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Isopropylidene Glycerol Hydrogen Phthalate: a New Resolving Agent. Application to the Resolution of 1-Arylethylamines

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Abstract. Hydrogen phthalates of (*R*)- and (*S*)-isopropylidene glycerol, obtainable from racemic isopropylidene glycerol by reaction with phthalic anhydride and successive resolution with (*S*)- and (*R*)-1-phenylethylamine or, alternatively, from (*R*)-and (*S*)-isopropylidene glycerol, were regarded as potential new resolving agents. A range of important 1-arylethylamines was selected to test their resolving capability. In particular, trial resolutions were carried out using equivalent amounts of racemic amine and hydrogen phthalate of (*R*)-isopropylidene glycerol. The salts of the *S* isomers selectively crystallized from methanol or 2-propanol allowing to recover the (*S*)-1-arylethylamines in high chemical and optical yields.
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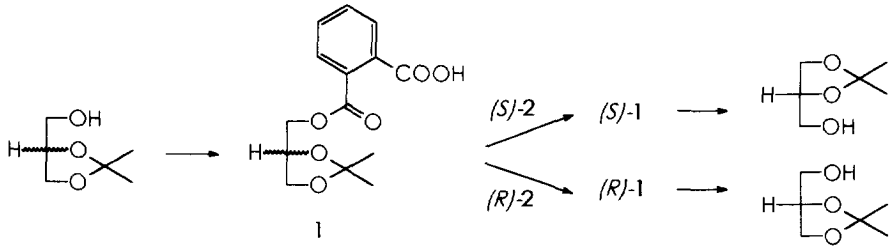
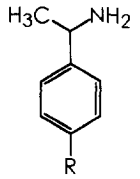
Notwithstanding the revolutionary advances in catalytic asymmetric synthesis and enzymatic kinetic resolution, diastereomer crystallization still constitutes the most important methodology for the industrial manufacture of pure enantiomers. Using this classical technique, we recently obtained both enantiomers of isopropylidene glycerol, a chiral synthon of highest importance, otherwise poorly available in the *R* form, in high chemical yield and enantiomeric excess.[1] The easy procedure, based on the resolution of isopropylidene glycerol hydrogen phthalate **1** with the enantiomers of 1-phenylethylamine (*S*)-**2** and (*R*)-**2** (Scheme 1), was successively improved and scaled up to the ton scale.

Scheme 1

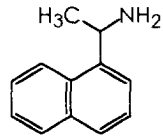


The reasonable chemical [2] and configurational [3] stability, the ready quantitative recovery from the crystallization step and, last but not least, the equally large availability, resulting from the above procedure, of (*R*)-**1** and (*S*)-**1** led us to consider their potential use as resolving agents. Such a project seemed even more attractive on account of the fact that the number of acidic resolving agents known is quite small and, moreover, their application is often seriously limited by inadequate availability of one of the two enantiomeric forms and/or by laborious recovery at the end of the process.

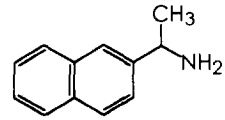
Relying on the effective resolution of **1** with (*S*)-**2** and (*R*)-**2**, it was conceivable that (*R*)-**1** and (*S*)-**1** could resolve racemic 1-arylethylamines. Therefore this class of amines was identified as the most suitable initial probe of the resolving capability of the chiral hydrogen phthalate. The choice of 1-(4-bromophenyl)-, 1-(4-nitrophenyl)-, 1-(1-naphthyl)- and 1-(2-naphthyl)ethylamine (**3**, **4**, **5** and **6**, respectively) was made considering the significantly different steric and electronic properties and the high value of the pure enantiomers, which are efficient, but also expensive, resolving agents,[4] chiral synthons[5] or chiral auxiliaries.[6]



2 R = H
3 = Br
4 = NO_2



5



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For our investigation we decided to utilize (*S*)-**1**, whose preparation required the following steps:[7] (a) reaction of phthalic anhydride with racemic isopropylidene glycerol in pyridine leading to **1**, (b) resolution of **1** by salt formation with (*S*)-**2** in methanol and recrystallization from the same solvent, and (c) recovery of (*S*)-**1** as a viscous colourless oil from the salt by ethyl acetate-2N H_2SO_4 extraction. Alternatively, (*S*)-**1** was obtained by reaction of (*R*)-isopropylidene glycerol with phthalic anhydride in pyridine. In both cases, chiral HPLC analysis of (*S*)-**1**, previously methylated by diazomethane, indicated enantiomeric excesses higher than 99%.

The results of trial resolutions with (*S*)-**1** are summarized in Table 1. Interestingly, the five amines, in spite of the different electronic and steric features, behaved in the same way, the *S* form invariably giving the less soluble diastereomeric salt. Though expected, resolution of **2** was included in the experiments to obtain reference values of chemical yield and enantiomeric excess. Indeed (*S*)-**1** excellently resolved **2** (entry 1). In fact, the white crystalline precipitate, collected from the methanolic mixture of equivalent amounts of (*S*)-**1** and **2**, afforded, after usual extractive procedures and vacuum distillation, enantiomerically pure (*S*)-**2** (e.e.>99%) in 62.8% yield (31.4% of the starting **2**).

Using stoichiometric (*S*)-**1** and methanol as a solvent, we analogously resolved **3** and **4** (entries 2 and 3). Again recrystallizations were unnecessary, (*S*)-**3** and (*S*)-**4** being recoverable from the first formed precipitates with very high 98.6% and >96% e.e. respectively. Chemical yields were even more satisfactory than in the case of **2**, namely 68.6% and 64.4%.

On the contrary initial attempts of resolving **5** were not entirely successful. (*S*)-**5** was obtained in only 50.5% e.e. and 45.5% yield, performing the resolution in methanol (entry 5). On the other hand, replacement of the

latter with water or ethanol produced noteworthy, but still inadequate increases in enantiomeric excess and chemical yield (entries 4 and 6). Finally, 2-propanol fulfilled our requirements (entry 7). (*S*)-**5** could be obtained in 86.3% e.e. and 77.6% yield. Recrystallization from the same solvent raised the enantiomeric excess to 99.5% with a moderately decreased chemical yield (63.6%).

Table 1. Preparation of (*S*)-1-arylethylamines from the corresponding racemates by selective crystallization of the respective salts with (*S*)-**1**[a]

(*RS*)-amine + (*S*)-**1** → (*R*)(*S*)-salt + (*S*)(*S*)-salt
more soluble less soluble

entry	amine	solvent	yield,[b] %			ee,[c] %		$[\alpha]_D$,[d]
			1st cryst.[e]	2nd cryst.	recovered amine	1st cryst.	2nd cryst.	
1	(*S*)-**2**	methanol	82.0	-[f]	62.8	>99	-	- 40.65 [g]
2	(*S*)-**3**	"	70.5	-[f]	68.6	98.6	-	- 26.3 [h]
3	(*S*)-**4**	"	70.7	-[f]	64.4	>96	-	- 6.95 [i]
4	(*S*)-**5**	water	55.0	-[j]	-	78.7	-	-
5	(*S*)-**5**	methanol	45.5	-[j]	-	50.5	-	-
6	(*S*)-**5**	ethanol	50.2	-[j]	-	64.7	-	-
7	(*S*)-**5**	2-propanol	77.6	66.4	63.6	86.3	99.5	- 62 [k]
8	(*S*)-**6**	"	54.6	46.6	45.6	94.9	99.5	- 20.9 [l]

a) All crystallizations were performed using equivalent amounts of racemic amine and (*S*)-**1**. b) Relative to the theoretical amount, i.e., half of starting racemate. c) Enantiomeric excess of the amines determined by reversed-phase chiral HPLC analysis of the corresponding salts with (*S*)-**1** on a Chiralcel OD-R column from *Daicel* (el. $NaClO_4$ aq./CH_3CN mixtures) or, in the only case of (*S*)-**4**, by ^1H NMR analysis of the free amine in the presence of $Eu(hfc)_3$. d) At 20°C, with the exception of (*S*)-**6**, whose optical rotation was measured at 25°C. e) From the solution of racemic amine and (*S*)-**1**. f) The recrystallizaion was not performed, since unnecessary. g) Neat (lit.[9] - 40.5). h) Neat (lit.[10] + 25, for the *R* isomer). i) *c* 1, 0.05 M NaOH (as hydrochloride); - 7.2 ± 0.5, for a reference sample (*Fluka*) of (*S*)-**4**·HCl. j) The resolution process was dropped because of poor enantiomeric excess and/or chemical yield. k) *c* 5, MeOH (lit.[12,13] - 62). l) c 2.5, EtOH (lit.[14] - 21).

On the basis of the above results, 2-propanol was also used for the resolution of **6** (entry 8). (*S*)-**6** was isolated, after recrystallization, with 99.5% e.e. and in a reasonable 45.6% yield (22.8% of the starting **6**). The first precipitate had been obtained in 94.9% e.e. and 54.6% yield.

The enantiomeric excesses of (*S*)-**3**, (*S*)-**5** and (*S*)-**6** were determined by reversed-phase chiral HPLC analysis under conditions effective in enantioseparation. By the same analytical method **2** was almost completely, but not baseline resolved, the *R* form eluting first. Therefore the enantiomeric excess of (*S*)-**2** was assumed to be greater than 99% on the basis of no chromatographic detection of (*R*)-**2**, consistently with measured -40.65

specific rotation. Finally, our attempts at resolving **4** by analytical chiral HPLC were completely unsuccessful. In contrast ^{1}H NMR analysis in the presence of Eu(hfc)$_3$ proved to be effective, though not very sensitive in the case of high enantiomeric excesses. On this basis the absence of (*R*)-**4** in the (*S*)-**4** spectrum led us to estimate its content lower than 2% (e.e. of (*S*)-**4** >96%). This value was consistent with measured -6.95 specific rotation.

The *R* amines were not isolated from the alcoholic solutions remaining from the original crystallizations of (*S*)-amine-(*S*)-**1** salts. Conceivably, they would have been recovered from these solutions in moderate optical yields and their enantiomeric excesses easily maximized by successive crystallization of the respective salts with (*R*)-**1**. The latter, analogously to (*S*)-**1**, is readily accessible either by resolution of **1** with (*R*)-**2** or reaction of (*S*)-isopropylidene glycerol with phthalic anhydride.

In summary, we have developed a new acidic resolvent agent, which is (a) readily available in both enantiomeric forms, (b) easily recoverable from the crystallization step, and (c) chemically and optically stable to our resolution conditions. It has proved to be very efficient in resolving an important class of amines, such as 1-arylethylamines. At present no more informations on its versatility are available. Further investigations about reuse and additional applications may reveal its full potential.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker 200 (200 MHz) instrument. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were measured in a 1-dm cell of 1 ml capacity using a Perkin-Elmer 1310 instrument. HPLC analyses were performed on Chiralcel columns (250x4.6 mm I.D.) from *Daicel*.

Starting Materials. Racemic amines **3**, **5** and **6** were readily synthesized by the Leuckart reaction according to the experimental procedure reported for **2**.[8] The latter was purchased from *Aldrich Chemical Co.*. **4** was prepared from **2** according to the methodology reported for (*R*)-**4** and (*S*)-**4**.[4a] (*R*)-Isopropylideneglycerol, $[\alpha]_D^{20}$ = - 15.2 (neat, *l* = 0.1), was purchased from *Chemi S.p.a.*.

(*S*)-Isopropylideneglycerol Hydrogen Phthalate (*S*)-1.

Method A: From (*R*)-isopropylideneglycerol. A mixture of (*R*)-isopropylideneglycerol (25 g, 189.2 mmol), phthalic anhydride (28 g, 189.2 mmol) and pyridine (17 ml, 210 mmol) was stirred at 90°C for 1 h. After cooling, ethyl acetate (300 ml) and 2N H_2SO_4 (120 ml) were added. The organic phase was separated, washed with saturated aq. NaCl, dried with Na_2SO_4, and concentrated to give (*S*)-**1** (52 g, 98%) as a colourless oil: $[\alpha]_D^{25}$ = - 10 (*c* 1, ethanol); e.e.> 99% [determined on the corresponding methyl ester, prepared by treatment with diazomethane, by HPLC on a Chiralcel OJ column from *Daicel*, using a mixture of *n*-hexane and 2-propanol (92:8) as a mobile phase (flow-rate 0.6 ml/min)]; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.4 (s, 3 H), 3.8 (dd, 1 H), 4.1 (dd, 1 H), 4.4 (m, 3 H), 7.4-7.7 (m, 3 H), 7.85 (m, 1 H), 11.1 (s, 1 H).

Method B: From racemic isopropylideneglycerol. **1** (52.5 g, 187.3 mmol), prepared from phthalic anhydride (28 g, 189.2 mmol) and racemic isopropylideneglycerol (25 g, 189.2 mmol) according to the above procedure, was diluted in methanol (250 ml) and treated, at 50°C, with (*S*)-**2** [*Aldrich*; 22.7 g, 187.3 mmol]. After slow cooling to about 10°C, the precipitate was recovered by filtration and rinsed with cold methanol. The resulting white solid (27 g) was dried, refluxed with methanol (75 ml) for 2 h, cooled to 5°C, and filtered to give the pure salt between (*S*)-**2** and and (*S*)-**1** (22.5 g) as a white crystalline solid: m.p. 142-143°C; ^{1}H NMR (DMSO) δ 1.3 (s, 3 H), 1.35 (s, 3 H), 1.55 (d, 3 H), 3.8 (dd, 1 H), 4.05 (pseudo t, 1 H), 4.2 (d, 2 H), 4.35 (m, 2 H), 7.3-7.6 (m, 8 H), 7.75 (m, 1 H). The salt was suspended in ethyl acetate. After removing (*S*)-**2** by acidic washing with 2N H_2SO_4, the solvent was evaporated under vacuum to give (*S*)-**1** (15.3 g, 29% of the starting **1**) as a colourless oil: e.e.> 99% [determined as described in Method A].

(*S*)-1-Phenylethylamine (*S*)-2. (*S*)-**1** (23.1 g, 82.5 mmol) and **2** (10 g, 82.5 mmol) were combined in methanol (70 ml) and heated to boiling temperature. The resulting solution was allowed to cool to room temperature to

yield a white precipitate of (*S*)-**1**-(*S*)-**2** salt (13.59 g), which was filtered and rinsed with cold methanol: e.e. of (*S*)-**2** > 99% [determined by HPLC analysis of the salt on a Chiralcel OD-R column from *Daicel*, using a mixture of 1.5M $NaClO_4$ and CH_3CN (85:15) as a mobile phase (flow rate 0.4 ml/min)]. The salt was decomposed by treatment with 10% HCl and CH_2Cl_2. The aqueous phase was separated, made alkaline with 1N NaOH, and extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave an oil, which was distilled under vacuum yielding (*S*)-**2** (3.14 g, 62.8% of the theoretical amount) as a colourless oil: $[\alpha]_D^{20}$ = - 40.65 (neat, d = 0.94) [lit.[9] $[\alpha]_D^{20}$ = - 40.5 (neat)]; ^1H NMR ($CDCl_3$) δ 1.4 (d, 3 H), 1.6 (s, 2 H), 4.1 (q, 1 H), 7.2-7.4 (m, 5 H).

(*S*)-1-(4-Bromophenyl)ethylamine (*S*)-3. (*S*)-**1** (14 g, 50 mmol) and **3** (10 g, 50 mmol) were combined in methanol (90 ml). The resulting solution was treated as described above for the resolution of (*S*)-**2** to give (*S*)-**1**-(*S*)-**3** salt (8.46 g): m.p. 147-148°C; e.e. of (*S*)-**3** 98.6% [determined by HPLC analysis of the salt on a Chiralcel OD-R column, using a mixture of 1M $NaClO_4$ and CH_3CN (85:15) as a mobile phase (flow rate 0.8 ml/min)]; ^1H NMR (DMSO) δ 1.3 (s, 3 H), 1.35 (s, 3 H), 1.5 (d, 3 H), 3.8 (dd, 1 H), 4.05 (pseudo t, 1 H), 4.2 (d, 2 H), 4.35 (m, 2 H), 7.4-7.55 (m, 5 H), 7.6 (d, 2 H), 7.75 (m, 1 H). The salt was decomposed in the same way as described for the hydrogen phthalate of (*S*)-**2** yielding (*S*)-**3** (3.43 g, 68.6% of the theoretical amount) as a colourless oil: $[\alpha]_D^{20}$ = - 26.3 (neat, d = 1.371) [lit.[10] $[\alpha]_D^{20}$ = + 25 (neat, for the *R* isomer)]; $[\alpha]_D^{20}$ = - 20.25 (*c* 2, MeOH) [lit.[11] $[\alpha]_D^{20}$ = - 20.3 (*c* 2, MeOH)]; ^1H NMR ($CDCl_3$) δ 1.35 (d, 3 H), 1.5 (s, 2 H), 4.1 (q, 1 H), 7.2 (d, 2 H), 7.45 (d, 2 H).

(*S*)-1-(4-Nitrophenyl)ethylamine (*S*)-4. (*S*)-**1** (8.44 g, 30 mmol) and **4** (5 g, 30 mmol) were combined in methanol (45 ml). The resulting solution was treated as described above for the resolution of (*S*)-**2** to give (*S*)-**1**-(*S*)-**4** salt (4.74 g): m.p. 142-143°C; ^1H NMR (DMSO) δ 1.3 (s, 3 H), 1.35 (s, 3 H), 1.5 (d, 3 H), 3.8 (dd, 1 H), 4.1 (pseudo t, 1 H), 4.2 (d, 2 H), 4.3-4.5 (m, 2 H), 7.35-7.6 (m, 3 H), 7.7-7.9 (m, 3 H), 8.25 (d, 2 H). The salt was decomposed by treatment with 10% HCl and CH_2Cl_2. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave (*S*)-**4** (1.61 g, 64.4% of the theoretical amount) as an oil: $[\alpha]_D^{20}$ = - 6.95 (*c* 1, 0.05M NaOH; as hydrochloride) [$[\alpha]_D^{20}$ = - 7.2 (*c* 1, 0.05M NaOH; for a reference sample (*Fluka*) of (*S*)-**4**·HCl)]; e.e. > 96% [determined by ^1H NMR in $CDCl_3$ in the presence of Eu(hfc)$_3$]; ^1H NMR ($CDCl_3$) δ 1.4 (d, 3 H), 1.6 (s, 2 H), 4.25 (q, 1 H), 7.5 (d, 2 H) 8.15 (d, 2 H).

(*S*)-1-(1-naphthyl)ethylamine (*S*)-5. (*S*)-**1** (8.18 g, 29 mmol) and **5** (5 g, 29 mmol) were combined in 2-propanol (70 ml). The resulting solution was treated as described above for the resolution of (*S*)-**2** to give a white crystalline solid (5.12 g), which was recrystallized from 2-propanol (20 ml) yielding (*S*)-**1**-(*S*)-**5** salt (4.36 g): m.p. 135-136°C; e.e. of (*S*)-**5** 99.5% (86.3%, before the recrystallization) [determined by HPLC analysis of the salts on a Chiralcel OD-R column, using a mixture of 0.1M $NaClO_4$ and CH_3CN (6:4) as a mobile phase (flow rate 0.5 ml/min)]; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.35 (s, 3 H), 1.65 (d, 3 H), 3.55 (pseudo t, 1 H), 3.75-4.25 (m, 4 H), 5.2 (m, 1 H), 6.8-7.95 (m, 11 H), 8.9 (br s, 3 H). The salt was decomposed by treatment with 1N NaOH and toluene. The organic phase was separated, washed with water, dried over Na_2SO_4, and concentrated affording (*S*)-**5** (1.59 g, 63.6% of the theoretical amount) as a colourless oil: $[\alpha]_D^{20}$ = - 62 (*c* 5, MeOH) [lit.[12,13] $[\alpha]_D^{20}$ = - 62 (*c* 5, MeOH)]; ^1H NMR ($CDCl_3$) d 1.55 (d, 3 H), 1.7 (s, 2 H), 4.95 (q, 1 H), 7.45-7.9 (m, 6 H), 8.15 (m, 1 H).

(*S*)-1-(2-naphthyl)ethylamine (*S*)-6. (*S*)-**1** (8.18 g, 29 mmol) and **6** (5 g, 29 mmol) were combined in 2-propanol (80 ml). The resulting solution was treated as described above for the resolution of (*S*)-**2** to give a white crystalline solid (3.6 g), which was recrystallized from 2-propanol (25 ml) yielding (*S*)-**1**-(*S*)-**6** salt (3.07 g): m.p. 126-127°C; e.e. of (*S*)-**6** 99.5% (94.9%, before the recrystallization) [determined by HPLC analysis of the salts on a Chiralcel OD-R column, using a mixture of 0.1M $NaClO_4$ and CH_3CN (6:4) as a mobile phase (flow rate 0.5 ml/min)]; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.35 (s, 3 H), 1.55 (d, 3 H), 3.5 (pseudo t, 1 H), 3.8 (pseudo t, 1 H), 4.0 (d, 2 H), 4.15 (m, 1 H), 4.4 (m, 1 H), 6.5--7.8 (m, 14 H). The salt was decomposed in the same way as reported above for the hydrogen phthalate of (*S*)-**5** yielding (*S*)-**6** (1.14 g, 45.6% of the theoretical amount) as a white solid: $[\alpha]_D^{25}$ = - 20.9 (*c* 2.5, EtOH) [lit.[14] $[\alpha]_D^{25}$ = - 21 (*c* 2.5, EtOH)]; ^1H NMR ($CDCl_3$) δ 1.5 (d, 3 H), 1.7 (s, 2 H), 4.3 (q, 1 H), 7.5 (m, 3 H), 7.8 (m, 4 H).

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References and Footnotes

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(2) The resolution procedure of **1** included heating of alcoholic solutions to boiling temperature and removal of (*S*)- and (*R*)-**2** by acidic extraction. Under these conditions no appreciable decomposition of the substrate was observed. The same stability was shown by (S)-**1** in the resolutions reported in this paper.

(3) The configurational stability results from the chemical one and is proved by unchanged optical rotations, measured at the end of the resolutions described herein.

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