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Resolution of β-unsaturated amines with isopropylidene glycerol hydrogen phthalate

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Abstract

1-Phenyl-2-propenylamine **2**, 1-phenyl-2-propinylamine **3**, 1-(1-cyclohexenyl)ethylamine **4**, (*E*)-2-ethylidenecyclohexylamine **5** and α-methylallylamine hydrochloride **6** were selected as candidates for resolution with isopropylidene glycerol hydrogen phthalate **1**, previously described as an efficient resolving agent of 1-arylalkylamines. With only the exception of **5**, all these substrates were resolved by (*S*)-**1**. In particular both the enantiomers of **2** and **3** were obtained in excellent yields and with very high enantiomeric excesses. The absolute configurations of non-racemic forms of **2**, **3** and **4**, not prepared before except those of **3**, were established by correlation with the respective hydrogenation products. The enantiomeric excesses of all the resolved substrates were accurately determined by chiral HPLC analysis. The fact that **1** resolves **4** and **6** but not their saturated analogues and shows higher efficiency in resolving **2** and **3** than 1-phenylpropylamine indicates the positive influence of the presence of β-unsaturation on the resolvability of aminic substrates with such an acid.

1. Introduction

A new chiral acid, the hydrogen phthalate of isopropylidene glycerol **1**, has been shown to resolve a wide range of 1-arylalkylamines with high efficiencies and with the same stereochemical outcome.[1,2] Some explanation of such a resolving ability has been provided by the study of the physicochemical and X-ray crystallographic data of the diastereomeric salts formed by (*S*)-**1** with one of the resolved amines, 1-phenylethylamine.[3] Furthermore, the effects of structural modifications of the resolving agent **1** and of the 1-phenylethylamine framework in the tested substrates on the resolution process have been investigated.[2,3] This has allowed some structural features of **1** and of the amines conditioning the resolvability of the latter by the former to be identified. In particular, the presence of a phenyl or a vinyl group bonded to the α-carbon of the amine seems to be critical, as shown by the fact that 1-phenylethylamine and α-methylallylamine

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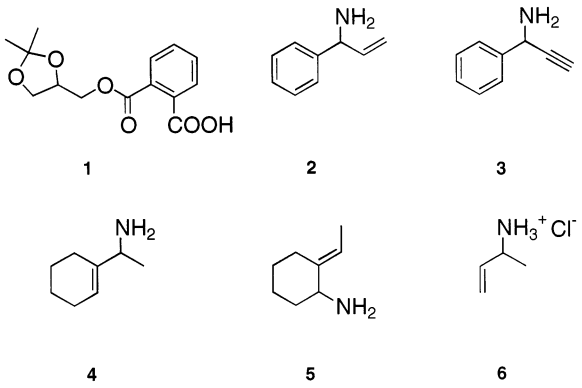
are resolved by (*S*)-**1**, in contrast to their saturated analogues, 1-cyclohexylethylamine and 2-butylamine, and to 1-phenyl-2-propylamine, which fail to form solid precipitates upon treatment with (*S*)-**1**.



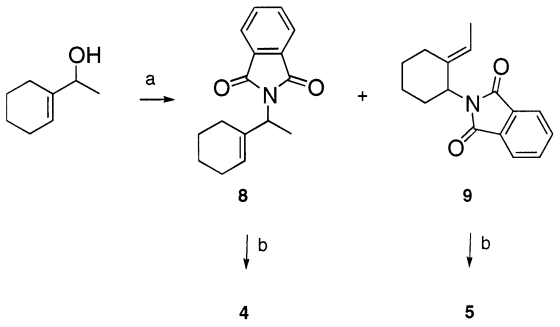
1 2 3 4 5 6

Believing that the presence of β,γ-unsaturation positively influences the resolvability of amines with **1**, as suggested by our precedent investigations,[2] we decided to explore the applicability of the same resolution procedure to 1-phenyl-2-propenylamine **2**, 1-phenyl-2-propinylamine **3** and 1-(1-cyclohexenyl)ethylamine **4**. We speculated that **2** and **3**, due to the additional unsaturation, should be resolved by **1** more efficiently than 1-phenylpropylamine, whose resolution we had previously described.[2] Analogously, **4** should, in principle, be resolvable with **1** unlike 1-cyclohexylethylamine. The interest in the preparation of these β,γ-unsaturated amines in non-racemic form was also aroused by their potential importance as chiral synthons and by the fact that no report on their synthesis had appeared except that in the case of **3**, a very efficient decigram-scale resolution via lipase catalysed acetylation has been published[4] just after we had terminated our experiments. These included two additional β,γ-unsaturated substrates, (*E*)-2-ethylidenecyclohexylamine **5**, which was isolated as a side product of the synthesis of **4**, and α-methylallylamine hydrochloride **6**. The free amine corresponding to the latter had been already resolved with (*S*)-**1**.[2] However, its resolution had been stopped at the first crystallisation recovering the *S* and *R* amines with 53 and 39% enantiomeric excess, respectively. Furthermore, those experiments, made difficult by the volatility of the substrate, had not included an accurate assessment of the enantiomeric compositions but simply relied on the comparison of the observed specific rotations with the maximum rotation reported for (*R*)-α-methylallylamine.[5] In order to overcome such difficulties and limitations, it seemed worthwhile to attempt the complete resolution of α-methylallylamine using the hydrochloride **6** and to develop an HPLC analytical method allowing the progress of its enantiomeric excess over the course of the resolution procedure to be monitored.

2. Results

The racemic amines **2** and **3** were prepared from cinnamyl alcohol and 1-phenyl-2-propyn-1-ol, respectively, according to literature methods.[6–8] For the preparation of amine **4** (Scheme 1), we decided to start from 1-(1-cyclohexenyl)ethanol, which was in turn obtained by regioselective 1,2-reduction of 1-acetylcyclohexene as reported in the literature.[9,10] Intermolecular dehydration

occurring between the above allylic alcohol and phthalimide on treatment with diethyl azodicarboxylate and triphenylphosphine gave *N*-1-(1-cyclohexenyl)ethylphthalimide **8** and (*E*)-*N*-2-ethylidenecyclohexylphthalimide **9**, which were isolated by chromatography in 39.2 and 26.8% yield, respectively. Subsequent hydrazinolysis of the two *N*-alkenylphthalimides **8** and **9** led to the corresponding amines **4** and **5**. The *E* configuration of **5** and of its precursor **9** was determined by comparison of the NMR spectrum of the former with reported data for the *E* and *Z* isomers of 2-ethylidenecyclohexylamine.[11,12] Finally, **6** was obtained by conversion into hydrochloride of α-methylallylamine, prepared as previously described.[13]



Scheme 1. (a) Phthalimide, diethyl azodicarboxylate, triphenylphosphine, THF. (b) Hydrazine monohydrate, 95% ethanol

As for our preceding resolutions of 1-arylalkylamines,[1,2] we decided to utilise the *S* enantiomer of **1** and to combine the amines **2**–**5** with stoichiometric quantities of such a resolving acid in methanol or ethanol or 2-propanol.

In the case of **2**, treatment of a methanolic solution of the racemic amine with equivalent amount of (*S*)-**1** produced a white crystalline precipitate, the salt of the levorotatory amine with (*S*)-**1**, in 82% yield (relative to the theoretical amount, i.e. half of the overall starting salt). The enantiomeric excess of (−)-**2** was determined by reversed-phase chiral HPLC analysis of the precipitated salt, without previous decomposition of the latter, under conditions effective for the separation of (*S*)-**1**, (+)-**2** and (*S*)-**1**, (−)-**2**. This describes the observed elution of three chromatographic peaks corresponding to the resolving agent (*S*)-**1**, the dextrorotatory amine (+)-**2** and the levorotatory amine (−)-**2**. It was assumed higher than 99.6% on the basis of no chromatographic detection of (+)-**2**. (−)-**2** was recovered from the salt in 80.2% overall yield (40.1% of the starting **2**). The HPLC analysis of the liberated amine under the same conditions adopted for the precipitated salt confirmed the above enantiomeric purity. (+)-**2** was isolated from the methanolic solution remaining from the crystallisation, precipitated from aqueous ethanol as a neutral sulphate and finally liberated with >99.6% e.e., determined by HPLC, and in 42.5% overall yield (21.2% of the starting **2**). To assign the absolute configurations to (−)-**2** and (+)-**2**, the levorotatory amine, recovered from the less soluble salt with (*S*)-**1**, was hydrogenated (H_2, 10% Pd/C, ethanol) leading to (*S*)-(−)-1-phenylpropylamine with >99.6% e.e., determined by HPLC according to the previously reported method.[2] On the basis of this result, the *S* configuration was established for (−)-**2** and, consequently, the *R* configuration for (+)-**2**.

The resolution procedure of **3** paralleled that of **2**. The only differences consisted in replacing methanol with 2-propanol in the diastereoselective crystallisation of the salt of (−)-**3** with (*S*)-**1** and in performing two crystallisations of the neutral sulphate of (+)-**3** liberated from the isopropanolic mother liquors. (−)-**3**·(*S*)-**1** precipitated from the solution of **3** and (*S*)-**1** in 72.1%

yield allowing to isolate (−)-**3** with >99.6% e.e. (determined by reversed-phase HPLC analysis of both (−)-**3**·(*S*)-**1** and (−)-**3**) and in 62.9% yield. (+)-**3** was liberated from the recrystallised sulphate of the amine recovered from mother liquors with 87.5% e.e. and in 49.2% yield. The respective *R* and *S* configurations of (−)-**3** and (+)-**3** were established on the basis of the fact that hydrogenation (H_2, 10% Pd/C, ethanol) of (−)-**3** led to (*R*)-(+)-1-phenylpropylamine with >99.6% e.e. This result is in agreement with reported data for the hydrogenation of (+)-**3** yielding (*S*)-(−)-1-phenylpropylamine.[4]

The resolution of **4** was performed in ethanol by the same procedure used for **2** and **3**. The salt of (+)-**4** with (*S*)-**1** precipitated in 60.3% yield and the enantiomeric excess of (+)-**4**, liberated from a sample of such a precipitate and transformed into benzamide before chiral HPLC analysis, proved to be 86%. Recrystallisation from the same solvent raised the enantiomeric excess to 98.1% with a moderately decreased chemical yield (44.7%). (+)-**4** was finally recovered in 41.8% yield. Unlike the amines (+)-**2** and (+)-**3**, the levorotatory antipode of **4** isolated from the mother liquors was not converted into sulphate and tentatively submitted to crystallisations considering its moderate starting enantiomeric excess (37%). The hydrogenation (H_2, 10% Pd/C, methanol) of (+)-**4** gave (+)-1-cyclohexylethylamine, to which the *S* configuration has been assigned,[14] allowing to establish the same configuration for the dextrorotatory enantiomer of **4**.

In contrast to **4**, the amine **5** turned out to be unresolvable with (*S*)-**1** failing to form solid precipitates upon treatment with this latter acid.

Finally, the resolution of **6** was accomplished by quantitative displacement of hydrogen chloride with (*S*)-**1** without isolating the free amine and by two successive crystallisations of the diastereomeric mixture from 2-propanol. The first precipitate was obtained in 59.2% yield and contained (*S*)-α-methylallylamine with 71% e.e. Recrystallisation raised the enantiomeric excess to 96.5% reducing the chemical yield to 40.5%. (*S*)-α-Methylallylamine was finally liberated from the recrystallised salt with (*S*)-**1** and its hydrochloride (*S*)-**6** isolated in 37.7% yield (18.9% of the starting **6**). The progress of the enantiomeric excess over the course of the resolution was verified by liberating the amine from its salts, i.e. the two salts with (*S*)-**1** and the final hydrochloride (*S*)-**6**, and analysing its benzamide by chiral HPLC. The *S* configuration was assigned to the resolved levorotatory hydrochloride on the basis of the fact that the previously reported partial resolution of α-methylallylamine had demonstrated that (*S*)-**1** generates the less soluble diastereomeric salt with (*S*)-α-methylallylamine.[2]

3. Discussion and conclusion

The definitive data for the preparation of (*S*)-**2**, (*R*)-**3**, (*S*)-**4** and (*S*)-**6** by selective precipitation of the salts formed with (*S*)-**1** are summarised in Table 1. Interestingly, the stereochemical outcome of the resolution of **3** is opposite to that of the other resolutions reported herein and of the previous ones of 1-arylalkylamines,[1,2] which had invariably produced the precipitation of the (*S*)(*S*)-salt. Comparison of the total resolution efficiencies (*E*) observed for **2** and **3**, 82 and 72%, respectively, with the lower efficiency (60%) achieved in the case of 1-phenylpropylamine[2] addresses the importance of the presence of the additional β,γ-unsaturation supporting our initial hypothesis. This is further substantiated by the resolvability, though with moderate efficiencies (44 and 39%, respectively), of **4** and **6** which contrasts the unfeasibility of the resolution of the corresponding saturated amines, 1-cyclohexylethylamine and 2-butylamine. In this context, the fact that, contrary to our expectation, the β,γ-unsaturated amine **5** is not

Table 1
Preparation of (*S*)-**2**, (*R*)-**3**, (*S*)-**4** and (*S*)-**6** by selective crystallisation of the salts with (*S*)-**1**

Compd	Yield (%)[a]		Ee (%)[b]	*E* (%)[c]
	Salt with (*S*)-**1**	Recovered substrate		
(*S*)-**2**	82.0	80.2	>99.6	82
(*R*)-**3**	72.1	62.9	>99.6	72
(*S*)-**4**	44.7	41.8	98.1	44
(*S*)-**6**	40.5	37.7	96.5	39

[a] Relative to the theoretical amount, i.e. half of the starting racemate.
[b] Enantiomeric excess determined by chiral HPLC.
[c] Total resolution efficiency = chemical yield of the crystallised salt with (*S*)-**1** (%) × enantiomeric excess of the recovered substrate (%)/100.

resolved by **1** would simply indicate that the only presence of a β,γ-unsaturation does not assure the resolvability, which is obviously conditioned also by other structural features of the aminic substrates.

Apart from these considerations, we finally wish to point out the very high efficiencies of the resolutions of **2** and **3**, which allow to obtain both the enantiomers of the two amines in excellent yields using only one antipode of the resolving acid, and the possibility of scaling up such procedures thanks to their simplicity, as made for the preparation of (*R*)- and (*S*)-isopropylidene glycerol via resolution of **1** with 1-phenylethylamine.[15]

4. Experimental

Reagents were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz on a Bruker 220 AC. Optical rotations were measured in a 1-dm cell of 1 ml capacity using a Perkin Elmer 241 polarimeter. HPLC analyses were performed on Chiralcel columns (250×4.6 mm i.d.) from Daicel using a Waters 510 pump and a Pye Unicam Pu 4025 UV detector ($\lambda = 254$ nm).

The resolving agent (*S*)-**1** was prepared by resolution of **1** with (*S*)-1-phenylethylamine.[16] Amine **2** was synthesised according to literature procedures.[6,7] Base-catalysed addition of trichloroacetonitrile to cinnamyl alcohol afforded the corresponding trichloroacetimidic ester, which was submitted to thermal rearrangement obtaining *N*-(1-phenyl-2-propenyl)-trichloroacetamide. Final removal of the trichloroacetyl group by treatment with dilute base yielded **2**. Amine **3** was synthesised by hydrolysis of the corresponding acetamide, which was in turn obtained from 1-phenyl-2-propyn-1-ol via Ritter reaction as described by Hacksell.[8] 1-(1-Cyclohexenyl)ethanol **7** was prepared by reduction of 1-acetyl-1-cyclohexene with sodium borohydride in the presence of cerium(III) chloride using the general procedure reported in the literature.[9,10] *N*-α-Methylallylphthalimide **10** was obtained from 3-chloro-1-butene and potassium phthalimide as described previously.[13]

4.1. N-*1-(1-Cyclohexenyl)ethylphthalimide* ***8*** *and (*E*)-*N*-2-ethylidenecyclohexylphthalimide* ***9***

Diethyl azodicarboxylate (79.57 g, 456.9 mmol) was added dropwise to a mixture of **7** (57.66 g, 456.9 mmol), phthalimide (67.22 g, 456.9 mmol) and triphenylphosphine (119.84 g, 456.9 mmol)

in tetrahydrofuran (700 ml) at room temperature. After the resulting solution had been stirred overnight at room temperature, the solvent was removed in vacuo. Diethyl ether was added to the residue to precipitate triphenylphosphine oxide and diethyl hydrazinedicarboxylate which were filtered off. The filtrate was concentrated and the oily residue was applied to a silica gel column which was eluted with *n*-heptane:ethyl acetate 95:5 obtaining, in sequence, 45.76 g (39.2%) of **8** and 31.29 g (26.8%) of **9** as white solids. **8**: mp 44.5–46.6°C; ^{1}H NMR ($CDCl_3$): δ 1.45–1.65 (m, 4H), 1.60 (d, 3H, $J=7$), 1.92 (m, 2H), 2.04 (m, 2H), 4.77 (q, 1H, $J=7$), 5.72 (m, 1H), 7.65–7.75 (m, 2H), 7.75–7.88 (m, 2H). **9**: mp 121–122°C; ^{1}H NMR ($CDCl_3$): δ 1.25–1.70 (m, 2H), 1.55 (d, 3H, $J=6.6$), 1.70–2.05 (m, 4H), 2.52 (ddd, 1H, $J=25$, 12.5, 3.5), 2.80 (m, 1H), 4.68 (m, 1H), 4.89 (q, 1H, $J=6.6$), 7.65–7.75 (m, 2H), 7.78–7.88 (m, 2H).

4.2. 1-(1-Cyclohexenyl)ethylamine ***4***

A mixture of **8** (40.26 g, 157.7 mmol), hydrazine monohydrate (16 ml) and 95% ethanol (400 ml) was heated to 60°C for 90 min, cooled to 20°C, treated with concd hydrochloric acid (40 ml) and filtered. The filtrate was concentrated and the resulting solid residue treated with water (200 ml) and diethyl ether (150 ml). The aqueous phase was made alkaline with KOH and, after separating the organic layer, extracted with diethyl ether (3×150 ml) again. The ethereal extracts were combined, dried and concentrated to give 19.1 g (96.7%) of **4** as a pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 1.11 (d, 3H, $J=6.5$), 1.38 (bs, 2H), 1.40–1.70 (m, 4H), 1.80–2.10 (m, 4H), 3.31 (q, 1H, $J=6.5$), 5.53 (bs, 1H).

*4.3. (*E*)-2-Ethylidenecycloexylamine* ***5***

Obtained, in 73.3% yield, from **9** as a yellow oil by the same procedure used to prepare **4** from **8**; ^{1}H NMR ($CDCl_3$): δ 1.1–1.9 (m, 9H), 1.56 (d, 3H, $J=6.6$), 2.40–2.55 (m, 1H), 3.10–3.20 (m, 1H), 5.27 (q, 1H, $J=6.6$).

4.4. α-Methylallylamine hydrochloride ***6***

A mixture of **10** (86.75 g, 431.1 mmol), hydrazine monohydrate (22 ml) and 95% ethanol (350 ml) was heated at 60°C for 3 h, cooled at 5°C, treated with concd hydrochloric acid (40 ml) and filtered. The filtrate was concentrated and the resulting solid residue treated with water (50 ml) and diethyl ether (150 ml). The aqueous phase was made alkaline with KOH and, after separating the organic layer, extracted with diethyl ether (5×150 ml) again. The ethereal extracts were combined, acidified by addition of 4N HCl/EtOH and concentrated to give a solid (31.4 g), which was crystallised from ethanol and diethyl ether obtaining 20.58 g (44.4%) of **6** as a white solid: mp 124.8–125.4°C; ^{1}H NMR (DMSO-d_6): δ 1.32 (d, 3H, $J=6.7$), 3.79 (m, 1H), 5.27 (d, 1H, $J=10.5$), 5.36 (d, 1H, $J=17.4$), 5.95 (ddd, 1H, $J=17.4$, 10.5, 6.4), 8.46 (bs, 3H). Anal. calc. for $C_4H_{10}ClN$ (107.58): C, 44.66; H, 9.36; Cl, 32.96; N, 13.02. Found: C, 44.36; H, 9.28; Cl, 32.49; N, 12.96.

*4.5. (*S*)-1-Phenyl-2-propenylamine (*S*)-**2**

(*S*)-**1** (17.74 g, 63.29 mmol) and **2** (8.43 g, 63.29 mmol) were combined in methanol (70 ml). The precipitate, which immediately separated, was redissolved by heating the stirred mixture to

boiling temperature. Stirring of the resultant solution was continued overnight at room temperature and then at 5°C for 30 min to yield a white precipitate of (*S*)-**1**·(*S*)-**2** (10.73 g), which was collected by filtration and rinsed with cold methanol: mp 144.8–145.2°C; e.e. of (*S*)-**2** >99.6% (by HPLC analysis of the salt on a Chiralcel OD-R column; 80/20 1 M $NaClO_4/CH_3CN$, 0.4 ml/min); ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 3H), 1.36 (s, 3H), 3.83 (dd, 1H), 4.06 (dd, 1H), 4.21 (d, 1H), 4.36 (m, 1H), 4.80 (d, 1H, $J=6$), 5.24 (d, 1H, $J=10$), 5.31 (d, 1H, $J=17$), 6.13 (ddd, 1H, $J=17$, 10, 6), 7.30–7.55 (m, 8H), 7.75 (dd, 1H). The salt was decomposed by treatment with 10% HCl (50 ml) and dichloromethane (50 ml). The organic layer was separated and extracted with 10% HCl (3×30 ml) again. The aqueous phases were combined, made alkaline by addition of NaOH and extracted with ethyl acetate (4×50 ml). Removal of the solvent from the organic extracts, previously washed with brine and dried over Na_2SO_4, gave (*S*)-**2** (3.38 g, 80.2% of the theoretical amount) as a pale yellow oil: $[\alpha]_D^{25}=-10.45$ (*c* 4, chloroform); e.e.>99.6% (by HPLC under the same conditions as described for (*S*)-**1**·(*S*)-**2**); ^{1}H NMR ($CDCl_3$): δ 1.58 (bs, 2H), 4.53 (d, 1H, $J=7$), 5.12 (d, 1H, $J=10$), 5.20 (d, 1H, $J=17$), 6.04 (ddd, 1H, $J=17$, 10, 7), 7.20–7.40 (m, 5H).

4.6. (R)-1-Phenyl-2-propenylamine (R)-2

The methanolic solution remaining from the isolation of (*S*)-**1**·(*S*)-**2** was concentrated and the residual salt decomposed in the same way as described for (*S*)-**1**·(*S*)-**2** obtaining the *R*-enriched amine (3.86 g): $[\alpha]_D^{25}=+8.37$ (*c* 4, chloroform). The recovered amine was dissolved in 95% ethanol (25 ml) and combined with a solution of concentrated sulphuric acid (0.81 ml) in 95% ethanol (25 ml). The solution was concentrated and the resultant solid dissolved in boiling ethanol (18 ml). The alcoholic solution was slowly cooled to room temperature under stirring to yield a white precipitate (2.46 g), which was isolated by filtration and treated with 1 M NaOH (30 ml) and ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3×20 ml) again. The organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give (*R*)-**2** (1.79 g, 42.5% of the theoretical amount, i.e. half of 8.43 g of starting racemic amine) as an oil: $[\alpha]_D^{25}=+10.23$ (*c* 4, chloroform); e.e.>99.6% (by HPLC under the same conditions as described for (*S*)-**1**·(*S*)-**2**); ^{1}H NMR identical to (*S*)-**2**.

4.7. (R)-1-Phenyl-2-propinylamine (R)-3

(*S*)-**1** (18.48 g, 65.94 mmol) and **3** (8.65 g, 65.94 mmol) were combined in 2-propanol (175 ml). The resultant solution was stirred overnight at room temperature to yield a white precipitate of (*S*)-**1**·(*R*)-**3** (9.78 g), which was collected by filtration and rinsed with cold 2-propanol: mp 105.3–106.5°C dec.; e.e. of (*R*)-**3**>99.6% (by HPLC analysis of the salt on a Chiralcel OD-R column; 85/15 1.5 M $NaClO_4/CH_3CN$, 0.5 ml/min); ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 3H), 1.36 (s, 3H), 3.50 (bs, 1H), 3.82 (dd, 1H), 4.08 (dd, 1H), 4.25 (d, 2H), 4.36 (m, 1H), 4.92 (bs, 1H), 7.30–7.50 (m, 3H), 7.50–7.70 (m, 5H), 7.78 (m, 1H). The salt was decomposed in the same way as described for (*S*)-**1**·(*S*)-**2** yielding (*R*)-**3** (2.72 g, 62.9% of the theoretical amount) as a white low-melting solid: $[\alpha]_D^{20}=-27.9$ (*c* 10, ethanol), $[\alpha]_D^{23}=-30.9$ (*c* 1, chloroform) [lit.[4] $[\alpha]_D^{23}=-31.3$ (*c* 1, chloroform)]; e.e.>99.6% (by HPLC under the same conditions as described for (*S*)-**1**·(*R*)-**3**); ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 2H), 2.50 (d, 1H, $J=2$), 4.79 (d, 1H, $J=2$), 7.30–7.45 (m, 3H), 7.50–7.60 (m, 2H).

4.8. (S)-1-Phenyl-2-propinylamine (S)-3

The filtrate from the crystallisation of (*S*)-**1**·(*R*)-**3** was concentrated and the residual salt decomposed in the same way as described for (*S*)-**1**·(*S*)-**2** obtaining the *S*-enriched amine (4.46 g): e.e. 55% (determined, before the decomposition, by HPLC analysis of the salt under the same conditions as described for (*S*)-**1**·(*R*)-**3**). The recovered amine was dissolved in 95% ethanol (22 ml), combined with a solution of concentrated sulphuric acid (0.95 ml) in 95% ethanol (23 ml) and stirred overnight at room temperature and then at 0°C for 30 min to yield a white precipitate (4.29 g) which was isolated by filtration and treated with 2.5 M NaOH (20 ml) and ethyl acetate (25 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3×25 ml) again. The organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give (*S*)-**3** (2.98 g). The latter was analysed by HPLC under the same conditions as described for (*S*)-**1**·(*R*)-**3** and its enantiomeric excess found to be 69%. Treatment with concentrated sulphuric acid (0.63 ml) in 95% ethanol (31 ml) was repeated isolating 3.03 g of precipitated sulphate, which yielded, upon decomposition of the salt as above, (*S*)-**3** (2.13 g, 49.2% of the theoretical amount, i.e. half of 8.65 g of starting racemic amine) as a white low-melting solid: $[\alpha]_D^{20} = +23.75$ (*c* 10, ethanol); e.e. 87.5% (by HPLC under the same conditions as described for (*S*)-**1**·(*R*)-**3**); ^{1}H NMR identical to (*R*)-**3**.

4.9. (S)-1-(1-Cyclohexenyl)ethylamine (S)-4

(*S*)-**1** (30.13 g, 107.50 mmol) and **4** (13.46 g, 107.50 mmol) were combined in ethanol (90 ml). The resultant solution was stirred overnight at room temperature and then at 0°C for 1 h to yield a white precipitate (13.14 g), which was collected by filtration and rinsed with ethanol cooled to –5°C. (*S*)-**4**, liberated from a sample of this precipitate, was 86% enantiomerically pure (e.e. determined by HPLC of the corresponding benzamide on a Chiralcel-OD column; hexane/2-propanol 9/1, 1 ml/min). The solid was recrystallised from ethanol (30 ml) to give 9.75 g of (*S*)-**1**·(*S*)-**4**: mp 132.8–133.8°C; e.e. of (*S*)-**4** 98.12% (determined, after liberation of a sample of amine and conversion into benzamide, by HPLC analysis under the above-mentioned conditions); ^{1}H NMR (DMSO-d_6): δ 1.28 (d, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.45–1.70 (m, 4H), 1.90–2.10 (m, 4H), 3.62 (q, 1H), 3.84 (dd, 1H), 4.06 (dd, 1H), 4.18 (d, 2H), 4.35 (m, 1H), 5.74 (bs, 1H), 7.30–7.55 (m, 3H), 7.73 (d, 1H). The salt was decomposed by treatment with 10% HCl (30 ml) and dichloromethane (30 ml). The organic layer was separated and extracted with 10% HCl (2×30 ml) again. The aqueous phases were combined, made alkaline by addition of NaOH and extracted with ethyl ether (4×100 ml). Removal of the solvent from the organic extracts, previously washed with brine and dried over Na_2SO_4, gave (*S*)-**4** (2.81 g, 41.8% of the theoretical amount) as a pale yellow oil: $[\alpha]_D^{25} = +1.0$ (neat); e.e. identical to that previously determined for the amine liberated from a sample of (*S*)-**1**·(*S*)-**4**; ^{1}H NMR identical to **4**.

4.10. (S)-α-Methylallylamine hydrochloride (S)-6

A solution of sodium methoxide (9.79 g, 181 mmol) in methanol (20 ml) was added to a stirred solution of **6** (19.5 g, 181 mmol) in methanol (30 ml) at 5°C. After 15 min, precipitated sodium chloride was quickly removed by suction filtration, maintaining the filtrate at 5°C. The latter was added with a methanolic solution of (*S*)-**1** (50.73 g, 181 mmol) and concentrated to give a yellow viscous oil (62 g), which was dissolved in 2-propanol (160 ml). The solution was

stirred overnight at room temperature and then at 0°C for 30 min to yield a white precipitate (18.84 g), which was collected by filtration and rinsed with 2-propanol cooled to 5°C. (*S*)-α-Methylallylamine, liberated from a sample of this precipitate by treatment with ether and 2N HCl, successive alkalisation of the separated aqueous phase with 6N NaOH and final extraction with ether, was 71% enantiomerically pure (e.e. determined by HPLC, after treatment of the ethereal solution of the amine with benzoyl chloride in the presence of triethylamine, on a Chiralcel-OD column; hexane/2-propanol 95/5, 0.7 ml/min). The solid was recrystallised from 2-propanol (40 ml) to give 12.89 g of the salt of (*S*)-α-methylallylamine with (*S*)-**1**: mp 108–110°C; e.e. of (*S*)-α-methylallylamine 96.50% (determined, after liberation of the amine from a sample of the salt and conversion into benzamide, by HPLC analysis under the above-mentioned conditions); ^{1}H NMR (DMSO-d_6): δ 1.28 (d, 3H, $J=6$), 1.28 (s, 3H), 1.33 (s, 3H), 3.72–3.84 (m, 2H), 4.04 (dd, 1H, $J=8.4$, 6.2), 4.16 (d, 2H, $J=5.9$), 4.33 (m, 1H), 5.20 (dd, 1H, $J=10.3$, 1.1), 5.30 (dd, 1H, $J=17.2$, 1.1), 5.94 (ddd, 1H, $J=17.2$, 10.3, 6.2), 7.34–7.48 (m 3H), 7.69–7.74 (m, 1H), 8.50 (bs, 3H). The salt was decomposed by treatment with 1N HCl (50 ml) and dichloromethane (140 ml). The aqueous phase was separated, washed with dichloromethane (2×40 ml) and concentrated to give a solid residue (4.03 g), which was crystallised from ethanol and ether yielding (*S*)-**6** (3.68 g, 37.7% of the theoretical amount) as a white solid: mp 130–132°C; $[\alpha]_D^{20}=-3.5$ (*c* 10, ethanol); e.e. identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**1**; ^{1}H NMR identical to **6**.

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16. As described in Ref. 1, (*S*)-**1** and (*R*)-**1** can be indifferently prepared either by resolution of **1** with 1-phenylethylamine or by esterification of (*R*)- and (*S*)-isopropylidene glycerol with phthalic anhydride, respectively.