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TETRAHEDRON: *ASYMMETRY*

On the enantiomers of 2-dimethylamino-3-pentanone, key intermediates in the synthesis of analgesic alkylaminoalkylnaphthalenes

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Abstract

2-Dimethylamino-3-pentanone **1** is the key intermediate in the synthesis of alkylaminoalkylnaphthalenic analgesics. In this paper the resolution of this compound with L- and D-dibenzoyltartaric acids is described. The behavior of the diastereomeric dibenzoyltartrates and of the enantiomers in solution is investigated by NMR spectroscopy, polarimetry and chiral gas-chromatographic analysis.

1. Introduction

Previous research on dialkylaminoalkyl- and cycloaminoalkylnaphthalenes led us to synthesize (Fig. 1) 1-ethyl-1-[2-(6-hydroxynaphthyl)]-1-hydroxy-2-methyl-3-dimethylaminopropane **B**,[1] 1,2-dimethyl-3-[2-(6-hydroxynaphthyl)]-3-hydroxypyrrolidine **C**,[2] and 1,2-dimethyl-3-[2-(6-fluoronaphthyl)]-3-hydroxypyrrolidine **D**,[3] racemic (1*R*,2*R*/1*S*,2*S*)-**B**, (2*R*,3*S*/2*S*,3*R*)-**C**, (2*R*,3*S*/2*S*,3*R*)-**D** and optically active (1*R*,2*R*)-**B**, (1*S*,2*S*)-**B**, (2*R*,3*S*)-**C**, (2*S*,3*R*)-**C**, (2*R*,3*S*)-**D**, (2*S*,3*R*)-**D**. These compounds are structural analogues of 17-methyl-17-azaequilenine **A** (Fig. 1), the component with the strongest analgesic properties of a group of phenolic heterosteroids.[4,5] They show in vivo opioid-like analgesic activity (hot plate test and writhing test) similar to those of peptide ligands, for which the role of the topochemical features has already been emphasized.[6–8]

The study of the structure–activity relationships led us to synthesize 1-ethyl-1-[2-(6-hydroxynaphthyl)]-1-hydroxy-2-methyl-2-dimethylaminoethane and 1-ethyl-1-[2-(6-fluoronaphthyl)]-1-hydroxy-2-methyl-2-dimethylaminoethane (Fig. 2, formulas A and B, respectively).[9] The key intermediate in the synthesis of these compounds is 2-dimethylamino-3-pentanone (±)-**1** (Fig. 2).

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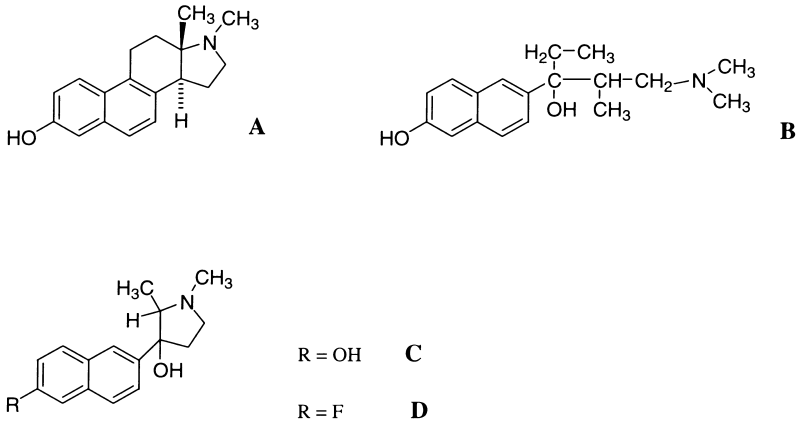


Figure 1.

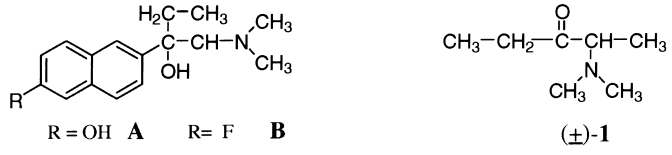


Figure 2.

Racemic and optically active compounds **1** have not been described in the literature. Jung and Love[10] only mentioned the preparation of the racemate and did not report the experimental conditions or chemical–physical properties. Moreover, in the literature only the resolution of cyclic α-amino-ketones is described, in particular for bicyclic α-amino-ketones (Fig. 3A)[11] and of 1,2-dimethyl-3-pyrrolidone (Fig. 3B).[12] To the best of our knowledge the resolution of open chain α-amino-ketones with Cα as the stereogenic center has never been reported.

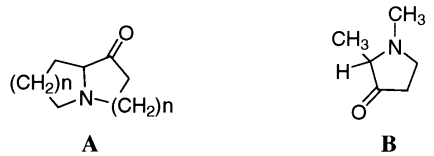


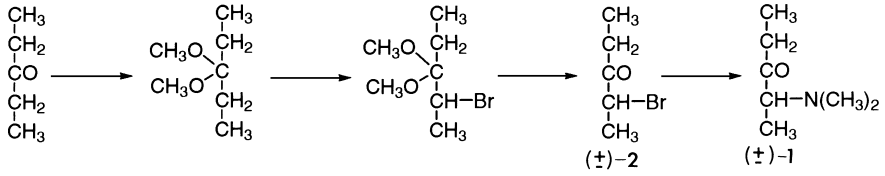
Figure 3.

Since an anomalous behavior was observed during the resolution of compound **1**, a detailed study of this problem is of high interest. In this paper the synthesis and resolution of 2-dimethylamino-3-pentanone is reported, and the behavior of the enantiomers of compound **1** is investigated by NMR spectroscopy, polarimetric analysis and chiral GC analysis.

2. Results and discussion

Compound (±)-**1** was prepared by reaction of 3-pentanone in methanol with bromine and water to obtain (±)-**2** and subsequent reaction of the latter with dimethylamine (Scheme 1).

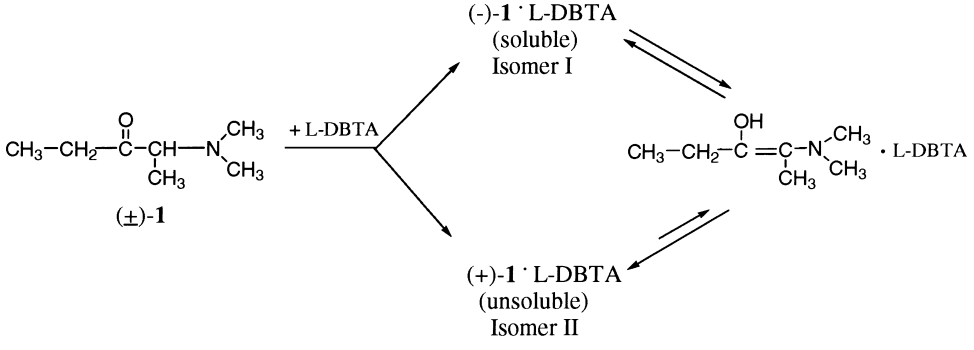
The resolution of compound **1** was carried out via fractional crystallization using (−)-L-dibenzoyltartaric acid monohydrate [(−)-L-DBTA·H_2O] and (+)-D-dibenzoyltartaric acid [(+)-D-DBTA] as resolving agents. On salification of (±)-**1** in ethanol with the appropriate dibenzoyltartaric acid, a white solid precipitated (almost 70% of the formed salt). (−)-**1** L-Dibenzoyltartrate monohydrate



Scheme 1.

[(−)-**1** L-DBT·H_2O] (mp 134–135°C, $[\alpha]_D^{23}$=−113.3, (*c* 1, CH_3OH)) or (+)-**1** D-dibenzoyltartrate monohydrate [(+)-**1** D-DBT·H_2O] (mp 134–135°C, $[\alpha]_D^{23}$=+112.8, (*c* 1, CH_3OH)) was obtained with only one crystallization from acetone/ethanol 50%. On further crystallization, both the specific rotatory power and melting point remained unchanged. A single crystallization is thus sufficient to obtain enantiomerically pure or almost pure salts.

This finding is ascribed (Scheme 2) to a tautomeric equilibrium in solution of **1** with the corresponding enol. The disappearance of the stereogenic center C(2) in the enol allows the equilibrium between the two diastereomeric salts. It is likely that during the crystallization the more soluble diastereomer transforms into the less soluble and more stable diastereomer which crystallizes and leaves the system, thus causing the partial interconversion of isomer I into isomer II.



Scheme 2.

A rapid decrease in the optical activity in methanol of (−)-**1** L-DBT·H_2O (and analogously of (+)-**1** D-DBT·H_2O) was observed. Consequently, polarimetric measurements were always performed at 6 min after the sample dissolution (a convenient time to measure $[\alpha]_D$). A kinetic study of the optical activity decay of (−)-**1** L-DBT·H_2O was carried out (Fig. 4). The steady value of specific rotatory power [$[\alpha]_D^{23}$=−95.8 (*c* 1, CH_3OH)] corresponds to the optical activity of the salt of (±)-**1** with L-DBTA·H_2O. This was verified by measuring the optical activity of a 1% methanolic solution of L-DBTA·H_2O and (±)-**1** in a 1:1 molar ratio solution. The value obtained was the same as that of a solution of (−)-**1** L-DBT·H_2O at the equilibrium. The chiral GC analysis of the base extracted from the latter solution confirmed the racemization of the base.

A rapid decay of the optical activity of (−)-**1** L-DBT·H_2O was also observed in 0.5% $NaHCO_3$ aqueous solution (Fig. 4), till a steady value of $[\alpha]_D^{23}$=−93.5, attributable to a mixture of L-DBT sodium salt and racemic **1**. As for the methanolic solution, the $[\alpha]_D^{23}$ of a 0.5% $NaHCO_3$ aqueous solution of (−)-L-DBTA and racemic compound **1** gave the same value as that of a (−)-**1** L-DBT·H_2O solution at equilibrium. Thus, the diastereoisomeric dibenzoyltartrates in methanolic and aqueous basic solution are optically unstable, owing to the racemization of the enantiomers of **1**. Consequently, recovery of the enantiomerically pure bases from the respective salts is a crucial method to establish. In order to study the experimental conditions, preliminary trials on (−)-**1** L-DBT·H_2O were performed. Two extraction experiments were performed. In the first, methylene chloride and 0.5% $NaHCO_3$ aqueous

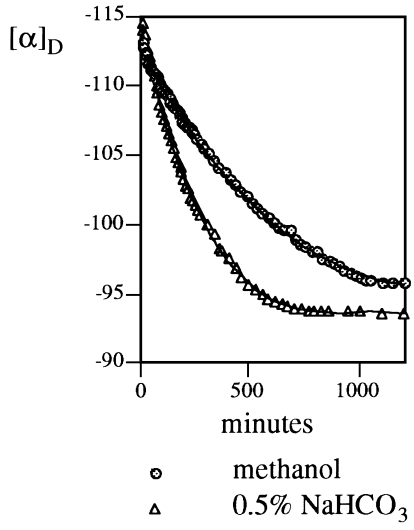


Figure 4. Decay of optical activity of (−)-**1** L-DBT·H_2O in 0.5% aq. $NaHCO_3$ and methanol

solution were used but the time from the addition of the aqueous solution was increased as shown in Table 1. In the second, the base was always extracted at the same time (15 min), but solutions with different amounts of $NaHCO_3$ were used (Table 2). The enantiomeric excess (e.e.) was then evaluated by chiral GC. The enantiomeric excess of the recovered base depends on the time (Table 1), but does not depend on the concentration of the aqueous $NaHCO_3$ solution (Table 2). Therefore, the extraction of the bases was performed by treating the finely powdered salts with a mixture of methylene chloride and saturated aqueous solution of sodium bicarbonate for not more than 15 min. Under these conditions (+)-**1** $[[\alpha]_D^{23}=+51.1$ (*c* 1, CH_2Cl_2), e.e.=83.1%] and (−)-**1** $[[\alpha]_D^{23}=-51.9$ (*c* 1, CH_2Cl_2), e.e.=86.4%] were obtained.

Table 1
Change of the e.e. of (−)-**1** recovered from (−)-**1** L-DBT·H_2O with aq. $NaHCO_3$ and extraction after time indicated

time (min)	E.e. (%)
2	85.6
5	85.6
10	85.5
15	85.3
20	84.9
25	83.1
30	82.2
35	81.7
40	81.0

All the measurements were effected using an aqueous solution of $NaHCO_3$ with a concentration of 0.5 % (p/v)

Table 2
Enantiomeric excess of (−)-**1** recovered from (−)-**1** L-DBT·H_2O with varying concentrations of aq. $NaHCO_3$ and extraction after 15 min

Concentration of $NaHCO_3$ aqueous solution (%)	E.e. (%)
0.5	85.6
1.0	85.5
1.5	85.5
2.0	85.7

The optical activity of compound **1** shows different behavior in the solution depending on the solvent. In particular, it does not change in some hydrophobic organic solvents such as CH_2Cl_2 and CH_3CN. However, in hydrophilic solvents, such as alcoholic solvents or water a rapid decay of the optical activity is observed (Fig. 5a–c). The rate of the decay decreases as the solvent hydrophilicity decreases. Moreover, the curves in both methanol and ethanol display a maximum (Fig. 5a,b) in the first 30 min of the sample dissolution.

To explain the behavior of optically active **1** in solution, ^{1}H NMR (500 MHz) and ^{13}C NMR (125.76 MHz) studies on various conditions were performed.

The ^{1}H NMR spectra, recorded in deuterated methanol at different times, show a decrease in the intensity of the peaks at 2.97 and 2.46 ppm (Table 3), assigned to C*H*(2) and CH_2(4), respectively. These data reveal the presence of two keto-enolic equilibria involving the C*H*(2) and CH_2(4) protons. These tautomeric equilibria in deuterated solvents allow the progressive incorporation of deuterium in the molecule with consequent decrease of the ^{1}H signals. Since the decrease of the signal intensity is directly related to the kinetics of the reactions, enol B (Fig. 6) proved to be the preferred one.[13] The formation of this enol is responsible for the racemization.

^{13}C NMR spectra were also registered in deuterated methanol at different times. The spectrum obtained immediately after sample dissolution, shows two signals at 69.69 and 11.86 ppm for *C*(2) and *C*(1), respectively. After 12 h (at the equilibrium) the spectrum presents additional chemical shifts for both *C*(2) and *C*(1), at 69.11 and 12.06 ppm, respectively. These new peaks were attributed to a partial deuteration of C*H*(2) (Fig. 7) confirming the prevalent formation of the enol B, since there is no evidence of an isotopic substitution at C4. Similar H/D isotopic substitutions have already been observed in ketones[13,14] and β-diketones.[15,16]

Moreover, the faster kinetics of the decay of compound (+)-**1** in 0.5% $NaHCO_3$ aqueous solution (Fig. 5d) compared to water (Fig. 5c) suggest that the tautomerism involving the C*H*(2) atom (responsible for the racemization) is base-promoted by abstraction of the hydrogen α to the carbonyl group. Thus, the racemization for compound **1** was faster in comparison to that for the dibenzoyltartrates.

NMR studies were performed to explain the maximum observed for the rotatory power of optically active **1** versus time in methanol and ethanol. This can be explained by the formation of a ketal. There is no direct NMR evidence of the presence of this species, probably because the reaction kinetics are too fast on the NMR timescale. However, it is possible to prove the formation of the ketal indirectly. In both A and D molecules (Fig. 6) the CH_2(4) protons are the AB part of an ABX_3 system; therefore, a complex multiplet is expected. A ^{1}H NMR spectrum recorded immediately after the dissolution of the sample in deuterated methanol shows a complex multiplet (the enlarged CH_2(4) signal is reported in Fig. 8a). At

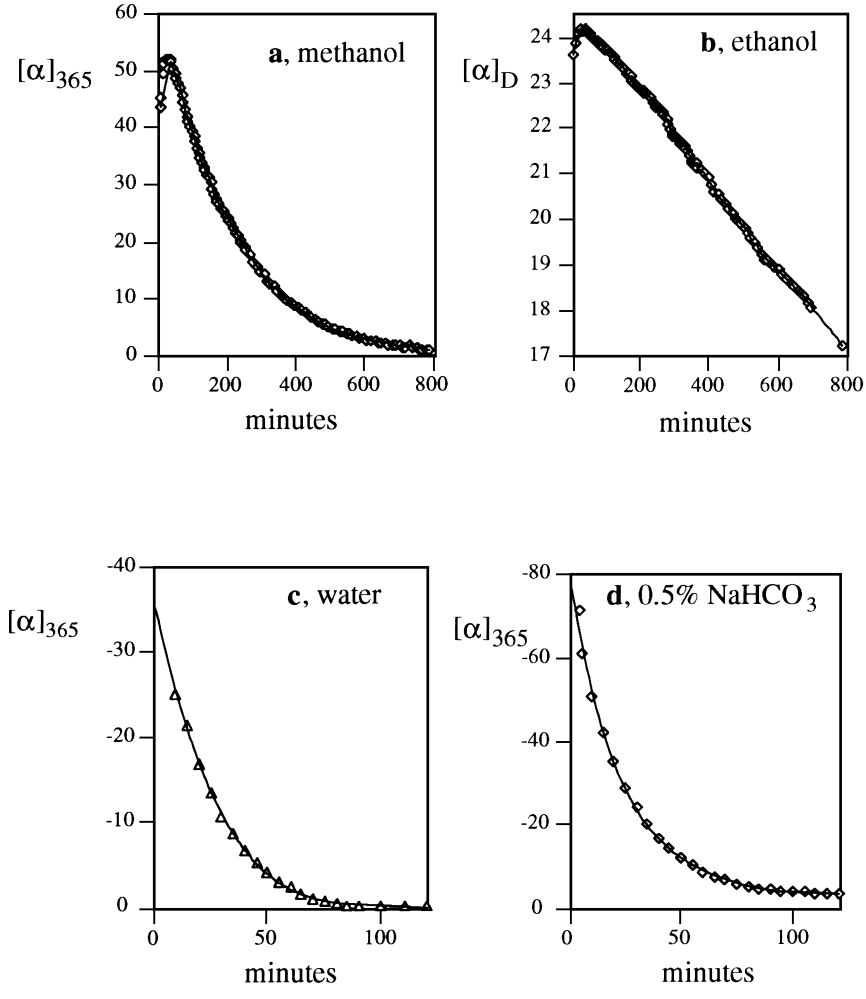


Figure 5. Decay of optical activity of (+)-**1** or (−)-**1** in different solvents

equilibrium the ^{1}H NMR spectrum is simplified: the C*H*$_2$(4) signal resulted in a simple quartet (Fig. 8b) due only to the coupling of C*H*$_2$(4) with methyl C*H*$_3$(5). It is suggested that the asymmetry induced at methylene 4 by the C*H*(2) is stronger in the ketal than in the ketone. Hence, it can change the appearance of the spectra. To study how the formation of the ketal affects the appearance of the signal, the sample was dissolved in an inert solvent (CD_3CN) and different ^{1}H NMR spectra were obtained after addition of an increasing amount of ethylene glycol (well known to give stable cyclic ketals). The signal of C*H*$_2$(4) in CD_3CN is a simple quartet (Fig. 9c), which changes gradually into a complex multiplet with the increase of the percentage of ethylene glycol in solution (Fig. 9a). This signal is similar to the multiplet attributed to the C*H*$_2$(4) in CD_3OD, recorded immediately after the dissolution of the sample (Fig. 8a). This similarity is consistent with the formation of the ketal D.

Table 3
Intensity changes with time in the ^{1}H NMR of (−)-**1** in CD_3OD

time (min)	Signal intensity	
	C*H*(2)	CH_2(4)
	δ = 2.97 ppm	δ = 2.46 ppm
5	0.95	2.00
15	0.91	1.90
30	0.79	1.80
60	0.75	1.80
3 hours	0.39	1.68
12 hours	0.14	1.60

all the integrals are normalized by assigning the value 6 to the signals at 2.18 ppm, corresponding to N(CH_3)$_2$

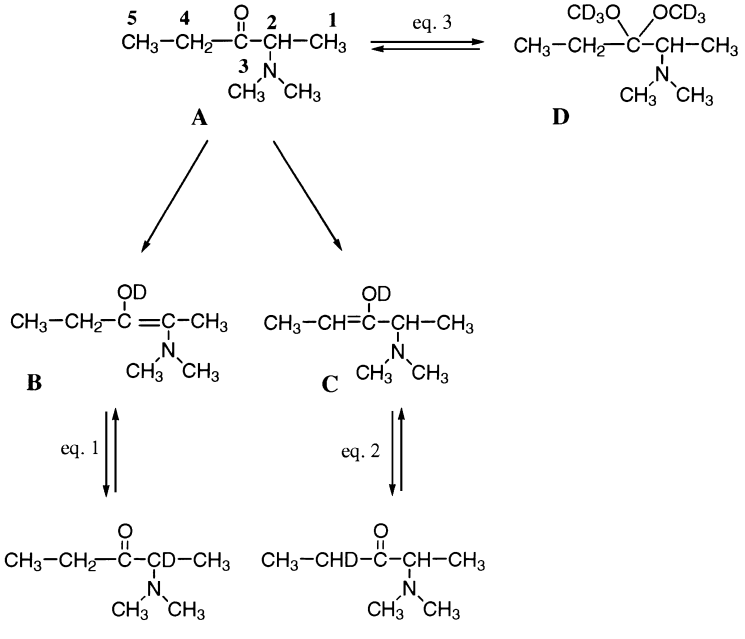


Figure 6.

3. Experimental

3.1. General

Melting points: uncorrected; Büchi Tottoli apparatus. Elemental analyses: Carlo Erba 1106 C-, H-, N-analyzer. TLC: 0.2 mm thick silica gel plates (Merck Kieselgel GF 254); detection of compounds with UV light. IR: Perkin–Elmer Mod. 682 spectrophotometer; only noteworthy absorptions are given in cm^{-1}.

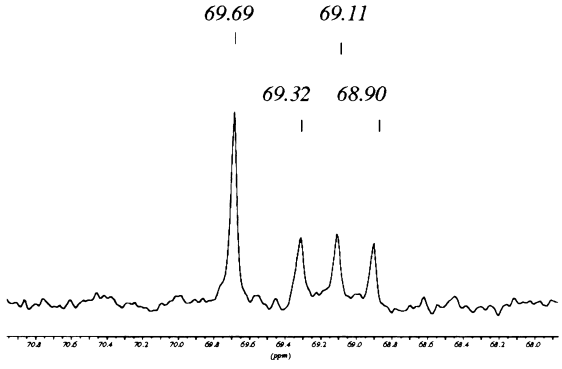


Figure 7. ^{13}C NMR spectrum of (+)-**1** after 12 h in CD_3OD

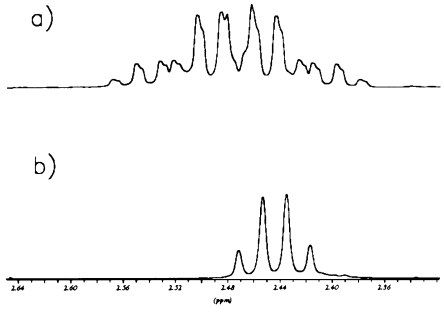


Figure 8. ^{1}H NMR spectra of (+)-**1** in CD_3OD

NMR: Hitachi R 1200 (^{1}H 60 MHz), Bruker AMX 400 (^{1}H 400 MHz, ^{13}C 100.617 MHz) or on a Bruker DRX 500 (^{1}H 500 MHz, ^{13}C 125.76 MHz) apparatus. Chemical shifts (δ) are reported in ppm relative to TMS (δ=0.00) and coupling constants (*J*) in hertz. Optical rotations: Jasco DIP-1000 photoelectric polarimeter (1 dm cell, sodium or mercury lamp); all measurements in methanol were recorded at 6 min from the dissolution of the sample (see results and discussion). Gas chromatography (GC): DANI 3800 apparatus; equipped with PTV and FID. [Method A: fused silica capillary column (DB-5, J and W) (nonpolar liquid phase, film thickness, 0.25 μm; 15 m×0.25 mm i.d.); carrier gas: helium (flow

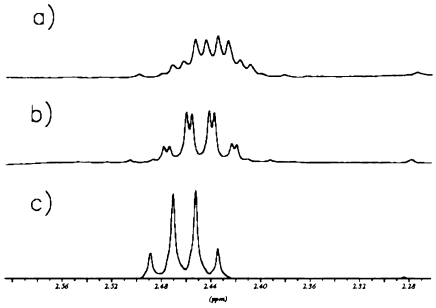


Figure 9. ^{1}H NMR spectra (H_4 signal) in CD_3CN of (+)-**1** and ethylene glycol, in the following molar ratios: (a) 1:40, (b) 1:30, (c) 1:20

rate, 45–48 cm/sec); oven and detector temperatures: 80 and 250°C, respectively; injection volume: 1 μl. Method B: permethylated β-cyclodextrin capillary column (β-DEX 120, Sulpelco) (nonbonded, film thickness, 0.25 μm; 30 m×0.25 mm i.d.); carrier gas: helium (flow rate, 48–52 cm/sec); detector temperature: 250°C; oven temperature: 80°C for 8 min and then 3°C/min till 120°C; injection volume: 1 μl.] All the reagents and solvents were obtained from commercial suppliers (Carlo Erba Reagenti and Fluka). Methanol was dried on molecular sieves (diameter 4 Å). Standard vacuum techniques were used.

*3.2. (±)-2-Bromo-3-pentanone (±)-**2***

CAUTION! This preparation must be carried out in a efficient hood; α-bromo ketones are highly lachrimatory and are skin irritants.[17] Compound (±)-**2**[18] was essentially prepared according to Gaudry and Marquet[17] for the preparation of 1-bromo-3-methyl-2-butanone. Starting from 3-pentanone (215.6 g, 2.5 mol) and bromine (400.0 g, 2.5 mol), crude (±)-**2** as a yellow oil (388.9 g, yield 94.1%) was obtained. It was purified by fractional distillation in the dark, under reduced pressure and under nitrogen, to obtain a colorless oil (287.7 g, yield 69.6%); bp_{30} 65–66°C. IR (film): 3400, 1720, 1440, 1310, 1100, 900, 750; ^{1}H NMR (60 MHz, in $CDCl_3$) δ: 1.12 (t, 3H, C*H*$_3$CH$_2$), 1.75 (d, 3H, C*H*$_3$CH), 2.70 (q, 2H, C*H*$_2$CO), 4.4 (q, 1H, C*H*CO).

*3.3. (±)-2-Dimethylamino-3-pentanone (±)-**1***

A mixture of (±)-**2** (287.7 g, 1.7 mol) in absolute ethanol (800 mL), anhydrous Na_2CO_3 (101.6 g, 1.0 mol) and 5.6 M dimethylamine in absolute ethanol (311 mL, 1.7 mol) was stirred under nitrogen. The temperature was gradually increased to 50°C and this temperature was maintained for 16 h. After this time the reaction mixture was filtered and the solvent removed. The resulting yellow oil was dissolved in water (100 mL) and then extracted with ethyl ether (5×200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to yield crude (±)-**1** as a yellow oil [91.0 g, yield 40.4%; purity 91.7% (GC, method A)]. This was purified by fractional distillation in the dark, under reduced pressure and under nitrogen to obtain a colorless oil [71.5 g, yield 31.5%; purity 99.99% (GC, method A, t_{ret} 3.6 min)], bp_{40} 63–64°C. IR, film: 2820, 2770, 1720, 1440, 1370, 1260, 1150, 1040, 940, 800; ^{1}H NMR (400 MHz, in $CDCl_3$) δ: 1.02 (t, 3H, C*H*$_3$CH$_2$, *J*=7.0); 1.06 (d, 3H, C*H*$_3$CH, *J*=7.0); 2.18 (s, 6H, N(C*H*$_3$)$_2$); 2.46 (dq, 2H, *CH*$_2$CO, *J*=2.5, 7.0); 2.97 (q, 1H, *CH*CO, *J*=7.0). TLC: hexane/ethyl acetate/(C$_2$H$_5$)$_2$NH 77/33/4 (v/v/v), R_f=0.68. Anal. calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.19; H, 11.75; N, 10.71.

3.4. Resolution of rac-2-dimethylamino-3-pentanone (±)-1

3.4.1. With (−)-L-dibenzoyltartaric acid·H_2O

Compound (±)-**1** (20 g, 0.16 mol) was added dropwise to a warmed solution (60°C) of (−)-L-dibenzoyltartaric acid·H_2O [58.25 g, 0.16 mol, $[\alpha]_D^{20}$=−110.5 (*c* 8.93, C_2H_5OH)] in ethanol (100 mL). The solution was slowly cooled to room temperature in the dark and (−)-2-dimethylamino-3-pentanone L-dibenzoyltartrate monohydrate [(−)-**1** L-DBT·H_2O] (53.80 g) precipitated as white needles, mp 132–134°C, $[\alpha]_D^{23}$=−103.7 (*c* 1, CH_3OH),[19] e.e.=64.1% (GC, Method B). On recrystallization (ethanol:acetone, 50:50) (540 mL), (−)-**1** L-DBT·H_2O (40.80 g) was obtained; mp 134–135°C, $[\alpha]_D^{23}$=−113.3 (*c* 1, CH_3OH).[19] On further crystallization both specific rotatory power and melting point remained unchanged. ^{1}H NMR (400 MHz, in CD_3OD, immediately after the dissolution of the sample) δ: 1.07 (t, 3H, C*H*$_3$CH$_2$, *J*=7.0); 1.55 (d, 3H, C*H*$_3$CH, *J*=7.0); 2.60 (dq, 2H, *CH*$_2$CO, *J*=7.0–15.0); 2.82 (s, 6H, N(C*H*$_3$)$_2$); 4.20 (q, 1H, *CH*CO, *J*=7.0); 5.9 (s, 2H, C*H*COOH); 7.4–8.1 (10H, arom). In the ^{1}H NMR spectrum recorded after 12 h from the sample dissolution, the signal at 4.20 ppm disappeared and the intensity of the signal at 2.60 ppm dramatically decreased. Anal. calcd for $C_7H_{15}NO·C_{18}H_{14}O_8·H_2O$: C, 59.40; H, 6.18; N, 2.77. Found: C, 59.62; H, 6.22; N, 2.72.

By recrystallization (ethanol:acetone, 50:50) of the product recovered from the mother liquors, another amount (15.6 g) of (−)-**1** L-DBT·H_2O was obtained; mp 134–135°C, $[\alpha]_D^{23}$=−113.3 (*c* 1, CH_3OH).[19]

By heating (−)-**1** L-DBT·H_2O at 80°C under vacuum for 24 h, anhydrous (−)-**1** L-DBT was obtained; mp 135–137°C, $[\alpha]_D^{23}$=−117.1 (*c* 1, CH_3OH).[19] Anal. calcd for $C_7H_{15}NO·C_{18}H_{14}O_8$: C, 61.59; H, 6.00; N, 2.87. Found: C, 61.54; H, 6.23; N, 2.71.

3.4.2. With anhydrous (+)-D-dibenzoyltartaric acid

According to the procedure described above, starting from 40.00 g of (±)-**1** (0.30 mol) and 110.90 g (0.30 mol) of anhydrous (+)-D-dibenzoyltartaric acid [$[\alpha]_D^{20}$=+116.0 (*c* 8.93, C_2H_5OH)], 93.1 g of (+)-2-dimethylamino-3-pentanone D-dibenzoyltartrate monohydrate [(+)-**1** D-DBT·H_2O] was obtained as white needles; mp 134–135°C, $[\alpha]_D^{23}$=+112.8 (*c* 1, CH_3OH).[19] From the mother liquor an additional amount (13.2 g) of (+)-**1** D-DBT·H_2O was obtained; mp 134–135°C, $[\alpha]_D^{23}$=+111.9 (*c* 1, CH_3OH).[19] ^{1}H NMR spectrum: identical with that of the enantiomer. Anal. calcd for $C_7H_{15}NO·C_{18}H_{14}O_8·H_2O$: C, 59.40; H, 6.18; N, 2.77. Found: C, 59.28; H, 5.96; N, 2.80.

By heating (+)-**1** D-DBT·H_2O under the same conditions described for (−)-**1** L-DBT·H_2O, anhydrous (+)-**1** D-DBT was obtained; mp 135–137°C, $[\alpha]_D^{23}$=+116.9 (*c* 1, CH_3OH).[19] Anal. calcd for $C_7H_{15}NO$ $C_{18}H_{14}O_8$: C, 61.59; H, 6.00; N, 2.87. Found: C, 61.75; H, 6.27; N, 2.78.

3.5. (+)-2-Dimethylamino-3-pentanone (+)-1

A saturated aqueous solution of $NaHCO_3$ (15 mL) was added to a suspension of 2.5 g of finely powdered (−)-**1** L-DBT·H_2O [$[\alpha]_D^{23}$=−113.3 (*c* 1, CH_3OH)[19]] in CH_2Cl_2 (25 mL) under magnetic stirring. Stirring was maintained for 15 min. The organic layer was immediately separated from the aqueous one and dried on anhydrous Na_2SO_4. The solvent was removed to give 0.6 g of (+)-**1** as a colorless oil, $[\alpha]_D^{23}$=+51.1 (*c* 1, CH_2Cl_2), $[\alpha]_D^{23}$=+23.6 (*c* 1, C_2H_5OH, *t*=5 min), $[\alpha]_{365}^{23}$=+45.2 (*c* 1, CH_3OH, *t*=5 min), $[\alpha]_{365}^{23}$=−25.6 (*c* 1, H_2O, *t*=5 min), $[\alpha]_{365}^{23}$=−71.4 (*c* 1, 0.5% $NaHCO_3$, *t*=5 min), e.e.=83.1% (GC, Method B: t_{ret} 18.6 min, α=0.96, R_s=3.4). IR and ^{1}H NMR spectra: identical with those of (±)-**1**. Anal. calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.93; H, 11.60; N, 10.72.

By further extraction of the aqueous phase with CH_2Cl_2 (6×10 mL) an additional amount (0.1 g) of (+)-**1** with lower optical activity was recovered, $[\alpha]_D^{23}$=+11.5 (*c* 1, CH_2Cl_2), e.e.=13.7% (GC, Method B). Compound (+)-**1** has to be stored at a temperature <4°C.

*3.6. (−)-2-Dimethylamino-3-pentanone (−)-**1***

Applying the same procedure used for the enantiomer, and starting from 2.5 g of [(+)-**1** D-DBT·H_2O [$[\alpha]_D^{23}$=+112.8 (*c* 1, CH_3OH)], 0.6 g of (−)-**1** were obtained: $[\alpha]_D^{23}$=−51.9 (*c* 1, CH_2Cl_2), e.e.=86.4% (GC, Method B: t_{ret} 17.6 min, α=0.96, R_s=3.4). IR and ^{1}H NMR spectra: identical with those of (±)-**1**. Anal. calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.89; H, 11.55; N, 10.63. Compound (−)-**1** has to be stored at a temperature <4°C.

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19. *t*=6 min, see results and discussion.