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Enantioselective synthesis of benzylic stereocentres via Claisen rearrangement of enantiomerically pure allylic alcohols: preparation of (*R*)- and (*S*)-3-methyl-2-phenylbutylamine

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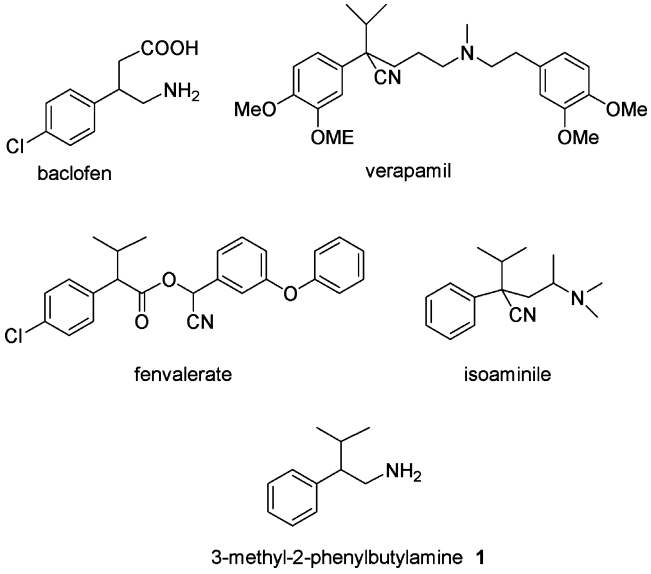
Abstract—The Johnson–Claisen rearrangement of enantiopure allylic alcohols in triethylorthopropionate is the key step for the preparation of chiral molecules with benzylic stereogenic carbon atoms bearing an isopropyl moiety. The synthetic procedure is applied to the preparation of (*R*)- and (*S*)-3-methyl-2-phenylbutylamine.

1. Introduction

Benzylic stereogenic carbon atoms very often occur in the skeleton of important organic molecules. This structural moiety can be found in thousands of isolated natural products, e.g. the *Sceletium* alkaloids, calamenene terpenes, several therapeutic agents, such as the profen non-steroidal anti-inflammatory drugs, and some of the top ten single-enantiomer drugs,[1] i.e. paroxetine, clopidogrel and sertraline.

Catalytic access to enantiomerically enriched molecules with benzylic stereocentres has been accomplished, for example, by hydrogenation,[2] by metallobenzene addition technology,[3] by the reaction of benzyllithium derivatives,[4] by enantioselective alkylation of arene rings with carbonyls and electron poor olefins,[5] or by intramolecular Heck reactions.[6]

A general successful approach to the preparation of chiral molecules is based on the intramolecular chirality-transfer processes (the so-called self-immolative reactions), in which a stereocentre is sacrificed while another is enantiospecifically created. A catalytic enantioselective reaction is usually combined with an enantiospecific intramolecular reaction, typically a rearrangement. We successfully adopted this strategy for the creation of the tertiary and quaternary benzylic stereocentres, of the chiral drugs baclofen[7] and verapamil[8] respectively (Scheme 1). We combined the kinetic resolution of allylic alcohols mediated by lipases with the Claisen rearrangement, according to the modifications of Johnson and Ireland, and transferred a C_2 fragment to the benzylic carbon atom.



Scheme 1.

We then decided to investigate the potential of this synthetic route as a general method for the creation of

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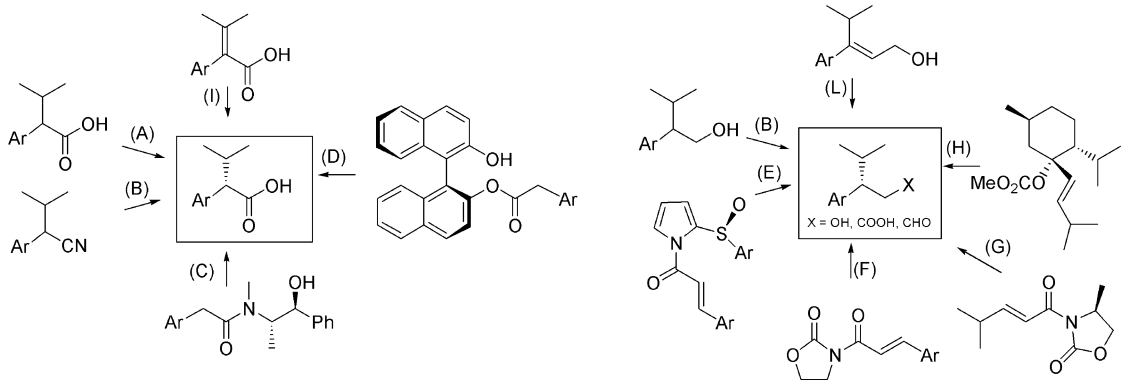


Scheme 2.

benzylic stereogenic centres, by converting, for example, a $CH_3CHCOOEt$ fragment, easily introduced by a Claisen rearrangement with ethyl orthopropionate, into an isopropyl substituent, which is much more difficult to locate on benzylic positions. The Ar-CH-CH$(CH)_3$ moiety can be found in all the derivatives of 3-methyl-2-aryl-butyric acid, such as the pyrethroid pesticide fenvalerate, and in several other structurally related compounds, e.g. the anti-tussive drug isoaminile, and the resolving agent 3-methyl-2-phenylbutylamine **1**. The most common synthetic approaches described in the literature for this kind of substrate are summarised in Scheme 2. They consist of classical resolutions (A[9]) or bio-catalysed kinetic resolutions (B[10]) of racemic substrates already bearing the isopropyl group. As an alternative, the isopropyl moiety has been introduced by enantioselective alkylation of the benzylic carbon atom (C[11], D[12]), or by enantioselective addition to double bonds (E[13], F[14]). Aryl magnesium bromide addition to chiral olefinic compounds (G[15]), cuprate addition to chiral carbonates derived from menthone (H[16]), hydrogenation of double bonds (I[17]), and isomerisation of allylic alcohols (L[18]) mediated by chiral phosphines have been also exploited.

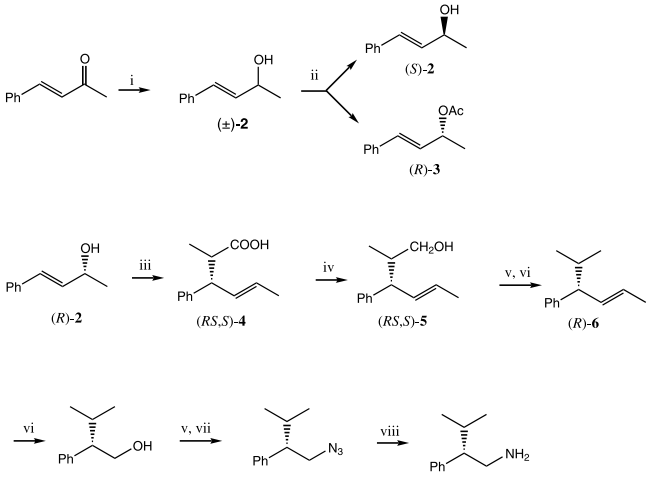
Herein we report on the preparation of both enantiomers of amine **1**, in order to show the efficiency and the applicability of our synthetic approach.

2. Results and discussion

3-Methyl-2-phenylbutylamine **1** has recently been introduced as a new and versatile chiral base for the classical resolution of chiral acids, in particular of the α-aryl propionic type.[19] To date, optically active **1** has been obtained by resolution with mandelic acid,[9c] by enzyme-mediated hydrolysis of a suitable amide,[10a] or by bio-catalysed hydration of a nitrile derivative.[10b]

The application of our synthetic route required the preparation of allylic alcohol **2**, which was easily obtained by $NaBH_4$ reduction of benzalacetone (Scheme 3). The kinetic resolution of (±)-**2** was accomplished by Lipase PS-mediated transesterification in *t*-butyl methyl ether, at room temperature, in the presence of vinyl acetate as an acyl donor.[20] Acetate (*R*)-**3** (ee = 98% ee, HPLC) and alcohol (*S*)-**2** (ee = 98%, HPLC) were separated by column chromatography. Acetate **3** was hydrolysed, and (*R*)-and (*S*)-**2** were submitted separately to Johnson–Claisen rearrangement in ethyl orthopropionate, at 140°C, in the presence of a catalytic amount of propionic acid. Acids (*RS*,*S*)- and (*RS*,*R*)-**4** were quantitatively recovered, after treatment of the crude product of the Claisen rearrangement with refluxing NaOH 10%. $LiAlH_4$ reduction gave alcohols **5**, which were treated with *p*-toluensulphonyl chloride, and reduced to convert the $CH_3CHCOOH$ fragment into an isopropyl unit, and obtain (*R*)- and (*S*)-**6**. The Johnson–Claisen rearrangement is a suprafacial, concerted, nonsynchronous pericyclic process, that can be considered as an intramolecular S_N2' process: Alcohol (*E*,*R*)-**2** afforded derivative (*E*,*R*)-**6**.[21] Ozonolysis of the double bond and $NaBH_4$ quenching afforded alcohols (*S*)- and (*R*)-**7**. The amine functionality was introduced through a classical sequence, via azide intermediates **8**.

(*S*)-**1** (ee = 96%, HPLC of the corresponding trifluoroacetic amide) and (*R*)-**1** (ee = 94%, HPLC of the



Scheme 3. *Reagents and conditions*: (i) $NaBH_4$, CH_2Cl_2, MeOH; (ii) Lipase PS, *t*-butylmethylether, vinyl acetate; (iii) $CH_3CH(OEt)_3$, acid propionic; NaOH 10%; (iv) $LiAlH_4$, THF; (v) *p*-TosCl, pyridine; (vi) O_3, MeOH–CH_2Cl_2; then $NaBH_4$; (vii) NaN_3, aq. EtOH; (viii) $LiAlH_4$, Et_2O.

corresponding trifluoroacetic amide) were obtained in very good overall yields, and both fully characterised as free bases[22] and as hydrochloride salts.

3. Conclusions

Recently the need for enantiopure molecules has grown greatly. The general opinion is that it is much better to put human beings in contact with the single enantiomers of chiral molecules. According to a recent review,[23] since 1990 the proportion of single-enantiomer drugs among approved new chemical entities worldwide has been consistently greater than that of racemates. The strategy of the chiral switch has also been introduced in the area of fragrance chemistry: Enantiomerically enriched odorants are now widely studied.[24]

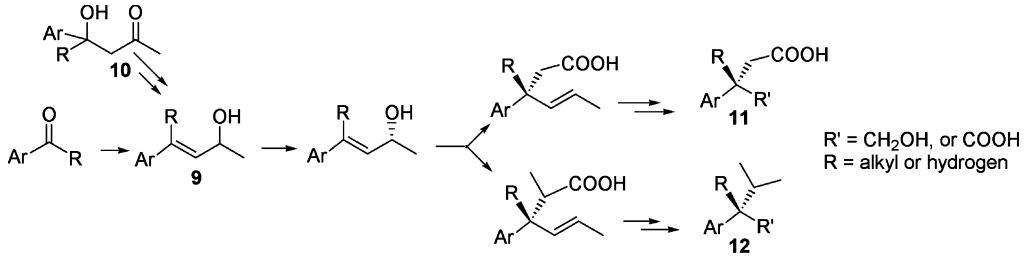
The optimisation of our procedure is aimed to complement the synthetic tools that can be satisfactorily employed for the preparation of enantiopure compounds. Our method has the great advantage of being a catalytic, rather than a stoichiometric resolution which affords both the enantiomers of the desired compounds. Allylic alcohols of type **9** are the starting materials of our synthetic route (Scheme 4). These can easily be prepared by the methods of classical organic chemistry, e.g. aldol condensation, condensation of aromatic ketones with acetonitrile and subsequent homologation,[8] dehydration of hydroxy ketones of type **10**. Transesterification, mediated by lipases, is a quick and efficient method to obtain two enantiopure isomers of the starting allylic alcohol. The wide commercial availability of the lipases gives the chance to find the right enzyme for each substrate. The Johnson–Claisen rearrangement allows for the transfer of a C_2 or C_3 unit to a benzylic carbon atom with high stereoselection. The C_3 moiety can be converted into an isopropyl unit. The remaining double bond can be manipulated according to several procedures, for example it can be submitted to ozonolysis, and a CH_2OH or a COOH substituent can be created. A tertiary or quaternary benzylic stereogenic carbon atom in structures **11** and **12** can be prepared with high stereoselection, by means of high yield reactions, occurring in mild conditions, using common reagents, and simple laboratory apparatus.

4. Experimental

Burkholderia cepacia lipase (Lipase PS, Amano Pharmaceuticals Co., Japan) was employed in this work. GC-MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m×0.25 mm×0.25 μm). The following temperature program was employed: 60°C (1 min)/6°/min/150° (1 min)/12°/min/280° (5 min). Chiral HPLC analyses of compounds **1** (as trifluoroacetamide **1**-$NHCOCF_3$) and **2** were performed on a Chiralcel OD column (Daicel-Japan) installed on a Merck-Hitachi L-6200 apparatus: 0.6 mL/min, UV detector (210 nm for **1**-$NHCOCF_3$, 254 nm for **2**), hexane/isopropanol 95:5. The following retention times were observed: (*R*)-**1**-$NHCOCF_3$ $t_R = 10.24$ min, (*S*)-**1**-$NHCOCF_3$ $t_R = 14.37$ min; (*R*)-**2** $t_R = 19.91$ min; (*S*)-**2** $t_R = 29.28$ min. ^1H NMR spectra were recorded at rt on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical shift scale was based on internal tetramethylsilane. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. Microanalyses were determined on a Analyzer 1106 Carlo Erba. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns. (±)-(*E*)-4-Phenyl-3-buten-2-ol **2** was prepared according to Ref. 20c.

4.1. (2*R*,3*E*)-2-Acetoxy-4-phenyl-but-3-ene (*R*)-3 and (2*S*,3*E*)-4-phenyl-3-buten-2-ol (*S*)-2

A mixture of (±)-**2** (20 g, 0.135 mol), lipase (10 g) and vinyl acetate (20 mL) in *t*-butylmethyl ether (150 mL) was stirred at rt for 24 h. The residue obtained upon evaporation of the filtered reaction mixture was chromatographed, using hexane:ethyl acetate 9:1 as the eluent with the acetate (*R*)-**3** (10.5 g, 41%) and alcohol (*S*)-**2** (7.59 g, 38%) being recovered. Acetate (*R*)-**3**: ee = 98% (HPLC of the corresponding alcohol), $[\alpha]_D^{20} = +139.6$ (*c* 3.18, $CHCl_3$) [lit.[20b] $[\alpha]_D^{20} = +142.2$, ee = 99% (*c* 1, $CHCl_3$)]; ^1H NMR: δ 7.40–7.20 (5H, m, aromatic hydrogens), 6.59 (1H, d, $J = 15.7$, PhC*H*=), 6.18 (1H, dd, $J = 6.8$, 15.7, PhCH=C*H*), 5.52 (1H, m, C*H*OAc), 2.07 (3H, s, OAc), 1.40 (3H, d, $J = 6.8$, CH_3CH); GC/MS: $t_R = 16.99$ min; *m*/*z*: 190 (M^+, 18), 148 (65), 129 (100), 115 (69).



Scheme 4.

Alcohol (*S*)-**2**: ee = 98% (HPLC), $[\alpha]_D^{20} = -30.0$ (*c* 1.22, $CHCl_3$) [lit.[20b] $[\alpha]_D^{20} = -32.0$, ee = 98% (*c* 1.8, $CHCl_3$)]; ^{1}H NMR: δ 7.43–7.16 (5H, m, aromatic hydrogens), 6.56 (1H, d, $J = 15.7$, PhC*H*=), 6.26 (1H, dd, $J = 6.1$, 15.7, PhCH=C*H*), 4.48 (1H, quintuplet, $J = 6.1$, C*H*OH), 1.37 (3H, d, $J = 6.1$, CH_3CH); GC/MS: t_R = 13.89 min; *m*/*z*: 148 (M^+, 75), 129 (47), 115 (50), 105 (100), 91 (53).

4.2. (2*R*,3*E*)-4-Phenyl-3-buten-2-ol (*R*)-2

Acetate (*R*)-**3** (10.4 g, 0.055 mol) was hydrolysed with KOH (4.59 g, 0.082 mol) in methanol (70 mL). After the usual work-up, alcohol (*R*)-**2** (9.67 g, 93%) was recovered by column chromatography, eluting with hexane:ethyl acetate 9:1: ee = 98% (HPLC), $[\alpha]_D^{20} = +31.4$ (*c* 1.38, $CHCl_3$). ^{1}H NMR and MS spectra were in accordance with those described for the enantiomer.

4.3. (2*RS*,3*S*,4*E*)-2-Methyl-3-phenyl-hex-4-enoic acid (*RS*,*S*)-4

A solution of (*R*)-**2** (9.50 g, 0.064 mol) in triethyl orthopropionate (200 mL), in the presence of propionic acid (0.5 mL) was heated at 140°C, removing ethanol by distillation. The residue, obtained upon evaporation of the solvent, was treated with NaOH 10% (50 mL) in refluxing ethanol (200 mL). The mixture was poured into water, acidified with 10% HCl, and extracted with diethyl ether. The organic phase was dried over Na_2SO_4, and evaporated under reduced pressure, to give the title compound as a mixture 1:1.6 (^{1}H NMR) of two diastereoisomers (11.1 g, 85%): ^{1}H NMR: δ 7.40–7.10 (5H, m, aromatic hydrogens), 5.72–5.40 (2H, m, C*H*=*CH*), 3.47 (m, C*H*Ph of the main diastereoisomer), 3.36 (m, C*H*Ph of the minor diastereoisomer), 2.78 (1H, m, C*H*CH_3), 1.66 (d, $J = 4.6$, CH_3C= of the main diastereoisomer), 1.60 (d, $J = 5.6$, CH_3C= of the minor diastereoisomer), 1.21 (d, $J = 6.4$, CH_3CH of the main diastereoisomer), 0.96 (d, $J = 7.0$, CH_3CH of the minor diastereoisomer); GC/MS: t_R = 19.28 min minor diastereoisomer, *m*/*z*: 204 (M^+, 1), 131 (100), 115 (11), 91 (23); t_R = 19.46 min main diastereoisomer, *m*/*z*: 204 (M^+, 4), 131 (100), 115 (9), 91 (23).

4.4. (2*RS*,3*R*,4*E*)-2-Methyl-3-phenyl-hex-4-enoic acid (*RS*,*R*)-4

According to the procedure described for (*R*)-**2**, alcohol (*S*)-**2** (7.40 g, 0.050 mol) gave the title compound as a 1:1.5 (^{1}H NMR) mixture of two diastereoisomers (8.26 g, 81%). ^{1}H NMR and MS spectra were in accordance with those described for the enantiomers.

4.5. (2*RS*,3*S*,4*E*)-2-Methyl-3-phenyl-hex-4-en-1-ol (*RS*,*S*)-5

Acid (*RS*,*S*)-**4** (11.0 g, 0.054 mol) was treated with $LiAlH_4$ (2.04 g, 0.054 mol) in THF (200 mL). After the usual work-up, alcohol (*RS*,*S*)-**5** (7.39 g, 72%) was recovered as a 1:1.5 mixture of two diastereoisomers (^{1}H NMR): ^{1}H NMR: δ 7.34–7.13 (5H, m, aromatic hydrogens), 5.74–5.42 (2H, m, C*H*=*CH*), 3.67 (dd, J = 5.1, 11.1, C*H*OH of the minor diastereoisomer), 3.54 (dd, $J = 5.5$, 11.1, C*H*OH of the minor diastereoisomer), 3.44 (dd, $J = 5.0$, 10.5, C*H*OH of the main diastereoisomer), 3.28 (dd, $J = 5.5$, 10.5, C*H*OH of the main diastereoisomer), 3.17 (t, $J = 8.3$, C*H*Ph of the main diastereoisomer), 3.08 (t, $J = 8.3$, C*H*Ph of the minor diastereoisomer), 1.96 (1H, m, C*H*CH_3), 1.66 (3H, m, CH_3C=), 0.97 (d, $J = 6.7$, CH_3CH of the main diastereoisomer), 0.76 (d, $J = 6.7$, CH_3CH of the minor diastereoisomer); GC/MS: t_R = 18.07, *m*/*z*: 190 (M^+, 5), 131 (100), 115 (12), 91 (23).

4.6. (2*RS*,3*R*,4*E*)-2-Methyl-3-phenyl-hex-4-en-1-ol (*RS*,*R*)-5

Acid (*RS*,*R*)-**4** (8.20 g, 0.040 mol) was treated with $LiAlH_4$ (1.53 g, 0.040 mol) in THF (200 mL). After the usual work-up, alcohol (*RS*,*R*)-**5** (5.32 g, 70%) was recovered as a 1:1.5 mixture of two diastereoisomers (^{1}H NMR). ^{1}H NMR and MS spectra were in accordance with those described for the enantiomers.

4.7. (2*E*,4*R*)-5-Methyl-4-phenyl-hex-2-ene (*R*)-6

p-Toluenesulphonyl chloride (11.0 g, 0.058 mol) was added to a solution of alcohol (*RS*,*S*)-**5** (7.30 g, 0.038 mol) in pyridine (40 mL). After work-up, the residue was dissolved in THF (30 mL) and dropped into a solution of $LiAlH_4$ (1.44 g, 0.038 mol) in refluxing THF (150 mL). After work-up, (*R*)-**6** (4.43 g, 67%) was recovered by column chromatography, eluting with hexane: $[\alpha]_D^{20} = -59.4$ (*c* 2.68, $CHCl_3$) [lit.[21] (*S*)-**6** $[\alpha]_D^{20}$ = +79.9 (heptane)]; ^{1}H NMR: δ 7.45–7.0 (5H, m, aromatic hydrogens), 5.62 (1H, ddq, $J = 15.3$, 8.8, 1.3, CH-C*H*=), 5.43 (1H, dq, $J = 15.3$, 6.2, =C*H*CH_3), 2.82 (1H, t, J 8.8, C*H*Ph), 1.89 (1H, m, *CH*$(CH_3)_2$), 1.65 (3H, dd, $J = 6.2$, 1.3, C=CMe_2) 0.93 (3H, d, $J = 6.6$, CH_3CH), 0.74 (3H, d, $J = 6.6$, CH_3CH); GC/MS: t_R = 12.31 min; *m*/*z*: 174 (M^+, 6), 131 (100), 115 (12), 91 (23).

4.8. (4*S*,2*E*)-5-Methyl-4-phenyl-hex-2-ene (*S*)-6

According to the procedure described for (*RS*,*S*)-**5**, alcohol (*RS*,*R*)-**5** (5.20 g, 0.027 mol) gave (*S*)-**6** (3.00 g, 64%): $[\alpha]_D^{20} = +58.3$ (*c* 1.27, $CHCl_3$) [lit.[21] (*S*)-**6** $[\alpha]_D^{20}$ = +79.9 (heptane)]; ^{1}H NMR and MS spectra were in accordance with those described for the enantiomer.

4.9. (2*S*)-3-Methyl-2-phenyl-butan-1-ol (*S*)-7

A solution of (*R*)-**6** (4.35 g, 0.025 mol) in CH_2Cl_2: methanol 1:1 (150 mL) was treated with ozone at −78°C. The reaction mixture was quenched with $NaBH_4$. After the usual work-up, alcohol (*S*)-**7** (3.24 g, 79%) was recovered, after column chromatography, using hexane:ethyl acetate 9:1 as the eluent: $[\alpha]_D^{20}$ = +12.4 (*c* 1.20, $CHCl_3$) [lit.[25] (*R*)-**7** $[\alpha]_D^{20} = -13.1$ (*c* 2.06, CH_2Cl_2), ee = 99%]; ^{1}H NMR: δ 7.48–7.12 (5H, m, aromatic hydrogens), 3.94 (1H, dd, J 11.0, 5.3 *CH*OH), 3.82 (1H, dd, J 11.0, 8.8, *CH*OH), 1.01 (3H, d, $J = 6.6$, CH_3CH), 0.74 (3H, d, $J = 6.6$, CH_3CH); GC/MS: t_R = 13.67 min; *m*/*z*: 164 (M^+, 16), 133 (52), 91 (100).

4.10. (2*R*)-3-Methyl-2-phenyl-butan-1-ol (*R*)-7

According to the procedure described for (*R*)-**6**, derivative (*S*)-**6** (2.90 g, 0.017 mol) gave (*R*)-**7** (2.18 g, 80%): $[\alpha]_D^{20} = -11.9$ (*c* 0.96, $CHCl_3$) [lit.[25] (*R*)-**7** $[\alpha]_D^{20} = -13.1$ (*c* 2.06, CH_2Cl_2), ee = 99%]; ^{1}H NMR and MS spectra were in accordance with those described for the enantiomer.

4.11. (*S*)-3-Methyl-2-phenyl-butylamine (*S*)-1

p-Toluensulphonyl chloride (5.33 g, 0.028 mol) was added to a solution of alcohol (*S*)-**7** (3.10 g, 0.019 mol) in pyridine (20 mL). After work-up, the residue was dissolved in aqueous ethanol (20 mL); NaN_3 (3.08 g, 0.0475 mol) was added. The reaction mixture was refluxed for 10 h. After work-up, the residue was dissolved in diethyl ether (10 mL) and dropped into a suspension of $LiAlH_4$ (0.866 g, 0.023 mol) in refluxing diethyl ether (50 mL). Amine (*S*)-(−)-**1** was isolated as HCl salt (2.46 g, 65%). (*S*)-**1**·HCl: mp = 160°C; $[\alpha]_D^{20} = -17.6$ (*c* 0.81, MeOH); ^{1}H NMR (D_2O): δ 7.40–7.20 (5H, m, aromatic hydrogens), 3.41 (1H, dd, $J = 4.4$, 12.9, C*H*N), 3.20 (1H, t, $J = 12.9$, C*H*N), 2.58 (1H, m, C*H*Ph), 1.86 (1H, m, C*H*CH_3), 0.92 (3H, d, $J = 6.6$, *CH_3*CH), 0.65 (3H, d, $J = 6.6$, *CH_3*CH). (*S*)-**1** (free base): ee = 96% (HPLC of the corresponding trifluoroacetamide); $[\alpha]_D^{20} = -12.9$ (*c* 1.12, $CHCl_3$) [lit.[22] (*R*)-**1**: $[\alpha]_D^{20} = -1.5$ (neat)]; ^{1}H NMR: δ 7.42–7.34 (5H, m, aromatic hydrogens), 3.07 (1H, dd, $J = 4.4$, 12.8, C*H*N), 2.90 (1H, dd, $J = 9.7$, 12.8, C*H*N), 2.32 (1H, m, C*H*Ph), 1.86 (1H, m, C*H*CH_3), 0.92 (3H, d, $J = 6.6$, *CH_3*CH), 0.72 (3H, d, $J = 6.6$, *CH_3*CH); GC/MS: $t_R = 12.76$ min; *m*/*z*: 163 (M^+, 5), 146 (11), 132 (27), 117 (25), 91 (100).

4.12. (*R*)-3-Methyl-2-phenyl-butylamine (*R*)-1

According to the procedure described for (*S*)-**7**, derivative (*R*)-**7** (2.05 g, 0.0125 mol) gave (*R*)-(+)-**1**·HCl (1.64 g, 66%). (*R*)-**1**·HCl: mp = 155°C; $[\alpha]_D^{20} = +16.9$ (*c* 0.59, MeOH); (*R*)-**1** (free base): ee = 94% (HPLC of the corresponding trifluoroacetamide); $[\alpha]_D^{20} = +12.1$ (*c* 1.15, $CHCl_3$) [lit.[22] (*R*)-**1**: $[\alpha]_D^{20} = -1.5$ (neat)]. ^{1}H NMR and MS spectra were in accordance with those described for the enantiomers.

Acknowledgements

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