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Highly efficient resolution of (±)-Tramadol with di-*p*-toluoyl-tartaric acid (DTTA)

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Abstract—A robust and efficient resolution of (±)-Tramadol has been developed using di-*p*-toluoyl-tartaric acid (DTTA). Both enantiomers have been efficiently separated and isolated in high chemical and optical purities. This requires the use of both antipodes of DTTA. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Tramadol (*trans* - (±) - 2 - dimethylaminomethyl - 1 - (3-methoxyphenyl-1-cyclohexanol) **1** is a chiral drug substance which is used as a high-potency analgesic agent.[1] Although Tramadol is currently marketed as the racemate only, there has been considerable interest in the physiological properties associated with its individual enantiomers, namely (1*S*,2*S*)-(−)-Tramadol **1b** and (1*R*,2*R*)-(+)-Tramadol **1a**. Both enantiomers have weak opiate activity, with the (−)-isomer inhibiting serotonin re-uptake, and the (+)-isomer inhibiting noradrenaline re-uptake. It has also been shown that the (+)-Tramadol is metabolised to the primary metabolite (+)-*O*-desmethyltramadol, which has significant opiate side effects (of the order of 100 times more than Tramadol isomers themselves).[2] It is possible that further investigations in this field will lead to a better understanding of the pharmacology of Tramadol enantiomers, which could in turn allow for improved pharmaceutical compositions to be identified.

In the literature there are three documented resolution procedures, which use tartaric acid,[3a] di-benzoyl-tartaric acid[3b] and more recently mandelic acid as the resolving agent.[3c] Very recently enzymatic resolutions of related compounds have been described[4a,b] and the use of SMB technology to separate the racemate has also been demonstrated.[4c] In connection with our own interest in this area, we required an efficient and reliable method for the preparation of the individual enantiomers of Tramadol.[5] While an enantioselective synthesis of each enantiomer is extremely challenging, the most expedient route appeared to be a classical resolution process.

Due to the ready availability of (±)-Tramadol, separation of diastereomeric salts by fractional crystallisation appeared ideal for our purpose. Initially, on trying to repeat the European patent[3a] procedure, we observed little or no diastereoselectivity. It is reported that the resolution of (±)-Tramadol with L-(+)-tartaric acid occurs with excellent diastereomeric excess (d.e.) and yield. A solution of (±)-Tramadol in ethanol is stirred at ambient temperature with tartaric acid. When this process was repeated, a copious amount of precipitated solid had formed to give, after isolation, around 90% total yield of solid Tramadol·tartaric acid salt. Analysis by chiral HPLC showed this material and the mother liquors to be essentially racemic. Various other attempts to effect separation of the enantiomers of Tramadol with this resolving agent met without success. In the case of di-benzoyl-tartaric acid multiple crystallisations were required to effect complete separation of the enantiomers. Mandelic acid was shown to give a crystallisation that was under kinetic control, and required cracking and reformation of the salt to effect total separation.[3c] This is impractical on a large scale. It was therefore necessary for an alternative resolving agent to be found that effected a ready and reliable separation. The preparation of (±)-Tramadol is shown in Scheme 1, the Tramadol Mannich free base **2** obtained from cyclohexanone is treated with the Grignard reagent of 3-bromo-anisole to give a mixture of all

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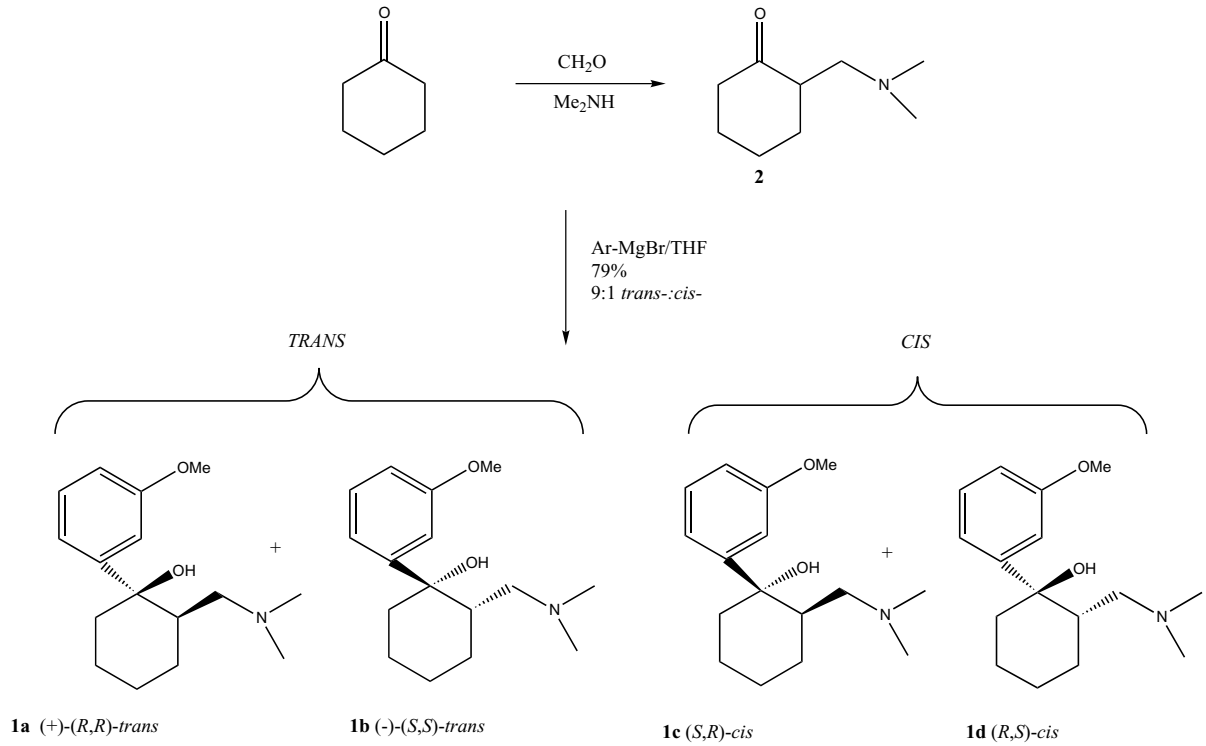


Scheme 1. Commercial preparation of crude Tramadol free base.

four isomers. The marketed product contains a 1:1 mixture of the *trans*-isomers **1a** and **1b**. (The importance of this will become apparent in the latter part of this paper.)

2. Results and discussion

Due to the tight time scale for providing the single enantiomers, a small screen for alternative resolving agents was conducted. From this screen two candidates are apparent, di-*p*-toluoyl-tartaric acid (DTTA) was shown to give crystalline material of high d.e.s (86–99%) and yields of 19–44%. Also, di-benzoyl-tartaric acid (DBTA) was shown to give good resolution, the precipitated material from the reaction had d.e. of 93% and was isolated in 33% yield when *iso*-propanol was used as the solvent,[3b] whereas mandelic and camphor sulfonic acids did not give any precipitated products.[3c] These results are summarised in Table 1. Due to the nature of this project and with the need for a rapid supply of material, the resolution with di-*p*-toluoyl-tartaric acid was quickly scaled up and developed to provide a commercial route to the single enantiomers of Tramadol hydrochloride. Di-*p*-toluoyl-tartaric acid (DTTA) was the resolving agent of choice not only because it gave slightly better results in the small screening study, but also due to the fact that we had a bulk supplier for this material and experience with its recovery and re-use.[6] This should aid the viability of this process. The development of this process to provide multi-kilogram quantities of material is detailed herein.

Examination of the solvent system indicated that ethanol was an ideal candidate, both absolute and 96% ethanol gave excellent results.[7] The resolution was scaled up to 90 g input of (±)-Tramadol (1.32 L of ethanol was employed, which is 6 volumes based on the free base and resolving agent). As can clearly be seen from the following results, the resolution of Tramadol with di-*p*-toluoyl-D-tartaric acid (D-(+)-DTTA) is excellent, high yielding and approaching an ideal case. (The efficiency of the resolution can be expressed by $S = 2\times$ the yield of the salt×the DE of the salt. In this instance the efficiency factor $S = 0.91$.)[8] At this scale the (+)-Tramadol·D-(+)-DTTA salt obtained requires a re-slurry in 5 volumes of ethanol. This routinely gives material of a very high d.e. of >98%. As there was a requirement for both the (+)- and (−)-enantiomers, the mother liquors were cracked to give the (−)-Tramadol enriched free base with an e.e. of approximately 85%. This free base was dissolved in a given volume of methanol and added to a solution of L-(−)-DTTA in methanol at 65°C.[9] Upon addition of the free base to the hot solution of resolving agent in methanol, a thick precipitate formed immediately. This gave, after stirring overnight, a good yield of the (−)-Tramadol·L-(−)-DTTA diastereoisomer, with high d.e. of ~98%. Upon re-slurry this gave diastereomerically pure material.

The next challenge was to prepare the single enantiomer hydrochloride salts from the DTTA salts. The first step was to crack these salts and effect a ready separation of the single enantiomer Tramadol free base from the resolving agent. This was readily achieved

Table 1. Resolution of (±)-Tramadol free base with a number of resolving agents

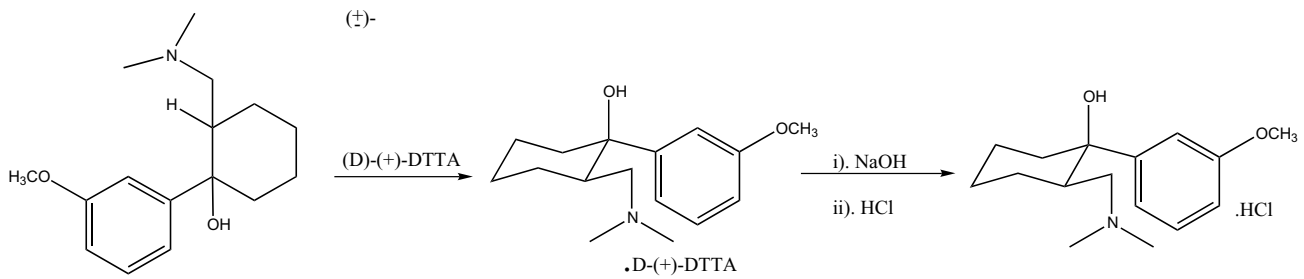
Entry	Resolving agent	Conditions	Enantiopurity of diastereomeric salt (1*S*,2*S*):(1*R*,2*R*)	Yield (%)
1	L-(−)-DTTA[a]	2 h, rt, ethanol (7 mL)	92.8:7.2	41
2	D-(+)-DTTA·H_2O[b]	20 h, rt, ethanol (7 mL)	3.6:96.4	40
3	D-(+)-DTTA·H_2O[b]	2 h, rt, methanol (5 mL)	3.3:96.7	19
4	L-(−)-DTTA[a]	20 h, rt, methanol (5 mL)	95.0:5.0	44
5	L-(−)-DTTA·H_2O[c]	20 h, rt, methanol (5 mL)+water (0.5 mL)	99.3:0.7	33
6	L-(−)-DBTA·H_2O[d]	20 h, rt, EtOAc (5 mL)	94.5:5.5	49
7	L-(−)-DBTA·H_2O[d]	20 h, rt, *i*-PrOH (5 mL)	96.7:3.3	33
8	CSA[e]	20 h, rt, ethanol (5 mL)	–	–
9	D-(−)-Mandelic acid	20 h, rt, ethanol (5 mL)	–	–

[a] Di-*p*-toluoyl-L-tartaric acid.
[b] Di-*p*-toluoyl-D-tartaric acid.
[c] Di-*p*-toluoyl-L-tartaric acid monohydrate.
[d] Di-benzoyl-L-tartaric acid monohydrate.
[e] (1*S*)-(+)-Camphor sulfonic acid.

using 2.05 equivalents of sodium hydroxide solution and extracting into dichloromethane. (n.b. a slight excess of base was employed, care needs to be taken not to use too much base, due to the sensitivity of the resolving agent to hydrolysis at high pH.) At pHs of >9 the hydrolysis of DTTA to tartaric and toluic acids can be quite rapid. After concentration of the dichloromethane solution of the free base, the residue was dissolved in 10 volumes of 2-butanone. Initially, chlorotrimethylsilane (TMSCl) and water (exactly one equivalent) was used to prepare the hydrochloride salts. Use of TMSCl to generate hydrogen chloride on a small scale (up to 1–2 kg) worked well; however, there are consequences of cost and environmental issues which preclude the use of this process on a larger scale.

Prior to scale-up of this process in our pilot plant, the preparation of the single enantiomer hydrochloride salts using alternatives to TMSCl was studied. Direct gassing in a variety of solvents did result in good yields of isolated products. However, the best yields were obtained in butan-2-one (MEK) and it was thought that use of a large excess of HCl could lead to degradation of the solvent and hence unwanted impurities. It was found that use of 1.05 equivalents of a ~20–25% solution (w/w) of HCl in *iso*-propanol gave high yields of the salts in excellent chemical and optical purities.[10] This process has now been successfully scaled up and provided in excess of 20 kg of both (+)- and (−)-Tramadol hydrochloride. The overall process is shown in Scheme 2 ((+)-enantiomer) and Scheme 3 ((−)-enantiomer).

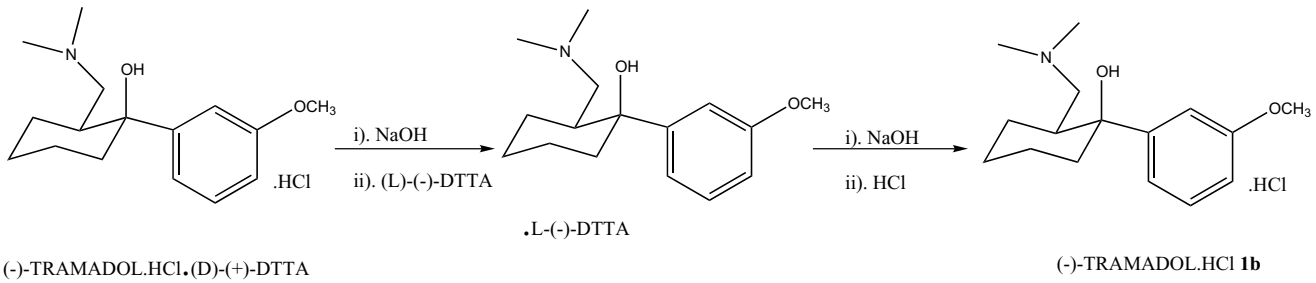
As can be seen in Scheme 1, Tramadol is obtained as a mixture of all four possible isomers from the Grignard reaction on the cyclohexanone **2** in a ratio of approximately 4:1 (**1a**/**1b**):(**1c**/**1d**). Typically, the unwanted *cis*-isomers are removed by crystallisation of the hydrochloride salt. This process can be very time consuming and in some cases uses toxic dioxane as solvent.[3b,11] In order to streamline the process further, it was decided to see if the resolving agent DTTA could effect separation of one of the isomers from the mixture of all four. This has indeed been shown to be the case. When L-(−)-DTTA is used, the resulting diastereomeric salt was obtained in 36.4% yield with a d.e. of 96.6% and a *trans*:*cis* ratio of 98.8:1.2. Upon re-slurry in ethanol the d.e. increases to 98.8% and the *trans*:*cis* ratio to 99.4:0.6. This salt was then converted to the hydrochloride salt **1b**, in 82% yield, with e.e. >99.5% and a *trans*:*cis* ratio of >99.5:<0.5. Likewise the (+)-enantiomer **1a** was also obtained in a good overall yield of 68% and with equally high purity. These results are summarised in Scheme 4.



(±)-*trans*-TRAMADOL **1a, 1b**

(+)-TRAMADOL.HCl **1a**

Scheme 2. Preparation of (+)-Tramadol hydrochloride.



Scheme 3. Preparation of (–)-Tramadol hydrochloride.

3. Conclusion

In summary, we have demonstrated that the resolving agent di-*p*-toluoyl-tartaric acid (DTTA) is very efficient in separating the enantiomers of Tramadol. This resolving agent is highly specific for the desired *trans*-Tramadol enantiomers, enabling isolation of a single isomer from a crude mixture of all four possible isomers. It has also been demonstrated that less than one equivalent of resolving agent is also effective in separating the enantiomers. The recovery and re-use of the resolving agent further highlights the efficiency of this process.

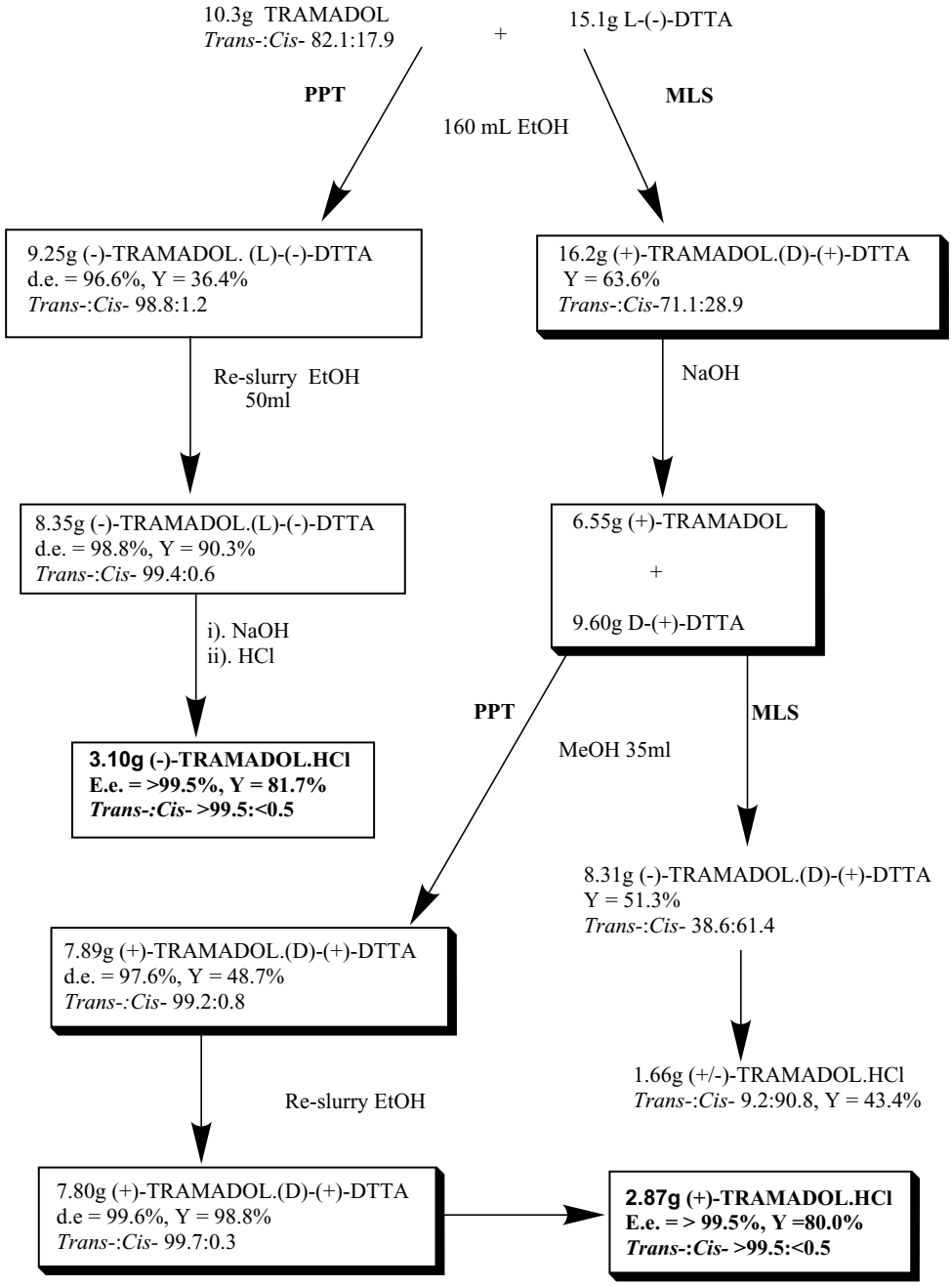
4. Experimental

4.1. General

Melting points were measured on a Perkin–Elmer Differential Scanning Calorimeter (DSC 6) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 instrument. The enantiopurities were determined by HPLC using a Chiralpak AD (250×4.6 mm) 5 μm column, mobile phase 95:5 *iso*-propanol:heptane containing 0.1% diethylamine, with a flow rate of 1 mL per minute and detection at 273 nm. The (+)-enantiomer eluted after 5.6 min and the (–)-enantiomer after 9.7 min. The *cis*:*trans* ratio was determined by HPLC using a Phenomenex Luna 2 C18 (150×4.6 mm) 5 μm column, mobile phase buffer at pH 2.2: acetonitrile gradient system, with a flow rate of 2 mL per minute and detection at 210 nm. The *cis*-isomers eluted after 4.90 min and the *trans*-isomers after 5.10 min. Optical rotations were obtained using a Perkin–Elmer 241 polarimeter. Racemic Tramadol hydrochloride, di-*p*-toluoyl-D-tarataric and di-*p*-toluoyl-L-tartaric acids were obtained commercially.

4.2. Resolution of (±)-Tramadol with di-*p*-toluoyl-D-tartaric acid in ethanol

Racemic Tramadol hydrochloride (69 kg, 230.2 mol) was dissolved in purified water (148 L) and dichloromethane (266 kg) was added to this colourless solution. A solution of 32% w/w sodium hydroxide (42.4 kg, 339.2 mol) was added to the Tramadol hydrochloride mixture stirred at 10°C in a 900 L vessel. After stirring the mixture for 10 min the layers were allowed to separate and the bottom organic layer removed to a second reactor. The basic aqueous layer was extracted with dichloromethane (59 kg) and combined with the first organic layer. The combined organic extract was washed with water (128 L). Concentration of the organic layers by distillation at atmospheric pressure gave racemic Tramadol free base in quantitative yield (60.6 kg). During this distillation 96% ethanol (276 kg) was added and the mixture was heated to over 70°C to ensure complete removal of dichloromethane. The solution of free base in ethanol was then added to a solution of di-*p*-toluoyl-D-tartaric acid (D-(+)-DTTA) (89.3 kg, 230.2 mol) in 96% ethanol (335 kg) at 70°C. Care was taken to maintain the temperature at 70±5°C during this addition. After stirring for 30 min a seed of (+)-Tramadol·di-*p*-toluoyl-D-tartaric acid was added which effected crystallisation. The mixture was gradually cooled to 25°C and stirred for a period of approximately 15 h. The copious white precipitate that formed was collected by centrifugation in two drops, washing with 96% ethanol (187 kg total). The liquors from the filtration and washes were retained as these contained the (–)-Tramadol diastereoisomer and they were used in the experiment directly following this one. This gave (+)-Tramadol·di-*p*-toluoyl-D-tartaric acid (66.1 kg, 44%) with a d.e. of 99.0% (chiral HPLC).[12] This damp material was slurried in 96% ethanol (266 kg), heating the suspension up to 70°C and then cooling to 20–25°C over a 3 h period. The white crystalline solid was again isolated by centrifugation, washing with ethanol (42 kg), to give the (+)-Tramadol containing salt, with a d.e. of >99.5% (chiral HPLC) (63.3 kg, 85% yield). $[\alpha]_D = +104.9$ ($c = 1.36$, MeOH). Mp = 167.5–168.0°C (DSC). ^{1}H NMR (CD_3OD), $\delta_H = 1.40$–1.85 (m, 8H), 2.20 (m, 1H), 2.35 (s, 6H), 2.52 (s, 6H), 2.70 (m, 1H), 3.72 (s, 3H), 5.75 (s, 2H), 6.70 (m, 1H), 7.05 (m, 1H), 7.10 (brs, 1H), 7.28 (m, 1H), 7.32 (d, 4H), 8.05 (d, 4H). ^{13}C NMR (CD_3OD), $\delta_C = 21.80$, 22.53, 26.21, 27.27, 41.72, 42.98, 55.76, 61.91, 74.97, 75.92, 109.13, 112.40, 113.00, 128.51, 130.27, 130.74, 131.20, 145.55, 150.73, 161.49, 167.49, 171.71.



Scheme 4. Resolution of crude *cis*-/*trans*-Tramadol free base with DTTA.

4.3. Resolution of (−)-enantiomer enriched Tramadol with di-*p*-toluoyl-L-tartaric acid in ethanol

The ethanol liquors containing the (−)-Tramadol salt from the above experiment were concentrated by distillation to the reactor minimum stir volume at atmospheric pressure, this was then cracked using 2.1 equivalents of sodium hydroxide as follows. The (−)-Tramadol·D-(+)-DTTA salt (83.5 kg, 128.5 mol) in ~1 volume of ethanol was dissolved in dichloromethane (350 kg) in a 900 L vessel at 10°C. Water (355 L) was added to this yellow solution and the mixture was stirred. Sodium hydroxide solution (32% w/w, 33.8 kg, 270 mol) was added and the mixture stirred for a further 15 min. The layers were then allowed to separate and the bottom organic layer was collected. The basic aqueous layer was extracted with dichloromethane (123 kg). The organic layers were combined and washed with water (129 L), then concentrated by atmospheric distillation, methanol (76 kg) was added and the distillation continued until the pot temperature exceeded 65°C. This gave approximately 33.8 kg of Tramadol free base enriched in the (−)-enantiomer as a slightly coloured solution. Meanwhile, di-*p*-toluoyl-L-tartaric acid (L-(−)-DTTA) (49.6 kg, 128.5 mol) was dissolved in methanol (130 kg) at 65°C in a 600 L vessel. The Tramadol free base solution in methanol was added to this solution. A precipitate formed almost immediately and careful addition was required to control the rate of reflux. The vessel was gradually cooled

to 20–25°C over several hours to give a fine white slurry. Stirring at 25°C was maintained overnight. The resulting white precipitate was collected by centrifugation, washing with ethanol (198 kg). This gave (–)-Tramadol·di-*p*-toluoyl-L-tartaric acid (64.7 kg, 78%), with a d.e. of 99.1%.[12] Re-slurry of this damp salt in ethanol (247 kg) and isolation as above gave 61.7 kg of the (–)-Tramadol containing salt, with a d.e. of >99.5% in 74% overall yield. $[\alpha]_D = -103.3$ ($c = 1.15$, MeOH). Mp = 162.1–167.8°C (DSC). ^{1}H NMR (CD_3OD), δ_H = 1.40–1.85 (m, 8H), 2.20 (m, 1H), 2.35 (s, 6H), 2.52 (s, 6H), 2.70 (m, 1H), 3.72 (s, 3H), 5.75 (s, 2H), 6.70 (m, 1H), 7.05 (m, 1H), 7.10 (brs, 1H), 7.28 (m, 1H), 7.32 (d, 4H), 8.05 (d, 4H). ^{13}C NMR (CD_3OD), $\delta_C = 21.72$, 22.46, 26.14, 27.15, 41.63, 42.92, 55.67, 61.85, 74.90, 75.85, 109.07, 112.33, 112.93, 128.45, 130.17, 130.67, 131.12, 145.44, 150.63, 161.43, 167.42, 171.62.

4.4. Small scale resolution of (+)-enantiomer enriched Tramadol with di-*p*-toluoyl-D-tartaric acid in ethanol with recovery of the resolving agent

The (+)-Tramadol·(L)-DTTA salt obtained by a procedure similar to that described above was used. This was cracked with 2.1 equivalents of sodium hydroxide as follows. The (+)-Tramadol·L-(–)-DTTA salt (131 g, 0.202 mol) in 1 volume of ethanol was dissolved in dichloromethane (150 mL) and placed in a jacketed vessel at 10°C. Water (300 mL) was added to this yellow solution and the mixture was stirred. A solution of sodium hydroxide (16.8 g, 0.423 mol) in distilled water (200 mL) was added dropwise with stirring. The layers were separated and the bottom organic layer was collected. The basic aqueous layer was re-extracted with dichloromethane (150 mL). The organic layers were combined and washed with water (200 mL) before being concentrated to dryness. This gave approximately 53 g of Tramadol free base enriched in the (+)-enantiomer as a slightly coloured oil. The basic aqueous layer was acidified with hydrochloric acid to pH 2.0, and this solution was extracted with *tert*-butylmethylether (TBME, 300 mL). Concentration of the TBME solution gave a slightly coloured oil in quantitative yield. This was dissolved in *iso*-propanol (150 mL) and heated under reflux. To this refluxing solution was added heptane (350 mL), which effected crystallisation. The crystallisation mixture was cooled to ambient temperature and stirred overnight. The white precipitate was collected by filtration to give L-(–)-DTTA (58.3 g, 75%), which compared to an authentic sample. Di-*p*-toluoyl-D-tartaric acid (D-(+)-DTTA) (77.3 g, 0.202 mol) was dissolved in ethanol (550 mL) at 70°C in a jacketed vessel. To this solution was added the Tramadol free base in ethanol (200 mL), a precipitate formed almost immediately. The mixture was cooled to 25°C over several hours to give a fine white precipitate. Stirring at 25°C was maintained overnight. The resulting white slurry was filtered at the pump. The filter cake was washed with ethanol (500 mL) and dried to afford (+)-Tramadol·di-*p*-toluoyl-D-tartaric acid (111.6 g, 85%), with a d.e. of 97.3%. Re-slurry of this salt from ethanol (500 mL) as above gave the (+)-Tramadol containing salt (108.5 g), with a d.e. of >99% in 97.8% yield. $[\alpha]_D = +103.3$ ($c = 1.15$, MeOH). mp = 162.1–167.8°C (DSC).

4.5. Resolution of (±)-Tramadol with recovered di-*p*-toluoyl-L-tartaric acid in ethanol

Racemic Tramadol hydrochloride (11.4 g, 0.038 mol) was converted to racemic Tramadol free base as colourless oil in quantitative yield (10.0 g, 0.038 mol) using the procedure outlined above. The free base was dissolved in ethanol (20 mL) and this solution is added to di-*p*-toluoyl-L-tartaric acid (L-(–)-DTTA) (recovered from a previous resolution) (14.7 g, 0. 038 mol) in ethanol (120 mL) at 70°C. On cooling to 65°C, a precipitate formed. The slurry was gradually cooled to 25°C and stirred for a approximately 15 h. The copious white precipitate that formed was collected by filtration and washed with ethanol (60 mL). This gave after drying (–)-Tramadol (11.40 g, 46.2%). Di-*p*-toluoyl-L-tartaric acid with a d.e. of 96.2% (chiral HPLC). Evaporation of the mother liquors gave a coloured oil of (+)-Tramadol (13.50 g, >55%). Di-*p*-toluoyl-L-tartaric acid with a d.e. of 84.9%.

4.6. Resolution of (±)-Tramadol with 0.55 equivalents of di-*p*-toluoyl-L-tartaric acid in ethanol

Racemic Tramadol hydrochloride (11.4 g, 0.038 mol) was converted to racemic Tramadol free base as yellow oil in quantitative yield (10.0 g, 0.038 mol) using the procedure outlined above. The free base was dissolved in ethanol (10 mL) and this solution was added to the di-*p*-toluoyl-L-tartaric acid ((L)-(–)-DTTA) (8.08 g, 0. 021 mol, 0.55 equivalents) plus acetic acid (1.26 g, 0.021 mol) in ethanol (40 mL) at 70°C. On cooling to 65°C a seed of (–)-Tramadol di-*p*-toluoyl-L-tartaric acid was added which effected crystallisation. The resolution was gradually cooled to 25°C and left to age over a period of approximately 15 h. The copious white precipitate that formed was collected by filtration and washed with ethanol (10 mL). This gave after drying (–)-Tramadol (7.10 g, 39%) di-*p*-toluoyl-L-tartaric acid with a d.e. of 97.1% (chiral HPLC). Evaporation of the mother liquors gave a coloured oil (12.50 g, 61%) of (+)-Tramadol·di-*p*-toluoyl-L-tartaric acid with a d.e. of 40.9%.

4.7. Small scale preparation of (+)-Tramadol hydrochloride from (+)-Tramadol·di-*p*-toluoyl-D-tartaric acid salt

(+)-Tramadol·di-*p*-toluoyl-D-tartaric acid salt (108 g, 0.166 mol) obtained above (d.e. >99%) was cracked according to procedure 4.2, this gave 43.0 g of (+)-Tramadol free base. This enantiomerically pure free base was dissolved in butan-2-one (475 mL) in a jacketed vessel and stirred at 20°C. To this solution was added distilled water (3.06 mL) in one portion. After this chlorotrimethylsilane (18.9 g, 22.1 mL, 0.174 mol) was added via syringe. The reaction was stirred at 20°C overnight. The white precipitate that formed was collected by filtration and washed with cold butan-2-one

(175 mL). The white solid was dried under vacuum at 70°C to give 43.2 g (87.3%), e.e. >99%. $[\alpha]_D = +34.3$ ($c = 1.22$, MeOH). Mp = 172.7–173.9°C. Lit.[2a] mp = 171–172°C; $[\alpha]_D^{rt} = +29.6$ ($c = 1.00$, MeOH).

4.8. Large scale preparation of (+)-Tramadol hydrochloride from (+)-Tramadol·di-*p*-toluoyl-D-tartaric acid salt

(+)-Tramadol·di-*p*-toluoyl-D-tartaric acid salt (63.3 kg, 97.4 mol), obtained in 4.2 above (d.e. >99%) was cracked according to a similar procedure as described in 4.2 but using 2.1 equivalents of sodium hydroxide solution. This gave ~25.7 kg of (+)-Tramadol enantiomerically pure free base. This was dissolved in butan-2-one (MEK) (200 kg) in a 600 L vessel stirred at 10–15°C. To this solution was added 22.7% w/w hydrogen chloride in *iso*-propanol (15.95 kg, 99.2 mol). Care was taken to keep the internal temperature below 15°C during the addition. After stirring for approximately 30 min a thick precipitate had formed. The crystallisation mixture was stirred overnight at ambient temperature. The vessel was then cooled to ~5°C for 1 h. The white precipitate was collected by centrifugation, washing with cold butan-2-one (68 kg). The white solid was dried under vacuum at 60°C to give the title compound (26.15 kg, 90%, e.e. >99.5%) (Chiral HPLC). Mp = 172.7–173.9°C.

4.9. Small scale (−)-Tramadol hydrochloride preparation from (−)-Tramadol·di-*p*-toluoyl-L-tartaric acid salt

(−)-Tramadol·di-*p*-toluoyl-L-tartaric acid salt (111 g, 0.171 mol), obtained above (d.e. >99%) was cracked in a similar way to procedure 4.2, this gave 45 g of (−)-Tramadol free base. This enantiomerically pure free base was dissolved in butan-2-one (500 mL) in a jacketed vessel and set to stir at 25°C. To this solution was added distilled water (3.08 mL) in one portion. Chlorotrimethylsilane (22.2 mL, 19.0 g, 0.175 mol) was added via syringe. The reaction was stirred overnight at 20°C. The white precipitate was collected by filtration washing with cold butan-2-one (200 mL). The white solid was dried under vacuum at 70°C to give the title compound (47.0 g, 92%, e.e. >99.5%) (Chiral HPLC). $[\alpha]_D = -34.3$ ($c = 1.27$, MeOH). Mp = 172.4–173°C. Lit.[2a] mp = 172–173°C; $[\alpha]_D^{rt} = -29.6$ ($c = 1.00$, MeOH).

4.10. Large scale (−)-Tramadol hydrochloride preparation from (−)-Tramadol·di-*p*-toluoyl-L-tartaric acid salt

(−)-Tramadol·di-*p*-toluoyl-L-tartaric acid salt (61.7 kg, 94.9 mol), obtained above (d.e. >99%) was cracked according to a similar procedure, as described in 4.2 above. This gave ~25.0 kg of (−)-Tramadol enantiomerically pure free base. This was dissolved in butanone (MEK) (196 kg) in a 600 L vessel and set to stir at 10–15°C. To this solution was added 22.8% w/w hydrogen chloride in *iso*-propanol (15.40 kg, 96.2 mol). Care was taken to keep the internal temperature below 15°C during the addition. After stirring for approximately 30 min a thick precipitate had formed. The crystallisation was left to age overnight at ambient temperature. The vessel was then cooled to ~5°C for 1 h. The white precipitate was collected by centrifugation, washing with cold butanone (66 kg). The white solid was dried under vacuum at 60°C to give the title compound (23.10 kg, 81%, e.e. >99.5%) (Chiral HPLC).

4.11. Attempted resolution of (±)-Tramadol with L-(+)-tartaric acid

(±)-Tramadol hydrochloride (60 g, 0.0228 mol) was suspended in water (96 mL) and treated with crushed ice (32 g). To this suspension was added a 36% sodium hydroxide solution (26 mL). The mixture was extracted with dichloromethane (140 mL), followed by re-extraction with a further dichloromethane (40 mL). The organic layers were combined and dried over magnesium sulphate. The solvent was then removed under vacuum to give the (±)-Tramadol free base quantitatively as a yellow oil. This was dissolved in ethanol (48 mL) and added to a solution of (L)-(+)-tartaric acid (30 g, 0.0228 mol) in ethanol (224 mL). This solution was stirred at 20°C for 2 h and then allowed to stand for 24 h at 4°C. After this time a copious amount of white precipitate had formed. This was collected by filtration and washed with cold ethanol (128 mL). After drying a white solid was obtained (approximately 77.6 g, ca. 94%). Analysis by chiral HPLC indicated that this material was essentially racemic. Further attempts were made to increase the d.e. by re-slurrying in ethanol and stirring overnight at 25°C, this however failed. Likewise hot slurries in ethanol and methanol also did not effect d.e. enhancement.

4.12. Resolution of racemic crude *cis*-/*trans*-Tramadol free base with DTTA

The crude racemic Tramadol free base was prepared using the procedure described by Flick et al.[1a] This gave a yellow oil (10.3 g, 0.0391 mol, 61%). HPLC indicated the *cis*:*trans* ratio to be 17.9:82.1. This crude material was dissolved in absolute ethanol (60 mL) and added to a solution of L-(−)-DTTA (15.1 g, 0.0391 mol) in absolute ethanol (80 mL) at 70–75°C. Stirring was continued for 30 min at this temperature. The reaction mixture was then cooled to 60°C and a seed sample added to effect crystallisation. The reaction mixture was gradually cooled to 25°C and then stirred overnight. The solid material was collected by filtration washing with ethanol (56 mL). This gave after drying (−)-Tramadol·L-(−)-DTTA (9.25 g, 36%) with d.e. = 96.6% (chiral HPLC). The *cis*:*trans* ratio was 1.2:98.8 (HPLC). This solid diastereoisomer was suspended in absolute ethanol (50 mL) and heated to 70°C and held at this temperature before cooling to 25°C over 2 h. The solid material was again collected by filtration, washing with absolute ethanol (25 mL). This gave (−)-Tramadol·L-(−)-DTTA (8.35 g, 90%), with d.e. = 98.8%. The *cis*:*trans* ratio was 0.6:99.4 (HPLC). This was converted to the hydrochloride salt, as described above, to give (−)-Tramadol·HCl (3.10 g, 82%). E.e. >99.5%. The *cis*:*trans* ratio was <0.5%:>99.5% (HPLC). The mother liquors from the initial resolution were cracked to give the (+)-enriched Tramadol free base

(6.55 g, 64%). The *cis*:*trans* ratio was 28.9:71.1. This yellow–orange oil was dissolved in methanol (13 mL) and the resultant mixture added to a solution of D-(+)-DTTA (9.60 g, 0.0248 mol) in methanol (38 mL) at 65°C. Stirring was continued at this temperature for 15 min and a seed crystal of (+)-Tramadol·D-(+)-DTTA was then added. On cooling further to 40°C, crystallisation occurred. The mixture was cooled to 25°C and allowed to stir overnight. The solid material was collected by filtration, washing the filter cake with absolute ethanol (45 mL). This gave (+)-Tramadol·D-(+)-DTTA (7.89 g, 49%), with d.e. = 99.5%. The *cis*:*trans* ratio was 0.8:99.2 (HPLC). This (+)-enantiomer-containing diastereoisomer was re-slurried in ethanol using the procedure described above to give (+)-Tramadol·D-(+)-DTTA (7.80 g) with a d.e. of 99.6% and a *cis*:*trans* ratio of 0.3:99.7 (HPLC). This was converted to the (+)-Tramadol hydrochloride salt with e.e. >99.5% (Chiral HPLC) and a *cis*:*trans* ratio of <0.5:>99.5 (HPLC).

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References

1. The biologically active isomer was developed by Grunenthal in the 1970s, here they describe this isomer as *trans*. Commercially and within the patent literature it is termed *trans*, however, under IUPAC terminology **1a** and **1b** would be classed as *cis*. In order not to confuse the issues, we have used *trans* nomenclature throughout for **1a** and **1b**. See (a) Flick, K.; Frankus, E. US Patent 3,652,589, March 28, 1972; (b) Frankus, E.; Friedrichs, E.; Kim, S. M.; Osterloh, G. *Arzneim.-Forsch./Drug Res.* **1978**, *28*, 107.
2. (a) Frankus, E.; Friedrichs, E.; Kim, S. M.; Osterloh, G. *Arzneim.-Forsch./Drug Res.* **1978**, *28*, 114; (b) Goeringer, K. E.; Logan, B. K.; Christian, G. D. *J. Anal. Toxicol.* **1997**, *21*, 529.
3. (a) Buschmann, W. W.; Graudums, I.; Jansen, P. US Patent 5,723,668, March 3, 1998; (b) Flick, K.; Frankus, E. US Patent 3,830,934, August 20, 1974. See also: Newman, P. *Optical Resolution Procedures for Chemical Compounds*; Volume 1, Amines and related compounds, Optical Resolution Information Center, Manhattan College, Riverdale: New York, 1981; p. 10471; (c) Zinovy, I.; Meckler, H. *Org. Pro. Res. Dev.* **2000**, *4*, 291. For an earlier report on the use of this resolving agent, see: Elsing, B.; Blaschke, G. *Arch. Pharm. (Weiheim, Ger.)* **1991**, *324*, 719. Attempts to crystallise the camphor sulfonate and mandelate salts of Tramadol in ethanol failed to give rise to a precipitate. Using an *iso*-propyl acetate/ethyl acetate solvent system described by Meckler did give rise to crystalline material with mandelic acid.
4. (a) Forro, E.; Kanerva, L. T.; Fulop, F. *Tetrahedron: Asymmetry* **1998**, *9*, 513; (b) Forro, E.; Fulop, F.; Kanerva, L. T. *Magy. Kem. Foly.* **1998**, *104* (11), 437; (c) Cavoy, E.; Deltent, M. F.; Lehoucq, S.; Miggiano, D. *J. Chromatogr. A* **1997**, *769*, 49.
5. (a) Gilbert, J. C.; Richards, A. J. M.; Bardsley, H. J. World Patent Application No. WO 98/40053, September 17, 1998; (b) Evans, G. R. World Patent Application No. WO 00/32554, June 8, 2000.
6. Previously we have used DTTA to resolve (±)-*threo*-methylphenidate. See: (a) Faulconbridge, S.; Zaverah, H. S.; Evans, G. R.; Langston, M. World Patent Application No. WO 98/25902, June 18, 1998; (b) Harris, M. C. J.; Zavareh, H. S. World Patent Application No. WO/97/27176, July 31, 1997. On a larger scale L-(−)-DBTA was shown to give (−)-Tramadol·(L)-(−)-DBTA diastereoisomer of 89.3% d.e. This required a minimum of two crystallisations to effect full separation.
7. Other solvents examined include methanol, *iso*-propanol and ethyl acetate. Ethanol gave the higher yields and higher d.e.s.
8. The efficiency factor S is used to indicate how effective a resolution is. When $S = 1.0$, the resolution is 100% efficient, see: Fogassy, E.; Faigl, F.; Darvas, F.; Acs, M.; Toke, L. *Tetrahedron Lett.* **1980**, *21*, 2841. In the case of Tramadol DTTA typically provides a resolution with $S > 0.85$.
9. Here 7.5 volumes of methanol are used for the (−)-Tramadol enriched free base (v/w). Ethanol can also be used, but 20 volumes with respect to free base are required, due to the formation of a very thick precipitate that necessitates this large volume.
10. Use of 0.95–1.50 equiv. of HCl in *iso*-propanol were tested. When 1.50 equiv. of HCl were used the yield was lowered to 65%, this compares to an 82% yield when 0.95 equiv. were employed. The single enantiomer hydrochlorides of Tramadol are partially soluble in *iso*-propanol. It should also be noted that they are hygroscopic and the presence of water in the final crystallisation solvent adversely effects the yield.
11. A number of patents have appeared recently which detail the separation of the required *trans*-isomers of Tramadol from the unwanted *cis*-isomers. This highlights the remarkable ability of DTTA in separating a single *trans*-enantiomer from the mixture of all four. See: (a) Jarvi, E. T.; Grayson, N. A.; Halvachs, R. E. World Patent Application No. WO/99/61405, December 2, 1999; (b) Archer, N.; Mitchell, M.; Hurley, B.; Ogden, H. World Patent Application No. WO/99/36389, January 14, 1999; (c) Carbi, W. European Patent Application, EP 0 940 385, March 3, 1999; (d) Cherkez, S.; Lerman, O.; Tennenbaum, M.; Avner, H.; Kunyevski, T. US Patent, 5,414,129, May 9, 1995; (e) Lerman, O.; Tennenbaum, M.; Gal, E.; Kaspi, J. US Patent, 5,672,755, September 30, 1997; (f) Lerman, O.; Kaspi, J.; Brenner, D. US Patent, 5,874,620, February 23, 1999; (g) Nikolopoulos, A.; Schickaneder, H. World Patent Application No. WO/99/03820, January 28, 1999.
12. In order to facilitate a more streamlined process, the crude damp (+)-Tramadol·(D)-(+)-DTTA salt was sampled and weighed. A loss on drying (LOD) was then used to calculate the actual amount of the diastereoisomer at 66.1 kg. This figure was needed to calculate the maximum amount of material in the liquors containing the (−)-Tramadol diastereoisomer at 83.5 kg. This method was also used to calculate the amount of (−)-Tramadol·(L)-(−)-DTTA.