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Development of Highly Efficient Resolutions of Racemic Tramadol Using Mandelic Acid

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Abstract:

Two methods for the resolution of tramadol are described. One uses the active pharmaceutical ingredient (API), tramadol hydrochloride as input material. The other utilises the crude free base obtained from the Grignard reaction on tramadol Mannich base. Both resolutions use mandelic acid; the cost and process implications of each approach are discussed.

Introduction

Tramadol, (*trans*-(±)-2-[(dimethylamino)methyl]-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**) (see Figure 1). Both enantiomers have weak opiate activity, with the (−)-isomer inhibiting serotonin reuptake and the (+)-isomer inhibiting noradrenaline reuptake. It has 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 those of tramadol isomers themselves.)[2] It is possible that further investigations in this field will lead to 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 four documented resolution procedures. Here, they use tartaric acid,[3a] dibenzoyl-tartaric acid (DBTA),[3b] di-*p*-toluoyl-tartaric acid (DTTA),[3c] and recently, mandelic acid.[3d] Very recently, enzymatic resolutions of related compounds have been described,[4a,b] and the use of SMB (simulated moving bed) 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 a chiral synthesis of each enantiomer is extremely challenging, the most expedient route appeared to be a classical resolution process. Due to the ready availability of racemic tramadol, separation of diastereomeric salts by selective crystallisation appeared ideal for our purpose. Initially, on trying to repeat the European patent[3a] procedure, we observed little or no diastereoselectivity. Here, racemic tramadol is resolved with (L)-(+)-tartaric acid in excellent diastereomeric excess (de) >98% and yield (49%). A solution of (±)-tramadol in ethanol is stirred at ambient temperature, and to this solution is added the tartaric acid in ethanol. When this process was repeated, a copious amount of solid had formed to give 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 DBTA multiple crystallisations were required to effect complete separation of the enantiomers. We have recently published our findings on the resolution of tramadol with DTTA.[3c] Whilst this resolving agent does give rise to an excellent resolution, there are several factors which make this economically less attractive. The initial resolution is carried out in 14 vols of ethanol with respect to the free base. The resolving agent DTTA is moderately expensive and has a higher molecular weight than tramadol itself. The ester functionality of DTTA is also readily hydrolysed during the base release of the intermediate salts; hence, recovery and reuse were envisaged to be problematical. Intrigued by the report by Meckler et al. on

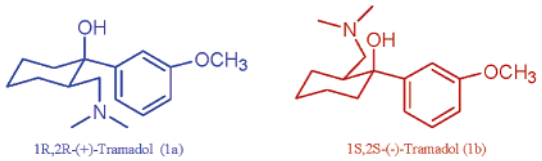

Figure 1.

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(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*. To not confuse the issue, we have used *trans* nomenclature throughout for **1a** and **1b**. See: (a) Flick, K.; Frankus, E. U.S. 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. U.S. Patent 5,723,668, March 3, 1998. (b) Flick, K.; Frankus, E. U.S. Patent 3,830,934, August 20, 1974. See also: Newman, P. *Optical Resolution Procedures for Chemical Compounds*; Vol. 1, Amines and Related Compounds; Optical Resolution Information Center, Manhattan College, Riverdale: New York, 1981. (c) Evans, G. R.; Henshilwood, J. A.; O'Rourke, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1663 and Evans, G. R. World Pat. Appl. No. WO 00/32554, June 8, 2000. (d) Itov, Z.; Meckler, H. *Org. Process Res. Dev.* **2000**, *4*, 291. For an earlier report on the use of this resolving agent, see: Elsing, B.; Blaschke, G. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 719.

(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*, 437. (c) Cavoy, E.; Deltent, M. F.; Lehoucq, S.; Miggiano, D. *J. Chromatogr., A* **1997**, *769*, 49.

(5) Gilbert, J. C.; Richards, A. J. M.; Bardsley, H. J. World Pat. Appl. No. WO 98/40053, September 17, 1998.

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Table 1. **Initial mandelic acid resolutions of tramadol (1a,1b)**

solvent	time/hr	yield of PPT, % (de %)	yield of MLS, % (de %)	*S*
IPrOAc/EtOAc	3.5	18.7 (93.0)	81.3 (20.0)	0.35
EtOAc	16	41.7 (93.4)	58.3 (76.0)	0.78
EtOAc	16	41.5 (93.2)	58.5 (76.2)	0.77
EtOAc*	16	41.4 (97.0)	58.6 (79.4)	0.80
EtOAc	5	44.6 (93.2)	55.4 (79.4)	0.83

[a] Here, recovered mandelic acid was used.

Table 2. **Effect of concentration on the mandelic acid resolutions of tramadol (1a,1b) in ethyl acetate**

yield of PPT, % (de %)	yield of MLS, % (de %)	$S \times$ efficiency factor	concn, g% (volume)[a]
43.6 (96.2)	56.4 (80.6)	0.84	15.0 (10)
44.6 (95.4)	55.4 (81.8)	0.85	18.3 (8)
44.9 (95.4)	55.1 (83.2)	0.86	20.3 (7)
75.0 (21.2)	25.0 (74.6)	0.32	22.3 (6)
76.0 (19.0)	24.0 (74.8)	0.29	25.9 (5)

[a] Volume with respect to free base.

the resolution of tramadol with mandelic acid,[3d] we sought to investigate this process and compare and contrast the economics to that of our DTTA approach. It should be noted that to fully effect the separation of the enantiomers of tramadol with mandelic acid, Meckler required that the mandelate salt be formed, cracked, and re-formed several times. Initially, on repeating the Meckler mandelic acid resolution using a mixture of *iso*-propyl and ethyl acetates (entry 1, Table 1) we were pleased to see the formation of a precipitate. The de of the isolated solid was high, 93.0%, but the recovered yield was only 18.7% which represents an efficiency of $S = 0.35$.[6] The efficiency factor $S = 2 \times$ yield $\times$ de of the solid obtained, for example, $0.187 \times 0.93 \times 2 = 0.35$.[6] Meckler and Itov state that the mandelic acid resolution is under kinetic control.[3d] Encouraged by this preliminary result we sought to ascertain the feasibility of developing this process further into an economically viable one. Table 1, highlights the initial experiments that were undertaken. As can be seen in Table 1, there is some variability in the results which can be indicative of a kinetic resolution; however, these results indicated that a reasonably efficient crystallisation might be achieved with *S* approaching 0.80. The lower efficiency of the resolution when carried out in the mixture of *iso*-propyl and ethyl acetates could be due to the lower polarity of the *iso*-propyl acetate (entry 1, Table 1).

Both diastereoisomers were independently prepared and their melting points and solubilities measured. The *p*-salt (+,+ or −,−), (−)-tramadol·(D)-(−)-mandelic acid has a melting point of 153.3−154.6 °C and a solubility of 4.5 mg per mL in ethyl acetate at 25 °C. In contrast the *n*-salt (+,− or −,+), (+)-tramadol·(D)-(−)-mandelic acid has a melting point of 106.3−107.6 °C and a solubility of 43.5 mg per mL in ethyl acetate at 25 °C. The large difference in melting points and almost 10-fold difference in their solubilities indicated that the mandelic acid resolution of tramadol was not under kinetic control.[7]

The next stage of the development was to look at the effect of concentration on the efficiency of the resolution. Table 2 illustrates the trend seen with variation on concentration of this resolution. Indeed, an optimum concentration appears to be 7 vols with respect to the free base (or ∼20 g %) with $S = 0.86$. However, at more concentrated conditions 5−6 vols (22−25 g %) the efficiency dramatically drops to $S = 0.3$. It is thought that at these higher concentrations the *n*-salt (more soluble diastereoisomer) starts to crystallise. Once this happens, it is entrained in the solid, which therefore badly affects the de. The phenomenon of solid solutions is well-known to be the cause of poor separations.[7] The method of Meckler to form the salt, to crack, and to reform and so on enables us to overcome this problem of solid solutions. Whilst this method is of limited commercial value, this may provide a way around the formation of solid solutions.

The next step was to re-slurry the mandelate salts obtained from the initial resolutions of varying de. Using the method described by Meckler and Itov,[3d] a hot slurry of the tramadol mandelate salt was undertaken. It was important to ascertain that high levels of optical purity could be obtained. It is also interesting to note that the low de material obtained from the initial resolution (∼20% de) upon re-slurry increased only to moderate de (55−71%). Analysis of the solid material by DSC indicated that two peaks were present which is again indicative of solid solutions as shown in Figure 2. The re-slurries shown in Table 3 are a little variable; it does seem to be necessary for the initial input salt to have a de of greater than 94% for the slurry to effect complete removal of the unwanted diastereoisomer.

To overcome the possibility of the wrong diastereoisomer coming out of solution, the resolution was routinely seeded with the pure required salt. For one equivalent of resolving agent the resolution was carried out using 8 vols of ethyl acetate. After complete addition of the free base to the resolving agent in ethyl acetate, the seed was added. Upon seeding, the crystallisation was relatively fast with the bulk of the solid coming out of solution after approximately 15 min; all the resolutions had similar stir-out times with isolation of the solid at 25 °C. A range of temperatures from 50 to 75 °C were studied; these showed little variation in the efficiency with $S = 0.83-0.85$. It was, however, felt to be more beneficial to carry out the crystallisations at the higher temperatures so that the unwanted diastereoisomer did not also crystallise.

The next development was to look at decreasing the number of equivalents of mandelic acid (Meckler and Itov[3d] had previously shown that less than one equivalent could be employed). This should have two benefits; the first obviously is use of less resolving agent that reduces the cost. The second is that the resolution can be conducted at higher concentrations, thus permitting better vessel utilisation for

(6) 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 $S \geq 0.85$.

(7) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*, 2nd ed.; Krieger: Florida, 1994;, pp 299−301 and 382−383.

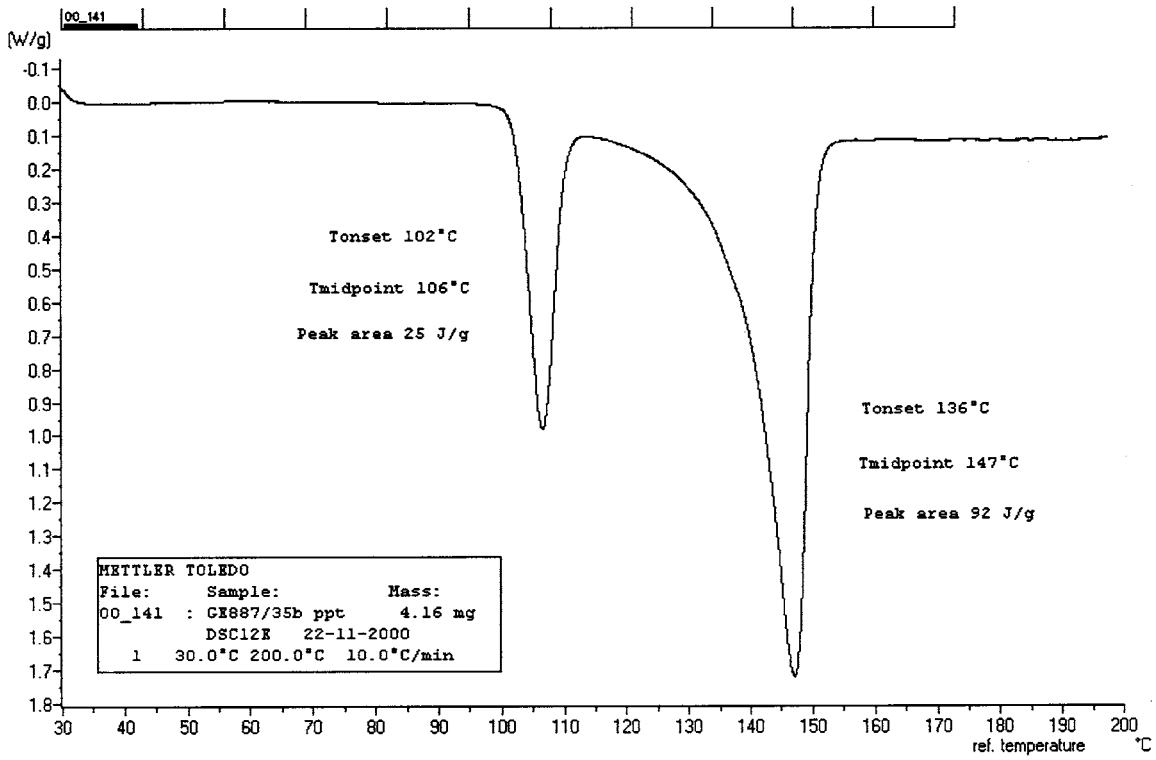


Figure 2. **DSC of *n*- and *p*-salt mixture of tramadol mandelate salts.**

Table 3. **Re-slurry of the tramadol mandelate salts in ethyl acetate**

volume[a]	input material, g (de %)	output material, g (de %)	yield, %
8	13.11 (93.4)	12.09 (95.0)	92.2
5	24.00 (19.4)	16.70 (54.8)	69.6
5	23.68 (21.1)	15.45 (70.6)	65.2
5	34.94 (99.0)	33.34 (99.4)	95.4
5	156.7 (94.0)	147.8 (99.0)	94.3

[a] Volume with respect to mandelate salt.

Table 4. **Effect of the number of equivalents of mandelic acid on the resolution of tramadol (1a,1b)**

mandelic acid equiv	concentrated g%	yield of PPT, % (de %)	yield of MLS, % (de %)	*S**
1.0	18.1	45.2 (93.8)	54.8 (78.8)	0.85
0.90	18.0	43.7 (95.4)	56.3 (76.0)	0.83
0.75	20.1	43.3 (98.2)	56.7 (80.8)	0.85
0.75	30.4	45.8 (96.0)	54.2 (83.8)	0.88
0.75	35.7	46.8 (96.4)	53.2 (86.2)	0.90
0.75	39.1	47.1 (92.4)	52.9 (86.6)	0.87
0.75	30.0	46.2 (97.4)	53.8 (84.6)	0.90
0.60	29.8	43.8 (98.6)	56.2 (79.0)	0.86
0.60	34.5	43.4 (98.6)	56.6 (79.2)	0.86
0.60	40.0	44.9 (98.0)	55.1 (82.6)	0.88
0.50	20.1	37.8 (95.2)	62.2 (62.4)	0.72
0.50	24.6	40.0 (95.4)	60.0 (66.0)	0.76
0.50	29.4	40.9 (98.0)	59.1 (69.4)	0.80
0.50	35.0	40.7 (97.2)	60.3 (69.4)	0.79

the crystallisation. Table 4, highlights a number of experiments using a range of 0.5−1.0 equiv of mandelic acid.[8]

(8) (a) Delepine, M.; Lareze, F. *Bull. Soc. Chim. Fr.* **1955**, 104. (b) Pope, W. J.; Read, J. *J. Chem. Soc.* **1910**, *97*, 988.

The results in Table 4 merit comment. For example, when one equivalent of mandelic acid is used, the volume for the crystallisation is 8 with respect to free base. When 0.6 equiv of the same resolving agent is utilised, the volume falls to 2 with respect to free base. This also lends itself to providing a more economic process. However, when 0.75 equiv of resolving agent is used if the concentration is greater than *c* = 35 g%, then the de of the precipitate falls away to the low 90's. This therefore requires careful control of the concentration and would appear to be optimum between *c* = 30 and 35 g %, for 0.75 equiv of mandelic acid.

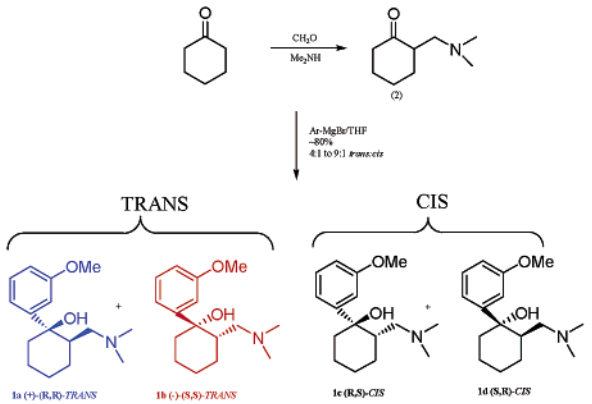
The project required that both enantiomers be obtained in high optical purity. Isolation of the (−)-tramadol-containing diastereoisomer was done in the initial resolution as illustrated above. By re-working the liquors with the opposite antipode of mandelic acid the (+)-tramadol-containing diastereoisomer could also be obtained in high yield and purity (again, this had already been shown by Meckler and Itov[3d]). It is possible to take the liquors from the first resolution and crack directly to the (+)-enriched free base. The ethyl acetate solution containing the free base is then concentrated to the desired volume. This solution is then added to the (L)-(+)-mandelic acid solution in ethyl acetate at 75 °C. Seeding with the pure diastereoisomer again effected crystallisation. These results are depicted in Table 5. For a good yield to be obtained the input mother liquors need to be enriched at greater than 78% de. When the de is below 60%, the recovered yield is below 70%, which is not unexpected. We are aiming to get a 45% yield of the precipitate with a de >95%, which leaves the liquors enriched with a de of >80% and in 55% yield. It is believed that for optimum results in reworking of the enriched tramadol-free base from the mother liquors, exactly one

Table 5. **Resolution of enriched tramadol free base (1a,1b) with (L)-(+)-mandelic acid**

volume[a]	input free base ee%	yield of PPT, % (de %)	yield of MLS, % (de %)
10	80.6	81.9 (99.0)	19.1 (40.6)
8	58.0	69.9 (99.0)	30.1 (67.8)
8	78.0	76.1 (99.6)	23.9 (27.8)
8	84.8[b]	84.4 (99.6)	15.6
8	85.2[c]	87.4 (99.6)	12.6

[a] Volume based on mandelate salt. [b] 0.9 equiv of mandelic acid used relative to tramadol free base. [c] Exactly 1 equiv of mandelic acid used relative to the (+)-tramadol isomer present.

Scheme 1. **Commercial synthesis of racemic tramadol**



equivalent of resolving agent for the specific enantiomer should be utilised. That is to say, if the mother liquors have a de of 85%, which corresponds to 92.5% of the (+)-isomer, then 0.925 equiv of the resolving agent ((L)-(+)-mandelic acid) should be employed to maximize the yield.

Separation of a Single *trans* Isomer from Crude *cis*/*trans* Mixture. Previously we have shown that when a mixture of *trans* (*RR*,*SS*)- and *cis*-tramadol (*RS*,*SR*)-free base is treated with specific chiral acids, the *cis* and *trans* isomers can be readily separated.[3c] Indeed with mandelic acid, the precipitated salt contains only the single *trans* isomer required (**1a** or **1b**) and little or none of the *cis* isomer, leaving in solution the unwanted *trans* isomer (**1a** or **1b**) and the *cis* isomers (**1c**,**1d**). Currently, tramadol (2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol (**1**) is prepared by the Grignard reaction of 3-methoxyphenylmagnesium bromide with 2-[(dimethylamino)methyl] cyclohexanone (**2**) as shown in Scheme 1.[1a] This gives rise to a mixture of the *cis* (*RS*,*SR*)-(**1c**,**1d**) and *trans* (*RR*,*SS*)-(**1a**,**1b**) isomers of tramadol free base. Separation of this mixture can be achieved by a lengthy crystallisation procedure. In the case of Flick and Frankus, dioxane is the solvent of choice for this separation.[1a] This process is costly from the processing time that is incurred and also uses the highly toxic solvent dioxane (category 1 carcinogen by OSHA). Other methods of separating the *trans* isomers have been published in the patent literature. For example crystallisation of *trans*-tramadol hydrochloride from the Grignard mixture in low-molecular weight alcohols has been achieved.[9] This, however, suffers from the need to carry out several crystallisations to remove completely the unwanted *cis* isomers. Likewise, use of electrophilic reagents, such as acetic anhydride, to react preferentially with the *cis* isomer enables crystallisation of the required *trans*-tramadol from the reaction mixture.[10] Again further crystallisations are needed to fully remove the *cis* isomer. Another example uses aqueous HBr to preferentially crystallise the *trans*-tramadol hydrobromide. This then requires conversion to the hydrochloride salt.[11]

The initial lab-based experiments used a crude mixture which was prepared according to the procedure described by Flick et al.[1a] This gave an approximate mixture of the *trans* to *cis* isomers of 4:1. Treatment of this crude free base with (D)-(−)-mandelic acid gave in respectable yield the (−)-*trans*-tramadol containing diastereoisomer of high de, with a small amount of the *cis* isomers in the solid. Subsequent re-slurry and conversion to the hydrochloride salt, gave (−)-tramadol hydrochloride of acceptable quality. The attraction of the crude free base was due to the low cost and the fact that processing time could be saved using the free base in preference to the hydrochloride salt. In essence the mandelic acid is being utilised to pull out one isomer from a mixture of all four and effecting two purifications at once. We were able to obtain a quantity of crude free base from commercial sources and put these into the mandelic acid resolution process. These results are shown in Tables 6 and 7.

We have modified the efficiency factor *S* to take account of the purity of the input material and called this *S**. Thus, the modified efficiency factor $S^* = 2 \times \text{yield} \times \text{de}$ of the solid obtained/purity of crude free base, for example, entry 1, Table 6, $S^* = (0.368 \times 0.988 \times 2)/0.83 = 0.87$. In Table 6, the crude free base has a purity level of just below 83%. For the first resolution a high efficiency *S** of 0.8−0.87 has been obtained, with de's in excess of 98% and the residual level of *cis* isomers at 0.3% or below. Note should be made that the really crude material in the liquors from this first crystallisation can also be taken and the (+)-*trans* tramadol·(L)-(+)-mandelate isolated in high de >99% again with low levels of *cis* impurity present. Table 7 has an input crude base, which has a purity of only 66.9%; once more the ability of mandelic acid to cleanly isolate a single *trans* isomer has been demonstrated: the efficiency *S** of 0.62−0.8 is slightly lower than that above. So that the *cis* isomer "impurity" was fully removed from the intermediate salt, a re-slurry of the mandelate salt was undertaken in 5 vols of ethyl acetate prior to conversion to the HCl salt.

Development of the HPLC System. So that the purity of the single enantiomer tramadol hydrochlorides could be determined, a number of HPLC methods needed to be developed. The chiral assay originally used for tramadol obtained from the DTTA resolution needed to be modified so that the *cis* isomers do not interfer with the two *trans* isomers. This was readily achieved by modifying the eluent composition. Likewise the achiral purity assay was amended to incorporate the resolving agent (mandelic acid). Typical

(9) Cherkez, S.; Lerman, O.; Tennenbaum, M.; Avner, H.; Kunyevski, T. U.S Patent, 5,414,129, May 9, 1995.

(10) Lerman, O.; Kaspi, J.; Brenner, D. U.S. Patent, 5,874,620, February 23, 1999.

(11) Anderson, K. E., U.S. Patent, 5,877,351, March 2, 1999.

Table 6. **Resolution of crude *cis*/*trans* free base (1a−1d) in ethyl acetate with mandelic acid**

free base input (g) (*cis/trans*)[a]	concentrated g%	yield of PPT, % (de %) (*cis/trans*)	yield of MLS, % (de %) (*cis/trans*)	*S** (real yield %)
10 (*13.8/86.2*)	20.1	36.8 (98.8) (*0.3/99.7*)	63.2 (78.2) (*21.8/78.2*)	0.87 (44.2)
28.3 (*13.8/86.2*)	20.5	33.7 (98.6) (*0.2/99.8*)	66.3 (71.6) (*21.1/78.9*)	0.80 (40.4)
18.8 (*21.1/78.9*)	20.0	55.2 (99.6) (*0.3/99.7*)	44.8 (28.2) (*55.4/44.6*)	0.82
18.6 (*21.2/78.8*)	20.2	56.6 (99.6) (*0.3/99.7*)	43.4 (30.4) (*55.9/44.1*)	0.83
16.1 (*13.8/86.2*)	34.3	36.7 (99.6) (*0.3/99.7*)	65.4 (72.0) (*21.2/78.8*)	0.87 (44.1)

[a] The crude free base had a purity of approximately 83%. The real yield is based on the amount of *trans*-tramadol (**1a**,**1b**) present in the crude free base.

Table 7. **Resolution of crude *cis*/*trans* free base (1a−1d) in ethyl acetate with mandelic acid**

free base input (g) (*cis/trans*)[a]	concentrated g%	yield of PPT, % (de %) (*cis/trans*)	yield of MLS, % (de %) (*cis/trans*)	*S** (real yield %)
28.4 (*12.8/87.2*)	22.9	20.8 (99.0) (*0.3/99.7*)	79.2 (47.3) (*18.0/82.0*)	0.62 (31.1)
28.4 (*12.8/87.2*)	25.4	24.9 (98.8) (*0.3/99.7*)	75.1 (62.6) (*19.1/80.9*)	0.75 (37.2)
28.4 (*12.8/87.2*)	36.4	26.7 (99.2) (*0.4/99.6*)	69.3 (69.0) (*19.7/80.3*)	0.80 (39.9)
28.4 (*12.8/87.2*)	40.3	20.8 (98.8) (*0.2/99.8*)	69.0 (69.0) (*18.0/82.0*)	0.80 (40.3)
18.8 (*20.5/79.5*)	18.3	71.8 (99.5) (*0.3/99.7*)	28.2	0.71 (40.3)

[a] The crude free base had a purity of approximately 66.9%. The real yield is based on the amount of *trans*-tramadol (**1a**,**1b**) present in the crude free base.

chromatograms for the single enantiomer hydrochlorides obtained from the crude free base are shown in Figure 3.

Comparison of the DTTA and Two Mandelic Acid Routes to Single Enantiomer Tramadol. Estimations as to the cost per kilogram of single enantiomer tramadol hydrochloride are presented in Table 8. A number of factors have been considered, which are based upon the cost of the raw materials, processing time, vessel utilisation, and final product output. In the case of DTTA, this represents the most expensive route presented. This is mainly due to the cost of the resolving agent (for L-DTTA ∼£40 per kg, D-DTTA ∼£60 per kg), the amount of the chiral acid (MW 386.4) required per kilo of tramadol free base (MW 263.4), and the volume of the inefficient initial resolution. It is also anticipated that problems on the recovery and recycle of DDTA from the intermediate salts could occur. The first mandelic acid process using commercially available API is expected to be cheaper than the DTTA route. This is based on the fact that mandelic acid (MW 152.2) is considerably cheaper (∼£35 per kg for either enantiomer) than DTTA (MW 386.4) the weight requirement per kilo of tramadol is less than half that of DTTA. The volume efficiency of the mandelic acid approach is also more favourable with a volume of 3.5−8.0 of ethyl acetate with respect to free base being required. This compares to 14 vols of ethanol for the DTTA route. The compatibility of ethyl acetate to extractions and base release of tramadol free base is also advantageous. The second mandelic acid process using a crude mixture of the *cis*/*trans* free base (available from commercial manufacturers of the API) is expected to be cheaper still due to savings inherent in the back integration into the current commercial process. A synopsis of the overall process of the separation of the enantiomers of tramadol with mandelic acid is given in Scheme 2.

In summary, we have shown that the mandelic acid resolution of tramadol is under thermodynamic and not kinetic control. The initial problems encountered and subsequently overcome by Meckler and Itov[3d] appear to be due to solid solutions. By careful control of the crystallisation conditions, a highly efficient and economic process has been developed. Either the API or crude free base can be utilised as the input material.

Experimental Section

The ^{1}H NMR spectra were determined using a Bruker AC-300 or 400 spectrometer, and signals are given in ppm using TMS as an internal standard in the solvent noted. Melting points were measured by a Mettler DSC 12E and are uncorrected. All reagents and solvents were of commercial quality. Chiral HPLC data were obtained using the following conditions: UV 273 nm; column: Chiralpak AD (250 mm × 4.6 mm, 10 μm); mobile phase composition of 6:94 v/v of 0.1% diethylamine in 1-propanol:*iso*-hexane; flow rate of 1.0 mL/min. The retention times were: (+)-*trans*-tramadol RT = 5.1 min, (±)-*cis*-tramadol RT = 6.6 min and (−)-*trans*-tramadol RT = 7.9 min.

The tramadol *cis/trans* ratio was measured by reverse phase HPLC under the following conditions: UV 210 nm;

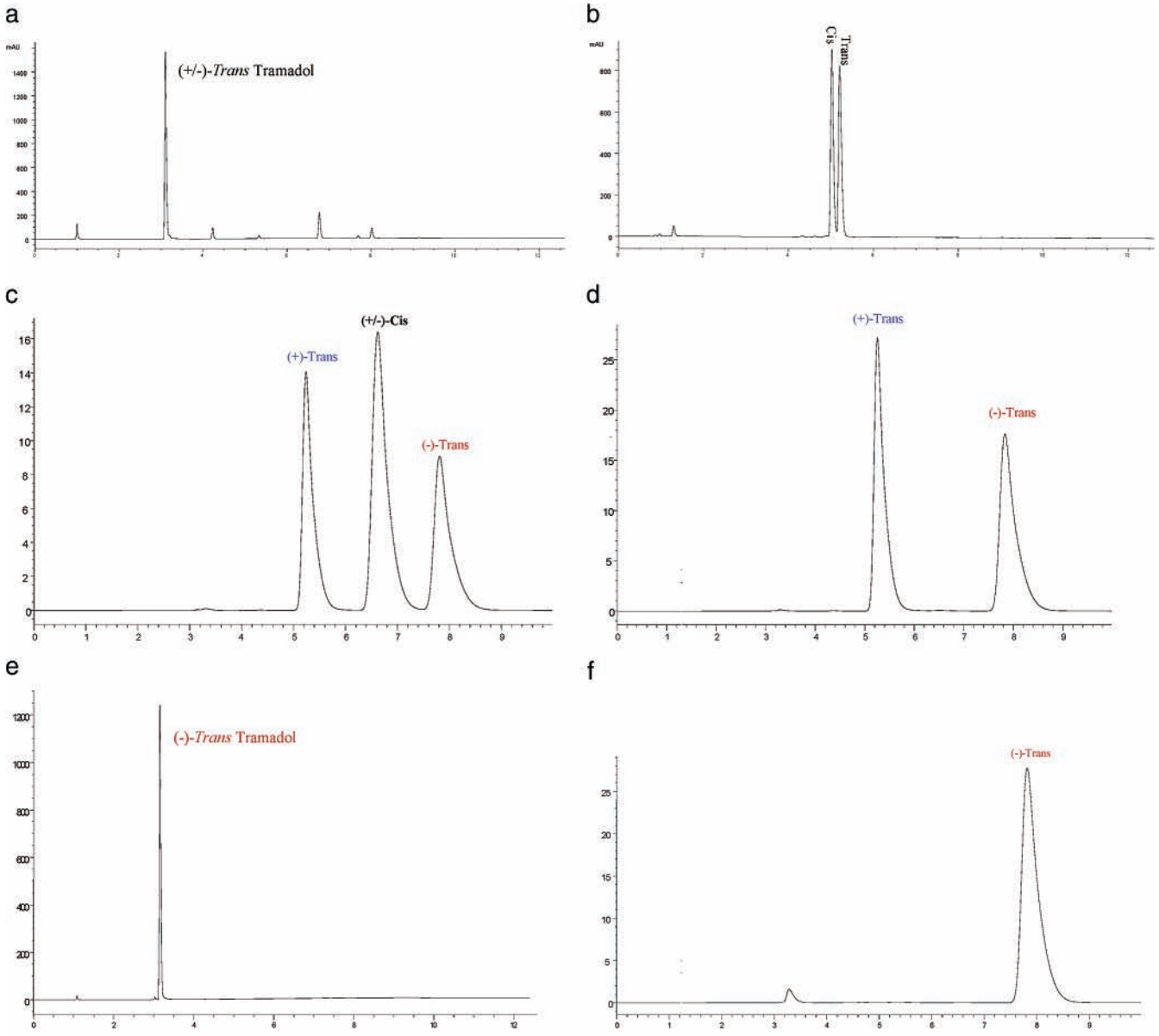


Figure 3. **(a) Achiral HPLC of crude *cis/trans* tramadol free base (1a−1d). (b) Analysis of *cis/trans* ratio of tramadol by HPLC. (c) Chiral HPLC, separation of the *cis* and *trans* isomers (1a−1d). (d) Chiral HPLC, separation of the two *trans* enantiomers (1a and 1b). (e) Achiral HPLC of (−)-tramadol·HCl obtained from crude free base. (f) Chiral HPLC of (−)-tramadol (1b) obtained from crude free base.**

Table 8. **Cost comparison of the DTTA and two mandelic acid routes to single enantiomer tramadol hydrochloride**

	total per kilo cost[a] (i.e 1 kg (−) and 1 kg (+)-tramadol·HCl)	
resolving agent	racemic tramadol HCl	crude free base *cis/trans* tramadol
DTTA	ca. £800	-
mandelic acid	ca. £500	ca. £300

[a] Note: Costs relate to the generation of equal amounts of each enantiomer and are calculated on the basis of ca. 8−10 tonnes per annum (of each enantiomer).

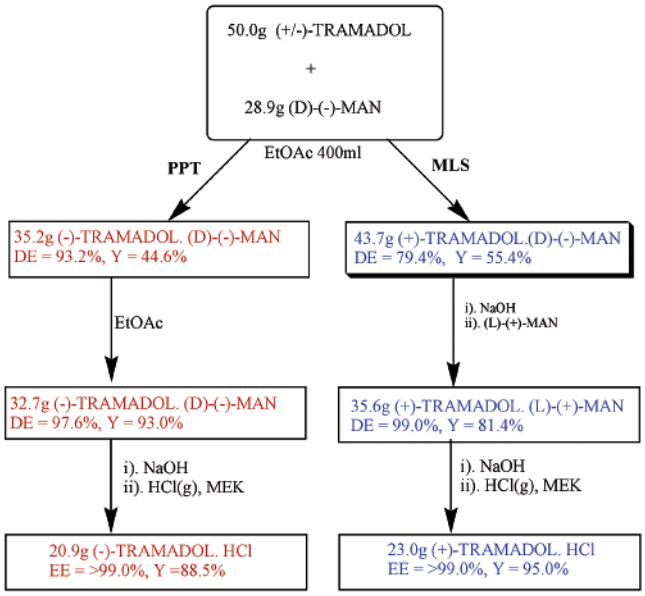
column: Phenomenex Luna (2) (C18, 150 mm × 4.6 mm, 5 μm); flow rate 2.0 mL/min, mobile phase solvents: 95% 20 mM KH_2PO_4 pH = 7.0 and 5% acetonitrile (A), and 25% 20 mM KH_2PO_4 pH = 7.0 and 75% acetonitrile (B), using a linear gradient of 5 to 65% B over 8 min. The retention times were as follows: mandelic acid RT = 1.5 min, (±)-*cis*-tramadol RT = 5.0 min, (±)-*trans*-tramadol RT = 5.2 min.

The achiral purity was determined by reverse phase gradient HPLC at both pH 2.2 and pH 7.0:

Method 1, pH 2.2: UV 210 nm; column: Phenomenex Luna (2) (C18, 150 mm × 4.6 mm, 5 μm); flow rate 2.0 mL/min, mobile phase solvents: H_2O pH = 2.2 adjusted with concentrated H_3PO_4 (A) and acetonitrile (B), using a linear gradient of 5 to 90% B over 8 min, then 90% B for 3.5 min. The retention times under these conditions were as follows: (±)-*cis*-tramadol RT = 3.0 min and (±)-*trans*-tramadol RT = 3.2 min.

Method 2, pH 7.0: UV 210 nm; column: Phenomenex Luna (2) (C18, 150 mm × 4.6 mm, 5 μm); flow rate 2.0

Scheme 2. **Separation of the enantiomers of tramadol with mandelic acid**



mL/min, mobile phase solvents: 95% 20 mM KH_2PO_4 pH = 7.0 and 5% acetonitrile (A), and 25% 20 mM KH_2PO_4 pH = 7.0 and 75% acetonitrile (B), using a linear gradient of 0 to 100% B over 8 min, then 100% B for 3.5 min. The retention times under these conditions were as follows: (±)-*cis* tramadol RT = 4.1 min and (±)-*trans* tramadol RT = 4.2 min.

Resolution of Racemic Tramadol (1a,1b) with Mandelic Acid (1 equiv). Racemic tramadol free base (50 g, 0.190 mol) (obtained from the hydrochloride, API) was taken up in ethyl acetate (100 mL, 89 g). This solution was added to the (D)-(−)-mandelic acid (28.9 g, 0.190 mol) in ethyl acetate (300 mL, 265.2 g) at 75 °C. NB care was taken to keep the contents of the jacketed vessel above 70 °C during the addition. Immediately after addition of the free base, the resolution was seeded (200 mg) with pure diastereoisomer which effected crystallisation. The crystallisation is then gradually cooled to 25 °C over a 5-h period and then left to age overnight. The copious white precipitate was collected by filtration, washing with ethyl acetate (2 × 40 mL). This gave after drying (−)-tramadol·(D)-(−)-mandelic acid 35.21 g (44.6%), HPLC (chiral) 93.2% de. The mandelate salt was returned to the vessel and given a hot slurry in ethyl acetate (280 mL, 245.4 g) heating to to 75 °C and then gradually cooling to 25 °C over a 5-h period. The solid mandelate salt was collected by filtration and washed with ethyl acetate (2 × 30 mL), to give (−)-tramadol·(D)-(−)-mandelic acid 32.73 g (93.0%), (chiral HPLC) 97.6% de, mp = 151.4−153.1 °C (DSC) [lit:[3d] = 153−155 °C]. ^{1}H NMR (CD_3OD) δ 1.40−1.90 (m, 8H), 2.20 (m, 1H), 2.55 (s, 6H), 2.75−2.95 (m, 1H), 3.30 (m, 1H), 3.80 (s, 3H), 4.85 (s, 1H), 6.80 (d, 1H), 7.25 (m, 4H), and 7.45 (m, 2H). The liquors from the initial resolution were used in the following experiment.

Resolution of the (+)-Tramadol-Enriched Free Base (1a,1b) with (L)-(+)-Mandelic Acid. The mother liquors from the above initial resolution containing approximately 43.69 g (0.105 mol) of (+)-tramadol·(D)-(−)-mandelic acid of 79.4% de in ethyl acetate (480 mL) was cracked to the free base as follows: water (200 mL) was added, and to this biphasic mixture was added sodium hydroxide solution 46−48% (∼12 mL) to pH > 12.0 with stirring. The layers were then separated, and the aqueous layer was back-extracted with ethyl acetate (100 mL, 88.1 g). The combined ethyl acetate layers were then water-washed (150 mL). The ethyl acetate solution of (+)-enriched tramadol free base was then concentrated so that a total of ethyl acetate (100 mL) remained. This solution was then added to (L)-(+)-mandelic acid (16.0 g, 0.105 mol) in ethyl acetate (220.5 g), maintaining the internal temperature above 70 °C during the addition. Immediately afterwards, a seed (200 mg) of pure diastereoisomer was added, which effected crystallisation. The resolution was then gradually cooled to 25 °C over a 7-h period. The precipitate was then collected by filtration, washing with ethyl acetate (2 × 30 mL). This gave (+)-tramadol·(L)-(+)-mandelic acid 35.55 g (81.4%), with 99.0% de (Chiral HPLC), mp = 153.3−154.6 °C (DSC) [lit:[3d] = 153−155 °C]. ^{1}H NMR (CD_3OD) δ 1.40−1.90 (m, 8H), 2.20 (m, 1H), 2.55 (s, 6H), 2.75−2.95 (m, 1H), 3.30 (m, 1H), 3.80 (s, 3H), 4.85 (s, 1H), 6.80 (d, 1H), 7.25 (m, 4H), and 7.45 (m, 2H).

Resolution of Racemic Tramadol (1a, 1b) with 0.75 equiv of Mandelic Acid. Racemic tramadol free base (40 g, 0.152 mol) which was obtained from 45.5 g of racemic tramadol hydrochloride, was taken up in ethyl acetate (100 mL, 89.9 g). This colourless solution was added to the (D)-(−)-mandelic acid (17.3 g, 0. 114 mol) in ethyl acetate (156 mL, 138.2 g) at 75 °C. A seed sample of (−)-tramadol·(D)-(−)-mandelic acid (200 mg) was added immediately after addition of the free base solution, which effected crystallisation. The resolution was gradually cooled to 25 °C over a period of approximately 6.5 h. The copious white precipitate that formed was collected by filtration and washed with ethyl acetate (2 × 30 mL). This gave after drying (−)-tramadol·(D)-(−)-mandelic acid 27.35 g (43.3%) with a de of 98.2% (chiral HPLC). Evaporation of the mother liquors from the resolution above gave a slightly coloured oil of (+)-tramadol·(D)-(−)-mandelic acid 29.95 g (56.7%), de = 80.8% (chiral HPLC).

Resolution of Tramadol Crude Free Base (1a−1d) with (D)-(−)-Mandelic Acid in Ethyl Acetate (*c* = 20.2 g%) and Reworking of the Liquors. Crude racemic tramadol free base (28.4 g, 0.108 mol) which was obtained from a commercial source and shown to consist of *trans* to *cis* in the ratio 86.2:13.8 and a purity of 83.2% was taken up in ethyl acetate (100 mL, 88.5 g). This orange-brown-coloured solution was added to the (D)-(−)-mandelic acid (16.4 g, 0. 108 mol) in ethyl acetate (100 mL, 88.6 g) at 75 °C. A seed sample of (−)-tramadol·(D)-(−)-mandelic acid (200 mg) was added which effected crystallisation. The resolution was gradually cooled to 25 °C and left to age over a period of approximately 5.5 h. The copious white precipitate that formed was collected by filtration and washed with ethyl acetate (2 × 30 mL). This gave, after drying, (−)-tramadol·(D)-(−)-mandelic acid 15.52 g (34.6%) with a de of 99.6% (chiral HPLC), *trans/cis* 99.7/0.3 (HPLC). Evaporation of

the mother liquors from the resolution above gave a slightly coloured oil of (+)-tramadol·(D)-(−)-mandelic acid 29.28 g (65.4%), de = 72.0% (chiral HPLC) with a *trans/cis* ratio of 77.8/22.2. This salt was cracked to the free base, to give ∼18.56 g of an orange-coloured oil. This was taken up in ethyl acetate (60 mL, 53.2 g), and this solution was added to a solution of (L)-(+)-mandelic acid (10.72 g, 0.070 mol) in ethyl acetate (70 mL, 62.7 g) at 75 °C. Upon seeding with a sample of (+)-tramadol·(L)-(+)-mandelic acid, crystallisation was effected. This was cooled to 25 °C over a 5.5-h period. The precipitate was collected by filtration, washing with ethyl acetate (2 × 30 mL). This gave (+)-tramadol·(L)-(+)-mandelic acid 16.57 g (56.6%), de = 99.6% (chiral HPLC) and with *trans/cis* ratio of 99.7:0.3. The liquors amounted to ∼12.71 g (43.4%), de = 30.4% (chiral HPLC) and with *trans/cis* ratio of 55.9:44.1. (NB: considerable amounts of other impurities were also present in the mother liquors.)

Resolution of Tramadol Crude Free Base (1a−1d) with (D)-(−)-Mandelic Acid in Ethyl Acetate (*c* = 36.4 g%) and Reworking of the Liquors. Crude racemic tramadol free base (28.4 g, 0.108 mol) which was obtained from a commercial source and shown to consist of *trans* to *cis* in the ratio 87.2:12.8 and a purity of 66.9% was taken up in ethyl acetate (36 mL, 32.3 g). This orange-brown-coloured solution was added to the (D)-(−)-mandelic acid (10.6 g, 0. 070 mol) in ethyl acetate (40 mL, 35.9 g) at 75 °C. A seed sample of (−)-tramadol·(D)-(−)-mandelic acid (200 mg) was added which effected crystallisation. The resolution was gradually cooled to 25 °C and left to age over a period of approximately 6.5 h. The copious white precipitate that formed was collected by filtration, washing with ethyl acetate (2 × 30 mL). This gave, after drying, (−)-tramadol·(D)-(−)-mandelic acid 11.96 g (26.7%) with a de of 99.2% (chiral HPLC), *trans/cis* 99.6/0.4 (HPLC). Evaporation of the mother liquors from the resolution above gave a slightly coloured oil of (+)-tramadol·(D)-(−)-mandelic acid 27.04 g (65.4%), de = 69.0% (chiral HPLC) and a *trans/cis* ratio of 80.3/19.7. This salt was cracked to the free base to give ∼18.56 g of a yellow-coloured oil. This combined with two other similarly obtained free bases to give a total of 34.43 g. The combined free base was taken up in ethyl acetate (75 mL, 66.2 g); this solution was added to a solution of (L)-(+)-mandelic acid (19.90 g, 0.131 mol) in ethyl acetate (100 mL, 88.9 g) at 75 °C. Upon seeding with a sample of (+)-tramadol·(L)-(+)-mandelic acid, crystallisation was effected. This was cooled to 25 °C over a 5.5-h period. The precipitate was collected by filtration, washing with ethyl acetate (3 × 40 mL). This gave (+)-tramadol·(L)-(+)-mandelic acid 35.55 g (64.2%), de = 99.6% (chiral HPLC) with a *trans/cis* ratio of 99.6:0.4. The liquors amounted to ∼19.81 g (43.4%), de = 18.6% (chiral HPLC) with *trans/cis* ratio of 59.1:40.9. (NB: a considerable amount of other impurities were also present in the mother liquors.)[12]

(12) We were able to obtain an analytically pure sample of *cis*-tramadol hydrochloride from these liquors by repeated crystallisation from dichloromethane as described in ref 1a. This reference standard was required by the quality department, to help to ascertain the level of the *cis* isomers in the final product.

Preparation of (−)-Tramadol Hydrochloride (1b) from the Mandelate Salt Obtained from API. (−)-Tramadol free base (63.5 g, 0.241 mol) which was obtained from the (−)-tramadol·(D)-(−)-mandelic acid salt as follows: the mandelate salt (100 g, 0.241 mol) was suspended in dichloromethane (400 mL) and water (200 mL). To this stirred mixture was added a solution of sodium hydroxide (11.60 g, 0.289 mol) in water (100 mL). After 10 min stirring the layers were allowed to separate, and the pH was checked and shown to be >12. The organic layer was removed, and the aqueous layer was re-extracted with dichloromethane (200 mL). The combined organic layers were then water-washed (200 mL). The (−)-tramadol dichloromethane solution was then concentrated under vacuum to give 63.5 g of a colourless oil. The free base thus obtained was taken up in 2-butanone (640 mL). To this colourless solution was added HCl(g) in IPA (29.3 g, 0. 115 mol) of ∼30 wt/wt% at 10−15 °C. After 15 min crystallisation had occurred. The crystallisation was gradually aged over a period of approximately 5 h and then held at 5 °C for 1 h. The copious white precipitate that formed was collected by filtration, washing with 2-butanone (150 mL). This gave after drying under vacuum at 50 °C (−)-tramadol·HCl 58.90 g, (81.5%) with an ee of >99.5% (chiral HPLC). Purity ≥99.5% (achiral HPLC); mp = 171.5−173.2 °C (DSC) [lit:[3d] = 172−174 °C].

Preparation of (−)-Tramadol Hydrochloride (1b) from the Mandelate Salt Obtained from Crude Free Base. (−)-Tramadol free base (30.4 g, 0.115 mol) which was obtained from the (−)-tramadol·(D)-(−)-mandelic acid salt, with a *trans*-to-*cis* ratio of 99.8:0.2 was taken up in 2-butanone (300 mL). To this colourless solution was added HCl(g) in IPA (14.1 g, 0. 115 mol) of ∼30 wt/wt% at 10−15 °C. A seed sample of (−)-tramadol·HCl (100 mg) is added which effected crystallisation. The crystallisation was gradually aged over a period of approximately 4 h and then held at 5 °C for 1 h. The copious white precipitate that formed was collected by filtration, washing with 2-butanone (100 mL). This gave after drying under vacuum at 50 °C (−)-tramadol·HCl 27.90 g, (80.9%) with an ee of 99.2% (chiral HPLC), *trans/cis* >99.5/<0.5. Purity ≥ 99.5% (achiral HPLC); mp = 168.2−171.9 °C (DSC) [lit:[3d] = 172−174 °C].

Twenty-Liter-Scale Resolution of Tramadol Crude Free Base (1a−1d) with (D)-(−)-Mandelic Acid in Ethyl Acetate (*c* = ∼38.9 g%). Crude racemic tramadol free base (4.00 kg, 15.1 mol) which was obtained from a commercial source and shown to consist of *trans* to *cis* in the ratio of 87.1:12.9 and a purity of 77.4% was taken up in ethyl acetate (4.0 L). This brown-orange-coloured solution was added to the (D)-(−)-mandelic acid (1.70 kg, 11.20 mol) in ethyl acetate (5.0 L) at 75 °C. A further wash of ethyl acetate (1.0 L) on the tramadol-free base flask was used to effect full transfer. A seed sample of (−)-tramadol·(D)-(−)-mandelic acid (20 g) was added which effected crystallisation. The resolution was gradually cooled to 25 °C and left to age over a period of approximately 16 h. The copious white precipitate that formed was collected by filtration, washing with ethyl acetate (2 × 2.0 L). This gave after drying (−)-

tramadol·(D)-(−)-mandelic acid 1.88 kg (33.0%) with a de of 98.6% (chiral HPLC), *trans/cis* 99.7/0.3 (HPLC). (The mother liquors from the resolution were shown to consist of (+)-tramadol·(D)-(−)-mandelic acid ∼3.82 kg (67.0%), de = 72.0% (chiral HPLC) and with a *trans/cis* ratio of 78.9/21.1.) A 100 g portion of the (−)-tramadol·(D)-(−)-mandelic acid salt was re-slurried in 5 vols of ethyl acetate (500 mL). This was heated to 75 °C and then cooled to 25 °C over a 5.0 h period. The precipitate was collected by filtration washing with ethyl acetate (3 × 40 mL). This gave (−)-tramadol·(D)-(−)-mandelic acid 92.8 g (92.8%), de = 99.2% (chiral HPLC) with a *trans/cis* ratio of 99.9:0.1. This salt was converted to the hydrochloride using the procedure described above to give 59.7 g (89.3%) of (−)-tramadol·HCl, ee ≥ 99.5% (chiral HPLC), *cis/trans* ratio of <0.5:>99.5 and a purity of >99% (achiral HPLC); mp = 168.5−171.6 °C (DSC) [lit:[3d] = 172−174 °C].

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