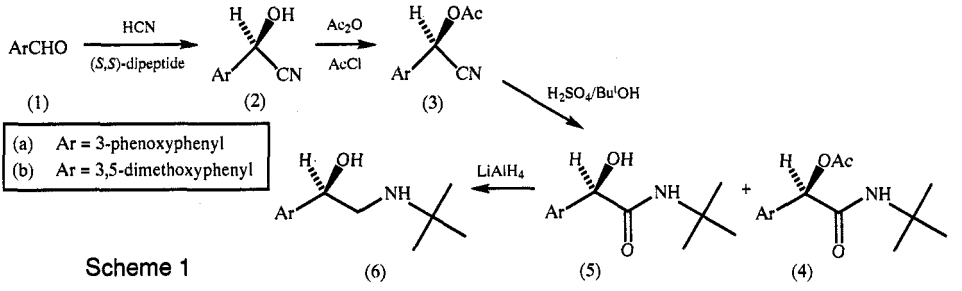

Scheme 1

quantities with moderately high enantiomeric excess (79%) as well as in racemic form. Acetylation (*c.* 90%) was followed by a Ritter reaction which gave a mixture of the hydroxy amide (5a) together with its acetate derivative (4a) in 60–65% yield. The hydroxy and acetoxy amides were readily separated by radial chromatography and the individual compounds or the mixture reduced to the *β*-hydroxy amine (6a) in high yield (82–95%). A sample of (2a) with an e.e. value of 79% was taken through the same reaction sequence. The e.e. value of the hydroxy amide (5a) was estimated from a ^{1}H n.m.r. spectrum recorded in (D_6)benzene in the presence of *O*-acetylmandelic acid.[6] The signals due to the Bu^t groups were clearly separated for the two enantiomers and the e.e. value was the same as that of the starting material (76%) within experimental error. It was not possible to determine the e.e. value of the acetoxy amide (4a) by this method and mild methods of hydrolysis which did not induce any racemization were sought. The mild hydrolysis method using KCN/MeOH[7] failed to give any product and a more conventional hydrolysis using LiOH in aqueous methanol gave a high yield (88%) of completely racemic material. Attempted hydrolysis with mild acid, *p*-toluenesulfonic acid/MeOH, was not successful but hydrolysis with 3 M HCl/acetone gave the hydroxy amide (5a) in good yield (81%) and without any racemization (e.e. 78%). Thus the initial cyanohydrin could be protected and converted into both the acetoxy amide (4a) and the hydroxy amide (5a) without any racemization.

Reduction of the 3 : 1 mixture of (4a) and (5a) or reduction of (4a) with lithium aluminium hydride in tetrahydrofuran under reflux gave the *β*-hydroxy amine (6a) in high yield but with e.e. values of *c.* 40% in each case. This partial racemization was surprising as closely related hydroxy amides, PhCH(OH)CONHMe[8] and PhCH(OH)CONHPr^i,[9] have been reduced with lithium aluminium hydride under very similar conditions without any reported racemization. However, the methyl[8] and isopropyl[9] reductions involved heating under reflux for 16 and 17 h respectively. Under these conditions, significant quantities of the amide (4a) were still present and a minimum of 48 h was required to achieve high yields. It was thought that extended exposure to the lithium aluminium hydride reaction was responsible for the racemization but material obtained from reactions with shorter reaction times showed a similar degree of racemization. Thus a reaction for 24 h gave

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[7] Mori, K., Tominaga, M., Takigawa, T., and Matsui, M., *Synthesis*, 1973, 790.
[8] Coote, S. J., Davies, S. G., Middlemiss, D., and Naylor, A., *J. Chem. Soc., Perkin Trans 1*, 1989, 2223.
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significant amounts of hydroxy amide (5a) (30%) together with (6a) with e.e. 40% compared with an e.e. of 79% for the amide (4a). The reason for this unexpected racemization is not known but presumably involves a proton abstraction competing with hydride transfer. Several different samples of lithium aluminium hydride were tried in the reaction and all gave similar results.

Attempts were also made to reduce the acetoxy amide with $BH_3.SMe_2$ and with $NaBH_4$/acetic acid. Both reagents led to cleavage of the acetoxy group but little reduction of the amide to amine.

Reactions Involving 3,5-Dimethoxybenzaldehyde Cyanohydrin (2b)

The sequence of reactions shown in Scheme 1 were also carried out using 3,5-dimethoxybenzaldehyde cyanohydrin (2b) with the (*R*)-enantiomer predominating (e.e. 50%). The hydroxy amine (6b), the dimethyl ether of terbutaline, was obtained with an e.e. of 32%. The e.e. values of the intermediate products were not determined and it was assumed that racemization had occurred during $LiAlH_4$ reduction.

Experimental

General

General conditions were as described previously.[10]

Cyanohydrins

(±)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (2a) was obtained from 3-phenoxybenzaldehyde (1a) by using the standard metabisulfite–cyanide method.[11]

(*R*)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile was prepared, by using (*S*,*S*)-cyclo(phenylalanylhistidyl), with e.e. 79% as determined from the ^1H n.m.r. spectrum of the ester with (*S*)-(−)-cyhalothrin acid.[12]

(*R*)-2-(3,5-Dimethoxyphenyl)-2-hydroxyacetonitrile (2b) was prepared, by using the (*S*,*S*)-dipeptide, as a colourless solid, m.p. 61·1–63·0°, after flash chromatography (ether/light petroleum, 2:3) (lit.[13] 58·7–60·7°) (Found: C, 62·4; H, 5·4. Calc. for $C_{10}H_{11}NO_3$: C, 62·2; H, 5·7%). $[\alpha]_D$ (corrected for chemical conversion) +9·5° (*c*, 1·08 in benzene).

Acetyl Cyanohydrins (3)

2-Acetoxy-2-(3-phenoxyphenyl)acetonitrile (3a) was prepared by heating a mixture of 2-hydroxy-2-(3-phenoxyphenyl)acetonitrile (2a) (3·60 g, 16 mmol), freshly distilled acetic anhydride (3·0 ml, 32 mmol) and acetyl chloride (0·5 ml, 7 mmol) at 70° for 30 min. Kügelrohr distillation of the cooled mixture gave 2-acetoxy-2-(3-phenoxyphenyl)acetonitrile as a colourless liquid (3·72 g, 87%), b.p. 200° (oven)/1 mm. ν_{max} (film) 2415m, 1760s, 1585s, 1490s, 1450s, 1370s, 1215s, 1025s, 1000m, 925m, 780m, 750m, 695s cm^{-1}. ^1H n.m.r. δ (200 MHz) 2·15, s, $COCH_3$; 6·34, s, CH; 7·00–7·43, m, 9×ArH. ^{13}C n.m.r. δ (50 MHz) 20·4, ($CO\mathbf{C}H_3$; 62·4, CH; 115·8, CN; 117·6, 120·0, C2′,4′; 119·3, C2″,6″; 122·0, C6′; 124·0, C4″; 129·9, C3″,5″; 130·6, C5′; 133·4, C1′; 156·1, C3′; 158·1, C1″; 168·7, (C=O). Mass spectrum: *m/z* 267 (M, 50%), 226 (16), 255 (100), 197 (16), 181 (26), 147 (22), 115 (22), 114 (59), 77 (44), 51 (27).

The (*R*)-cyanohydrin gave a sample of the (*R*)-acetoxy compound, $[\alpha]_D$ −25·7° (*c*, 1·05 in benzene).

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[11] Vogel, A. I., 'Textbook of Practical Organic Chemistry' 5th Edn, p. 729 (Longman: London 1991).
[12] Matthews, B. R., Jackson, W. R., Jayatilake, G. S., Wilshire, C. S., and Jacobs, H. A., *Aust. J. Chem.*, 1988, **41**, 1697.
[13] Pirrung, M. C., and Shuey, S. W., *J. Org. Chem.*, 1994, **59**, 3890.

(*R*)-2-Acetoxy-2-(3,5-dimethoxyphenyl)acetonitrile (3b) was obtained by heating a mixture of crude (*R*)-2-(3,5-dimethoxyphenyl)-2-hydroxyacetonitrile (98% by mass, 0·85 g, 4·4 mmol), freshly distilled acetic anhydride (1·0 ml, 10·6 mmol) and acetyl chloride (0·14 ml, 2·0 mmol) at 70° for 30 min. Kügelrohr distillation of the cooled mixture gave (R)-*2-acetoxy-2-(3,5-dimethoxyphenyl)acetonitrile* as a colourless liquid (0·83 g, 80%), b.p. 125° (oven)/0·05 mm, $[\alpha]_D$ −15·4° (*c*, 1·10 in benzene) (Found: C, 60·8; H, 6·0. $C_{12}H_{13}NO_4$ requires C, 61·1; H, 5·6%). ν_{max} (film) 2940m, 2360w, 1755s, 1680s, 1465m, 1490m, 1210s, 1180s, 1070m, 1025m, 840m, 690m cm^{-1}. ^1H n.m.r. δ (300 MHz) 2·18, s, $COCH_3$; 3·81, s, OCH_3; 6·32, s, CH; 6·51, t, *J* 2·3 Hz, H4′; 6·64, d, *J* 2·4 Hz, H2′+H6′. ^{13}C n.m.r. δ (50 MHz) 20·4, $CO\mathbf{C}H_3$; 55·5, OCH_3; 62·7, CH; 102·1, C4′; 105·7, C2′,6′); 116·1, CN; 113·6, C1′; 161·3, C3′,5′; 168·9, C=O. Mass spectrum: *m/z* 235 (M, 47%), 194 (15), 193 (100), 192 (17), 176 (39), 167 (17), 166 (25), 139 (21), 138 (22).

N-*t-Butylacetamides (4)*

2-Acetoxy-N-(t-butyl)-2-(3-phenoxyphenyl)acetamide (4a). 2-Acetoxy-2-(3-phenoxyphenyl)-acetonitrile (3a) (2·50 g, 9·3 mmol) and t-butyl alcohol (1·75 ml, 19 mmol) were added succcessively, dropwise, to a magnetically stirred solution of concentrated sulfuric acid (1 ml) and glacial acetic acid (12·5 ml) at 5–7°. The solution was kept at this temperature for 30 min before being warmed to room temperature and stirred for a further 16 h. The reaction mixture was poured into ice/water (150 ml) with stirring, basified to pH 5 by the dropwise addition of aqueous sodium hydroxide (4 M), and extracted with dichloromethane (3×100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under vacuum to leave a cream-coloured solid. Radial chromatography (ether/light petroleum, 1:1) gave *2-acetoxy-N-(t-butyl)-2-(3-phenoxyphenyl)acetamide* (4a) (1·95 g, 61%), m.p. 110·3–111·5° (Found: C, 70·6; H, 6·7. $C_{20}H_{23}NO_4$ requires C, 70·4; H, 6·8%). ν_{max} (Nujol) 3275s, 3093m, 1740s, 1660s, 1585s 1460s, 1375s, 1240s, 760m, 690m cm^{-1}. ^1H n.m.r. δ (200 MHz) 1·33, s, $C(CH_3)_3$; 2·16, s, $COCH_3$; 5·91, br s, CH+NH; 6·93–7·39, m, 9×ArH. ^{13}C n.m.r. δ (75 MHz) 21·0, $CO\mathbf{C}H_3$; 28·7, $C(\mathbf{C}H_3)_3$; 51·6, $\mathbf{C}(CH_3)_3$; 75·3, CH; 117·3, 118·9, C2′,4′; 119·2, C2″,6″; 122·3, C6′; 123·5, C4″; 129·8, C3″,5″; 130·0, C5′; 137·8, C1′; 156·7, C3′; 157·6, C1″; 166·9, CONH; 168·9, $\mathbf{C}OCH_3$. Mass spectrum: *m/z* 341 (M, 2%), 242 (82), 200 (77), 199 (100), 171 (30), 141 (16), 93 (18), 89 (27), 77 (39), 65 (28), 58 (26), 57 (100), 51 (25).

This was followed by *N-(t-butyl)-2-hydroxy-2-(3-phenoxyphenyl)acetamide* (5a) (0·89 g, 32%), m.p. 86–88° (Found: $M^{+\bullet}$, 299·153±0·003. $C_{18}H_{21}NO_3$ requires $M^{+\bullet}$, 299·152). ν_{max} (Nujol) 3398s, 2970s, 1652s, 1584s, 1526s, 1488s, 1456s, 1246s cm^{-1}. ^1H n.m.r. δ (200 MHz) 1·28, s, $C(CH_3)_3$; 4·30, br s, OH; 4·79, s, CH; 6·23, s, NH; 6·90–7·35, m, 9×ArH. ^{13}C n.m.r. δ (75 MHz) 28·7, $C(\mathbf{C}H_3)_3$; 51·5, $\mathbf{C}(CH_3)_3$; 73·9, CH; 117·0, 118·7, C2′,4′; 119·2, C2″,6″; 121·8, C6′; 123·6, C4″; 129·9, C3″,5″; 130·2, C5′; 142·1, C1′; 156·9, C3′; 157·7, C1″; 171·2, CONH. Mass spectrum: *m/z* 299 (M, 6%), 200 (100), 199 (68), 171 (27), 93 (19), 78 (20), 65 (22), 57 (80).

A repeat reaction with the (*R*)-acetoxy compound (3a), $[\alpha]_D$ −25·7°, gave a sample of (4a), m.p. 126·9–128·4°, $[\alpha]_D$ −50·1° (*c*, 1·02 in benzene).

(R)-N-*(t-Butyl)-2-hydroxy-2-(3-phenoxyphenyl)acetamide (5a).* (*R*)-2-Acetoxy-*N*-(t-butyl)-2-(3-phenoxyphenyl)acetamide (4a) (150 mg, 0·44 mmol) dissolved in acetone (5 ml) containing 3 M hydrochloric acid (1·7 ml) was heated under reflux for 45 min. A further 1·7 ml of 3 M hydrochloric acid were added and the solution was refluxed for a further 3 h. After cooling to room temperature the acetone was removed under vacuum and the aqueous residue was extracted with ethyl acetate (3×30 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed under vacuum to give a white solid. Purification by preparative t.l.c. (ether/light petroleum, 3:2) gave (*R*)-*N*-(t-butyl)-2-hydroxy-2-(3-phenoxyphenyl)acetamide (5a) as a white solid (106 mg, 81%), m.p. 84–85·5°, $[\alpha]_D$ −25·0° (*c*, 1·00 in benzene). Spectral details were as described previously.

(R)-*2-Acetoxy-N-(t-butyl)-2-(3,5-dimethoxyphenyl)acetamide (4b).* (*R*)-2-Acetoxy-2-(3,5-dimethoxyphenyl)acetonitrile (3b) ($[\alpha]_D$ −15·4° (*c*, 1·1 in benzene); 0·75 g, 3·2 mmol) was reacted with t-butyl alcohol (0·60 ml, 0·47 g, 6·40 mmol) as described for the preparation of 2-acetoxy-*N*-(t-butyl)-2-(3-phenoxyphenyl)acetamide (4a) to give (R)-*2-acetoxy-N-(t-butyl)-2-(3,5-dimethoxyphenyl)acetamide* (4b) as a cream-coloured solid (0·85 g, 86%). A sample

was purified by preparative t.l.c. (ether/light petroleum, 1:1) to give a colourless solid, m.p. 128·4–130·1°, $[\alpha]_D$ −29·8° (*c*, 1·005 in benzene) (Found: C, 62·3; H, 7·2. $C_{16}H_{23}NO_5$ requires C, 62·1; H, 7·5%). ν_{max} (Nujol) 3285s, 1740s, 1660s, 1595s, 1560m, 1455s, 1430s, 1370s, 1300m, 1245s, 1210s, 1155s, 1060s, 825m cm^{-1}. ^1H n.m.r. δ (200 MHz) 1·35, s, $C(CH_3)_3$; 2·18, s, $COCH_3$; 3·78, s, OCH_3; 5·84, br s, NH; 5·86, s, CH; 6·42, t, *J* 2·3 Hz, H4′; 6·55, d, *J* 2·2 Hz, H2′+H6′. ^{13}C n.m.r. δ (50 MHz) 21·0, $CO\mathbf{C}H_3$; 28·6, $C(\mathbf{C}H_3)_3$; 51·5, $\mathbf{C}(CH_3)_3$; 55·3, OCH_3; 75·5, CH; 100·7, C4′; 105·4, C2′,6′; 137·9, C1′; 160·9, C3′,5′; 167·0, CONH; 169·1, $COCH_3$. Mass spectrum: *m/z* 309 (M, 6%), 210 (40), 168 (100), 167 (79), 139 (54), 57 (58).

2-Amino-1-arylethanols (6)

2-(t-Butylamino)-1-(3-phenoxyphenyl)ethanol (6a). A solution of 2-acetoxy-*N*-(t-butyl)-2-(3-phenoxyphenyl)acetamide (4a) (1·0 g, 3·0 mmol), in dry tetrahydrofuran (10 ml), was added dropwise to a stirred suspension of lithium aluminium hydride (0·26 g, 6·8 mmol) in dry tetrahydrofuran (15 ml). The mixture was heated to reflux for 24 h, cooled to 0° and quenched with ethyl acetate (2 ml) and then water until there was no observable reaction. The mixture was stirred and aqueous sodium hydroxide (4 M) was added dropwise until a white precipitate formed. The tetrahydrofuran was decanted and the precipitate was washed with ether (3×10 ml). The combined tetrahydrofuran/ether extracts were washed with water (50 ml), dried ($MgSO_4$) and the solvent removed under vacuum to give a yellow solid. Recrystallization (dichloromethane/light petroleum) gave *2-(t-butylamino)-1-(3-phenoxyphenyl)ethanol* (6a) (0·78 g, 91%) as colourless crystals, m.p. 99·5–100·3° (Found: C, 76·0; H, 8·3; N, 4·9. $C_{18}H_{23}NO_2$ requires C, 75·8; H, 8·1; N, 4·9%). ν_{max} (Nujol) 3290s, 3065s(br), 1585s, 1490s, 1480s, 1455s, 1445s, 1375s, 1265s, 1240s, 1225s, 1075s, 750s, 700s cm^{-1}. ^1H n.m.r. δ (200 MHz) 1·09, s, $C(CH_3)_3$; 2·57, dd, *J* 8·7, 11·8 Hz, C**H**H; 2·86, dd, *J* 3·7, 11·8 Hz, CH**H**; 4·57, dd, *J* 3·5, 8·6 Hz, CH; 6·86–7·38, m, 9×ArH. ^{13}C n.m.r. δ (50 MHz) 29·0, $C(\mathbf{C}H_3)_3$; 50·0, 50·4, CH, $\mathbf{C}(CH_3)_3$; 71·7, C1; 116·4, 117·7, C2′,4′; 118·1, C2″,6″; 120·6, C6′; 123·1, C4″; 129·6, C5′; 129·7, C3″,5″; 145·4, C1′; 157·2, 157·3, C3′,1″. Mass spectrum: *m/z* 286 (M+1, 11%), 252 (13), 86 (100), 57 (27).

A reaction of the (*R*)-acetoxyacetamide (4a), $[\alpha]_D$ −25°, gave a sample of the (*R*)-aminoethanol (6a), m.p. 96–99°, $[\alpha]_D$ −16·4° (*c*, 1·03 in benzene), e.e. 40% determined by using (*R*)-*O*-acetylmandelic acid as described previously.[1,6]

(R)-*2-(t-Butylamino)-1-(3,5-dimethoxyphenyl)ethanol (6b).* A solution of (*R*)-2-acetoxy-*N*-(t-butyl)-2-(3,5-dimethoxyphenyl)acetamide (0·26 g, 0·85 mmol) was reduced with lithium aluminium hydride (90 mg, 2·3 mmol) as described above to give (R)-*2-(t-butylamino)-1-(3,5-dimethoxyphenyl)ethanol (6b)* (0·20 g, 93%) as a waxy solid, m.p. 64–68°. $[\alpha]_D$ −12·2° (*c*, 1·02 in benzene). Determination of the enantiomeric excess by using (*R*)-*O*-acetylmandelic acid indicated the e.e. was 32% (Found: $M^{+\bullet}$, 253·166±0·002. $C_{14}H_{23}NO_3$ requires $M^{+\bullet}$, 253·167). ν_{max} (Nujol) 3385s(br), 1595s, 1525m, 1465s, 1430s, 1365s, 1320s, 1300s, 1205s, 1155s, 1060s, 925m, 840s, 700m cm^{-1}. ^1H n.m.r. δ (200 MHz) 1·10, s, $C(CH_3)_3$; 2·59, dd, *J* 8·6, 11·8 Hz, C**H**H; 2·89, dd, *J* 3·7, 11·8 Hz, CH**H**; 3·79, s, OCH_3; 4·56, dd, *J* 3·6, 8·5 Hz, CH; 6·37, t, *J* 2·3 Hz, H4′; 6·53, d, *J* 2·3 Hz, H2′+H6′. ^{13}C n.m.r. δ (50 MHz) 29·0 $C(\mathbf{C}H_3)_3$; 50·1, 50·4 CH, $\mathbf{C}(CH_3)_3$; 55·3, OCH_3; 72·2, C1; 99·3, C4′; 103·6, C2′,6′; 145·7, C1′; 160·8, C3′,5′. Mass spectrum: *m/z* 254 (M+1, 13%), 168 (50), 166 (16), 139 (48), 86 (100), 57 (50).

Attempted Reductions with $NaBH_4$/AcOH and $BH_3.SMe_2$

(A) Glacial acetic acid (0·27 ml, 4·75 mmol) in tetrahydrofuran (1·5 ml) was added dropwise over 15 min to a stirred mixture of $NaBH_4$ (180 mg, 4·75 mmol) and 2-acetoxy-*N*-(t-butyl)-2-(3-phenoxyphenyl)acetamide (4a) (204 mg, 0·6 mmol; $[\alpha]_D$ −50·1°) in tetrahydrofuran (6 ml) at 0°. The solution was then refluxed for 48 h with an aliquot being taken at 18 h. The solution was cooled, diluted with water (50 ml), and extracted with dichloromethane (3×50 ml), dried ($MgSO_4$) and the solvent removed under vacuum. ^1H n.m.r. analysis of the aliquot taken at 18 h showed starting material (5%), *N*-(t-butyl)-2-hydroxy-2-(3-phenoxyphenyl)acetamide (5a) (78%) and the desired 2-(t-butylamino)-1-(3-phenoxyphenyl)ethanol (6a) (17%). ^1H n.m.r. analysis of the final reaction mixture showed no starting material, but *N*-(t-butyl)-

2-hydroxy-2-(3-phenoxyphenyl)acetamide (5a) (80%) and the desired 2-(t-butylamino)-1-(3-phenoxyphenyl)ethanol (6a) (20%) were present.

(B) $BH_3.SMe_2$ (0·5 ml of 2 M in tetrahydrofuran, 1 mmol) was added to 2-acetoxy-*N*-(t-butyl)-2-(3-phenoxyphenyl)acetamide (4a) (100 mg, 0·3 mmol) in tetrahydrofuran (10 ml), and the solution stirred overnight at room temperature. Methanol (10 ml) was added and the solution stirred for a further 1 h. Water (10 ml) was added, the solution diluted with diethyl ether (20 ml), and extracted with both ether (3×20 ml) and dichloromethane (3×20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed under vacuum to give a wax-like solid (87 mg). ^1H n.m.r. analysis of the crude product showed it to be starting material (32%) and *N*-(t-butyl)-2-hydroxy-2-(3-phenoxyphenyl)acetamide (5a) (68%). When the reaction mixture was stirred for 2 days at room temperature similar results were obtained.

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